

THE STATE OF SOUTH CAROLINA
In The Supreme Court

APPEAL FROM SPARTANBURG COUNTY
Court of Common Pleas

Roger L. Couch, Circuit Court Judge

Case No. 2007-CP-42-1438

State of South Carolina ex. rel. Alan Wilson in his
capacity as Attorney General of the State of South
Carolina, ... Respondent,

v.

Ortho-McNeill-Janssen Pharmaceuticals, Inc., f/k/a
Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and
Johnson & Johnson, Inc., ... Defendants.

Of whom Ortho-McNeill-Janssen Pharmaceuticals, Inc.
is Appellant.

RECORD ON APPEAL - VOLUME XVIII

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VII. CERTIFICATE OF COUNSEL

STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA, ex rel.
Alan Wilson, in his capacity as
Attorney General of the State of South
Carolina,

Civil Action No.: 2007-CP-42-1438

PLAINTIFF,

PLAINTIFF THE STATE OF SOUTH
CAROLINA'S RESPONSE
IN OPPOSITION TO
DEFENDANTS' MOTION FOR
SUMMARY JUDGMENT

v.

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC. f/k/a
JANSSEN PHARMACEUTICA, INC.
and/or JANSSEN, LP, AND JOHNSON
& JOHNSON, INC.,

AS TO PLAINTIFF'S UNFAIR TRADE
PRACTICES CLAIM BASED ON THE
FDA-APPROVED PACKAGE INSERT

DEFENDANTS.

TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR
DEFENDANTS

Plaintiff the State of South Carolina, ex rel. Alan Wilson,¹ in his capacity as Attorney

General of the State of South Carolina (the "State"), hereby responds in opposition to the Motion
for Summary Judgment as to Plaintiff's Unfair Trade Practices Claim Based on the FDA-
Approved Package Insert (the "Motion") filed by the above-captioned "Defendants," and would
respectfully show the Court as follows:

¹ Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been
substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

I.
SUMMARY OF RESPONSE

Defendants' Motion as to the State's Risperdal labeling claim under the South Carolina Unfair Trade Practices Act ("SCUTPA") largely reasserts arguments that the Court considered at length, including taking extensive written briefs under advisement and hearing oral argument, in *State v. Eli Lilly & Co.* Significantly, the Court rejected those very arguments in *Lilly*. That fact, however, did not restrain Defendants from either ignoring the Court's prior Orders, or effectively asking the Court to overrule itself.

The two recycled arguments that Defendants offer here concern whether the State's SCUTPA claim is time-barred because of general awareness or specific, anecdotal knowledge in the State's possession regarding Risperdal's side-effect profile, as well as whether Defendants' unfair and deceptive Risperdal labeling is protected by SCUTPA's so-called "safe harbor" provision. This Court—in accordance with controlling case law—soundly rejected both arguments in *Lilly* and should reach the same result here.

The only (arguably) "new" contention that Defendants offer in their Motion concerns whether Risperdal's labeling—to the extent that it is directed at and intended for physicians and not for consumers—may serve as the basis for the State's allegations of unfairness and deception with respect to the labeling. But that argument depends upon the Court finding that Defendants' "duty" to warn physicians (as opposed to consumers) somehow factors into the SCUTPA analysis. The problem for Defendants is that there is no such "duty" element or consideration that need be made by the Court under SCUTPA (nor any requirement that the State prove any of the nine elements of a common law fraud claim, for example). Furthermore, Defendants' entire argument in that regard ignores that SCUTPA makes actionable not only conduct that tends to *deceive*, but also *unfair* conduct that violates the State's public interests or offends its public

policy. And, lastly, there can be no question that regardless of whether a physician or consumer receives and/or reads the Risperdal labeling, its statutory purpose is to protect the end user from harm.

For all the reasons detailed below, the Court should deny Defendants' Motion.

II. STATEMENT OF THE CASE

On April 23, 2007, the State initiated this action against Defendants, manufacturers of the atypical antipsychotic drug Risperdal, to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for their willful, deceptive and unfair course of conduct in Risperdal's product labeling. On March 19, 2010, the State filed its Second Amended Civil Action Complaint, (hereinafter, "Amended Complaint"), petitioning the Court to assess against Defendants such penalties in an amount up to five thousand dollars for each willful method, act or practice declared unlawful by § 39-5-20. . . ." S.C. Code Ann. § 39-5-110(a). The State's Amended Complaint alleges, in short, that Defendants: (1) "willfully engaged in a protracted, deceptive and unfair course of conduct in violation of SCUTPA" through their "labeling of Risperdal, which willfully, deceptively, and unfairly minimized, misrepresented, and/or concealed the drug's dangerous side effects"; (2) "had actual knowledge that Risperdal causes weight gain" and "other severe adverse effects" upon product launch, but "failed to include a warning of the potential for weight gain and the possible development of diabetes as a result of the use of Risperdal in its U.S. labeling for many years," and "failed to warn adequately of these adverse effects," in all subsequent label changes; (3) was "chastised by the FDA for being brazenly 'false' and 'misleading'" in its Dear Doctor Letters by "[f]ailing to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the labeling; [m]inimizing the risks of potentially fatal hyperglycemia-related adverse events; [f]ailing to recommend regular

glucose control monitoring to identify diabetes mellitus as soon as possible; and [m]isleadingly claiming that Risperdal is safer than other atypical antipsychotics"; and, (4) "made, and continue[s] to make, orally and in writing, false, misleading or deceptive representations," and "continue[s] to disseminate false, misleading, or deceptive information to the public . . . regarding the health risks and benefits associated with using Risperdal." (Pl.'s 2d Am. Compl. ¶¶ 8, 13, 24, 26, 45, 46, 57, 58.)

III. ARGUMENT & AUTHORITIES

A. Standard

"Summary judgment is a drastic remedy, which should be cautiously invoked so that no person will be improperly deprived of a trial of the disputed factual issues." *Thomas Sand Co. v. Colonial Pipeline Co.*, 563 S.E.2d 109, 112 (S.C. Ct. App. 2002) (quoting *Doe ex rel. Doe v. Batson*, 548 S.E.2d 854, 857 (S.C. 2001)). It "is proper *only* when it is *clear* that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." *Koester v. Carolina Rental Center, Inc.*, 443 S.E.2d 392, 394 (S.C. 1994) (citing S.C. R. Civ. P. 56(c)) (emphasis added). "In determining whether any triable issues of fact exist, the evidence and all inferences which can be reasonably drawn from the evidence must be viewed in the light most favorable to the non-moving party." *Id.* (citing *Hamilton v. Miller*, 389 S.E.2d 652, 653 (S.C. 1990)). "[E]ven where there is no dispute as to the evidentiary facts, but only as to the conclusions or inferences to be drawn therefrom, summary judgment should not be granted." *Jamison v. Howard*, 247 S.E.2d 450, 451 (S.C. 1978). Thus, "[i]t is the duty of the court, on a motion for summary judgment, not to try issues of fact, but only determine whether there are genuine issues of fact to be tried; and, once having found that triable issues exist, must leave those issues for determination at a trial." *Thomas Sand Co.*, 563 S.E.2d at 112; *see also*

Hammond v. Scott, 232 S.E.2d 336, 339 (S.C. 1977) (“A court should never attempt to determine contested material factual issues on a motion for summary judgment.”).

B. Defendants’ Argument Concerning To Whom The Risperdal “Package Insert” Is “Addressed” is a Red Herring: SCUTPA Broadly Regulates the “[C]onduct of [A]ny [T]rade or [C]ommerce,” With No Requirement that the Package Insert Reached or Deceived Any Particular Consumer.

Defendants assert—in essence—that because prescription drug “package inserts”—i.e., labeling that accompanies a prescription drug—is directed at physicians rather than consumers, there can be no SCUTPA violation based on that labeling. Defendants’ contentions are mistaken for at least three reasons.

First, Defendants’ argument addresses claims the State does not make. To be perfectly clear, Defendants seek to interject into the State’s SCUTPA claim an element that does not exist and does not apply, so that Defendants may take advantage of a widely recognized (but entirely inapposite here) learned intermediary *exception* to that inapplicable element of proof.

Defendants argue that because the Risperdal “package inserts are written for physicians,” and not for consumers, “the State cannot pursue a SCUTPA claim on the theory that the package insert had a tendency to deceive or was likely to deceive *consumers*.” (Defs.’ Mot. at 15.) Defendants, therefore, contend that “[a]s a matter of law . . . pharmaceutical manufacturers *have no duty* to warn consumers as to the risks of prescription medicines . . .” (*Id.* at 13 (emphasis added).)

More specifically, and entirely based upon common law fraud/failure to warn cases (most not from South Carolina courts), Defendants contend that the “duty” to inform about dangerous side effects of drugs runs only to physicians. (Defs.’ Mem. at 13-15.) But the State is not bringing common law negligence, failure to warn, or other fraud claims; thus any existence or absence of common law “duty” is irrelevant. That is because SCUTPA “creates *new substantive*

rights by making unlawful conduct that was *not actionable under the common law*.” *State v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984) (emphasis added). No “duty” prerequisite may be found in SCUTPA’s express language, and none has been determined to exist by any court. Indeed, as the South Carolina cases make abundantly clear (to all but Defendants, apparently) that, unlike a common law fraud or negligence claim, there exists no requirement that the State prove that any prescriber or consumer was actually deceived, or that anyone relied upon deceptive information disseminated by Defendants about Risperdal. *See id* (“[T]here is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive.”); *Dowd v. Imperial Chrysler-Plymouth, Inc.*, 381 S.E.2d 212, 213-214 (S.C. Ct. App. 1989) (“To recover for fraud, the familiar [sic] nine elements must be proved ‘by clear, cogent, and convincing evidence.’ No such proof is required to recover under [SCUTPA].”). The Court should disregard Defendants’ red-herring “no duty” argument because it constitutes an *inapplicable* exception to a *non-existent* element of proof under SCUTPA.

Second, the overriding concern of SCUTPA is not which person in particular (consumer or otherwise) received or was affected by a deceptive representation about a product, but is instead unfairness or deception “in the conduct of any trade or commerce . . .” *that affects the public interest generally*. S.C. Code Ann. § 39-5-20(a) (2009); *see Bessinger v. Food Lion, Inc.*, 305 F. Supp. 2d 574, 582 (D.S.C. 2003) (“[SCUTPA] is not available to redress a private wrong where the public interest is unaffected.”); *Noack Enters., Inc. v. Country Corner Interiors of Hilton Head Island, Inc.*, 351 S.E.2d 347, 349 (S.C. Ct. App. 1986) (“The legislature’s intent [was] to limit the application of the [SC]UTPA to only those unfair or deceptive acts or practices in the conduct of trade or commerce *that affect the public interest . . .*”) (emphasis added).

Indeed, momentarily setting aside the *deceptiveness* of Defendants' conduct, all the State need show to recover penalties under section 39-5-110 is that Defendants willfully committed *unfair* trade practices that affected the public interest. See S.C. Code Ann. §§ 39-5-20, 39-5-110 (2009). "An unfair trade practice has been defined as a practice which is offensive to public policy or which is immoral, unethical, or oppressive." *Wright v. Craft*, 640 S.E.2d 486, 500 (S.C. Ct. App. 2006) (emphasis added); see *Bessinger*, 305 F. Supp. 2d at 582 (construing SCUTPA—per section 39-5-20(b)²—in accordance with the Federal Trade Commission Act, under which courts have determined that a practice is *unfair* when it "offends established public policy and when the practice is immoral, unethical, oppressive, unscrupulous, or substantially injurious to consumers"); accord *Dowd*, 381 S.E.2d at 214 (holding that, in order to impact the public interest, unfair or deceptive acts or practices in the conduct of trade or commerce must simply have "the *potential* for repetition") (emphasis added) (citations omitted).³

This Court, in fact, already recognized and upheld the critical public interests underlying these SCUTPA actions in *State v. Eli Lilly & Co.*:

I am surprised by the fact that most of the members of the public who are involved in this case are economically disadvantaged individuals who suffer from such debilitating conditions as schizophrenia, bi-polar mania, [and] [A]lzheimer[']s, [are] children, and [suffer from] dementia. They were in these [Medicaid] programs because they could not pay for or arrange

² It is the intent of the legislature that in construing paragraph (a) of this section the courts will be guided by the interpretations given by the Federal Trade Commission and the Federal Courts to § 5(a)(1) of the Federal Trade Commission Act (15 U.S.C. 45(a)(1)), as from time to time amended.

S.C. Code Ann. § 39-5-20(b).

³ "The potential for repetition may be demonstrated in either of two ways: (1) by showing the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) by showing the company's procedures create a potential for repetition of the unfair and deceptive acts." *Id.* at 502. Of course, "[those] two ways are not the only means for showing the potential for repetition or public impact, and each case must be evaluated on its own merits[.]" *Id.* A "plaintiff need not allege or prove anything further in relation to the public interest[.]" *Crary v. Djebelli*, 496 S.E.2d 21, 23 (S.C. 1998).

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their own care. In other words, they were unable to care for themselves.

When looking at the purpose of SCUTPA, one comes to the conclusion that the legislature intended [to] cast a wide net for causes of action in order to prevent and discourage deceit and fraud perpetrated on both the public at large and the business community of this state. It is clear that the legislature speaks in broad terms as to the activities that it seeks to make actionable and allows various avenues of enforcement of its prohibitions. Once a deceptive or unfair act in the commerce of this state is identified as affecting the public interest as a whole, and as such, the act is capable of repetition; then it would seem that the legislature seeks broad enforcement of the act.

In reviewing the above issues I found that the discussion in City of Charleston, S.C. v. Hotels.com, LP, 520 F.Supp.2d 757 (D.S.C. 2007) is relevant concerning the broad enforcement of SCUTPA. In that case the City of Charleston brought action against Hotels.com under the SCUTPA for charging consumers, on a national basis, a hospitality tax which it represented to be for a City tax. Instead of remitting the funds to the City (which it was under no apparent obligation to do in the first place) Hotels.com kept the funds and thus collected [them] as additional profit. Charleston was not a party to the transactions, had no right to collect the tax, and had no contractual connection with Hotels[.com]. In determining the legislative intent of SCUTPA and whether it would apply to this relationship, Judge Duffy held that the [d]efendants are clearly involved in trade and commercial activity of the type that legislators intended to regulate by enacting SCUTPA. He took this action in spite of the lack of a close connection between the city and the defendant and the fact that the victims could have protected themselves. *It appears he looked to the nature of the wrong and its relationship to public policy and considerations in find[ing] the City could proceed. In reviewing SCUTPA as a whole it is clear to me that the legislature intended to provide many avenues for the enforcement of its prohibitions.*

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No. 2007-CP-42-1855, slip op. at 27-28 (S.C. Ct. Com. Pleas Sept. 22, 2009) (emphasis added) (attached as Exhibit A). In light of the Court's observations and the standards set forth above, Defendants certainly do not contend—because they cannot—that the State is not entitled to prove to the jury that Defendants' unfair, immoral, unethical, oppressive, unscrupulous, or substantially injurious failure to fully disclose Risperdal's risks violated the State's public

interests, or offended the public policy of this State. Indeed, Defendants offer *no* argument in that regard in their Motion.

Lastly, there can be no disagreement that the purpose of prescription drug labeling, whether directed at physicians or consumers, is to provide the essential “information needed for the safe and effective use of the drug” *ultimately by the consumer*. 21 C.F.R. § 215.56(1)(1); *see* 21 C.F.R. § 201.57(a)(10) (labeling must contain “information . . . critical to the *safe use* of the drug” by the consumer “and measures that can be taken to prevent or mitigate harm” to the consumer) (emphasis added). Against that backdrop, and for all the reasons stated above, Defendants’ contention regarding any targeted audience of prescription drug labeling is simply immaterial to the State’s SCUTPA claim.

C. The State’s Risperdal Labeling-Based Claim Under SCUTPA Is Not Time-Barred By General or State-Agency Anecdotal Knowledge of Risperdal’s Side-Effect Profile.

Defendants’ bottom-line argument relative to the statute of limitations and SCUTPA—under which Defendants argue the State’s SCUTPA claim is time-barred—is that, upon publication of the Consensus Statement in February 2004, “the State knew or should have known of the very ‘risks’ that it now asserts as a basis for its claim” (Defs.’ Mot. at 19.) Defendants also cite testimony by the State’s pharmacologist, toxicologist, and regulatory expert, Dr. Laura Plunkett, regarding the medical community’s general awareness of aspects of the side-effect profile of antipsychotic drugs, including in some instances Risperdal, as well as other anecdotal instances of certain State agencies’ apparent understanding of the same. (*Id.* at 16-20.)

But, Defendants boldly ignore this Court’s prior Order on defendant’s Motion for Summary Judgment on Statute of Limitations Grounds in *Lilly*:

The information cited by Lilly stating that the Plaintiff should have been on notice that it had a claim or potentially had a claim is *separate and distinct from the wrongs alleged by the State*.

Knowledge by the State that Zyprexa may have contributed to weight gain, diabetes or related diseases . . . does not place the State on notice that Lilly is involved in any of the enumerated wrongful acts above[.]

which include

deceptive promotions, misrepresentations and concealment of information about the safety and efficacy of Zyprexa.

Further, the anecdotal information . . . does not rise to the level of putting the State on notice that Lilly was involved in any of the above specified wrongs.

Lilly, slip op. at 10-11 (emphasis added) (Ex. A).

Denying defendant's motion in *Lilly*, Your Honor concluded that

[i]n this case at the very least there is a substantial conflict of evidence as to the date upon which the statute of limitations would have begun to run. In such cases, "*where there is conflicting testimony regarding the time of discovery, it becomes an issue for the jury to decide.*" *Arrant v. Kressler*, 489 S.E.2d 206 (S.C. 1997).

Lilly, slip op. at 11 (Ex. A) (emphasis added).

The Court should, therefore, have no difficulty deciding that the recycled arguments presented by Defendants' Motion are without merit or, at a minimum, unpersuasive. Defendants have offered no new legal authority or facts to support their claims; rather, they largely relied upon speculation and anecdotal information, which this Court carefully distinguished in *Lilly*.

More specifically, in *Lilly*, this Court detailed the applicable statute of limitations attendant to the "discovery rule," which runs from the date the injured party either knows or should have known by the exercise of reasonable diligence that *a cause of action arises from the wrongful conduct* of the defendant. See *id.* at 9 (citing S.C. Code Ann. § 15-3-535 (Supp. 2007) (Ex. A); *Burgess v. Am. Cancer Soc'y, South Carolina Div., Inc.*, 386 S.E.2d 798, 800 (S.C. Ct. App. 1989); *Epstein v. Brown*, 610 S.E.2d 816, 818 (S.C. 2005)) (emphasis added). The Court

emphasized that the State's acquisition of bits and pieces of anecdotal information about Zyprexa prior to the filing of its Original Complaint was insufficient to trigger the running of the statute. *Lilly*, slip op. at 11 (Ex. A). Without "facts concerning the . . . specified incidences of *wrongdoing*, of which the State was aware or should have been aware prior to February 27, 2004 or 2005," Lilly's argument that the statute had been triggered in 2004, and had run, would fail. *Id.* (emphasis added) (Ex. A). "The burden of establishing the bar of the statute of limitations rests upon the one interposing it" *Turner v. Milliman*, 671 S.E.2d 636, 641 (S.C. Ct. App. 2009). "The limitations period is intended to run against those who are neglectful of their rights and who fail to exercise reasonable diligence in enforcing their rights. However, it is not the policy of the law to unjustly deprive an injured person of a remedy." *Moriarty v. Garden Sanctuary Church*, 534 S.E.2d 672, 679 (S.C. 2000).

That same policy applies to the State here in determining Defendants' Motion. Like the failed argument in *Lilly*, Defendants "reveal[] *no facts concerning the . . . specified incidences of wrongdoing*, of which the State was aware or should have been aware," prior to February 2004. Slip op. at 11 (emphasis added) (Ex. A). Rather, Defendants speculate that the State knew or should have known that a cause of action arose from Defendants' willful, deceptive and unfair course of conduct in violation of SCUTPA purely upon publication of the Consensus Statement, because the "Consensus Statement was widely distributed," allegedly, and one State Department of Mental Health official possessed a copy of the Consensus Statement in his files.⁴ (Defs.' Mot. at 19.) Defendants' note that the State also produced a copy of a letter from Pfizer, Inc. "announcing the publication of the Consensus Statement." (*Id.*) Additionally, the State

⁴ Of course, as Defendants know, the State does not assert any claims on behalf of the South Carolina Department of Mental Health in this case.

references the Consensus Statement in its Amended Complaint and acknowledges that the Consensus Statement addressed certain diabetes-related risks attendant to Risperdal.

But, the mere fact that the State references and describes the Consensus Statement in its Amended Complaint is insufficient to show what the State knew, or should have known, relative to Defendants' deceptive labeling *and when it knew it*, so as to trigger the running of the statute. In other words, the retrospective discussion of the Consensus Statement or any similar publication or study in the State's Amended Complaint is inadequate to show that the State knew of Defendants' unfair and deceptive labeling upon the issuance of the Consensus Statement and has no bearing on the State's discovery at that time or at any other time thereafter. Further, Defendants' Motion fails to squarely address *misrepresentations and concealed information in Risperdal's labeling*—the very “specified incidences of wrongdoing” of which the State was allegedly aware. *Lilly*, slip op. at 11 (Ex. A).

Defendants' reliance on the Consensus Statement's purportedly “wide[] distribut[ion]” to show that the State knew, or should have known of its right to recovery for Defendants' misconduct in South Carolina, is similarly inadequate. (Defs.' Mot. at 19.) A publication not targeted at the State, or its consumers, but at the specialty medical fields of diabetes, psychiatry, and obesity, does not qualify, without more, as having “widespread publicity” for purposes of charging the State with notice of Defendants' wrongdoings. *See Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 333-334, 337-338 (S.C. Ct. App. 2001) (holding that plaintiffs' claims would be barred by the applicable statute of limitations only where “the record is *replete* with *uncontested evidence of widespread publicity and awareness of the alleged [wrongdoing]*,” combined with ... plaintiffs' “*affidavits affirm[ing] that [p]laintiffs knew*,” prior to the running of the statute of limitations “of the alleged problems concerning” defendants' plant emitting

environmental pollution, the basis of plaintiffs' nuisance causes of action). Moreover, the requisite "widespread publicity" must be sufficient to charge the State with notice of the *particularized harm* that it seeks to redress by its Amended Complaint. *Id.* at 333-34 ("widespread publicity" included "widespread . . . community concerns and allegations that the plant was the alleged source of personal injury and property damage in the surrounding areas," "community forums, town meetings, government involvement, local political debates, door-to-door communications, media coverage, grassroots organization initiated by local citizens groups, and lawsuits brought by hundreds of residents . . . who . . . were friends, neighbors, and, in many instances, relatives of [p]laintiffs," in the action at bar, *inter alia*). Defendants' Motion is obviously devoid of evidence of "widespread publicity and awareness" of its illegal conduct in South Carolina.

In sum, Defendants wholly fail to tie to the State any alleged notice of such *actionable offenses in South Carolina causing the State injury*, or legitimately explain how, with reasonable diligence, the State should have known of such conduct, as they must. The State was arguably unaware of Defendants' deceptive and unfair conduct with regard to Risperdal's labeling until April 2007 upon the filing of its Original Complaint.⁵ Defendants' statute of limitations argument should be rejected and its Motion must be denied.

⁵ Even if the Court could find that the State tardily filed its Complaint in this lawsuit—which for reasons amply described herein it did not—the doctrines of equitable estoppel and/or equitable tolling nevertheless permit the State to bring its claims. Because Defendants' intentionally deceptive conduct was designed to avoid detection, Defendants are equitably stopped from asserting a limitations defense and/or the applicable limitations period is equitably tolled. *See Hooper v. Ebenezer Senior Servs. & Rehab. Ctr.*, 659 S.E.2d 213, 225 (S.C. Ct. App. 2008) ("A defendant will be estopped to assert the statute of limitations in bar of a plaintiff's claim when the delay that otherwise would give operation to the statute has been induced by the defendant's conduct."). Moreover, "[s]ilence, when it is intended, or when it has the effect of misleading a party, may operate as equitable estoppel." *Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 339 (S.C. Ct. App. 2001).

With respect to equitable tolling, the Court of Appeals of South Carolina observed that "[i]t has been held that equitable tolling applies principally if the plaintiff is actively misled by the defendant about the cause of action or is prevented in some extraordinary way from asserting his or her rights." *Hooper*, 659 S.E.2d at 221. "[T]he

D. Defendants Ignore Established Precedent of the United States Supreme Court, the South Carolina Supreme Court, and this Court in Maintaining That S.C. Code Ann. § 39-5-40 Establishes a “Safe Harbor” for Their Unfair and Deceptive Conduct in the Labeling of Risperdal.

Defendants brazenly seek to have this Court ignore established precedent of the United States Supreme Court and the South Carolina Supreme Court—as well to as overrule this Court’s own orders—in arguing that their unfair and deceptive labeling practices are exempt from SCUTPA as actions or transactions *permitted* under laws administered by a regulatory body or officer acting under statutory authority of the United States. *See* S.C. Code Ann. § 39-5-40(a).⁶ But, the South Carolina Legislature has specifically required that such actions or transactions be “permitted” under law in order to qualify for SCUTPA’s narrow exemption, and it is unarguable that Defendants’ misconduct does not fall within that category.

Defendants, however, attempt to impose artificial limitations on SCUTPA enforcement powers established under South Carolina law by its unsubstantiated argument that Risperdal’s deceptive labeling was “approved and authorized” by the FDA, and thus evades the reach of the State’s law enforcement powers. (Defs.’ Mot. at 25.) Yet, Defendants fail to explain satisfactorily how Risperdal’s labeling would qualify as “permitted” for purposes of statutory exemption in light of their willful refusal to strengthen Risperdal’s warnings section in the

equitable tolling doctrine does not require wrongful conduct on the part of the defendant, such as fraud or misrepresentation.” *Id.*

Defendants’ false representations, concealment of material facts, and knowledge of the true facts, intending to mislead the State about any cause of action it may have had against Defendants, demands the application of the equitable estoppel or equitable tolling doctrines here. The State has thoroughly described Defendants’ unfair, deceptive, and manipulative conduct relative to the State and the South Carolina public in the Factual Bases for the Attorney General’s Complaint of its Amended Complaint, which is incorporated herein by reference. Given the scope of deceptive activities in which Defendants engaged, the Court should necessarily find that the applicable statute of limitations period is equitably tolled and/or Defendants are equitably estopped from asserting its statute of limitations defense.

⁶ As an initial matter, Defendants’ advancement of unmeritorious arguments disposed of in prior orders and cases, and by this Court in particular, is without merit.

labeling, as they were required to do by the FDA, once they became aware of reasonable evidence of an association between Risperdal use and a serious hazard. 21 C.F.R. § 201.57(e) (2006). More specifically, Risperdal labeling contained false and misleading information, and omitted true information, since the drug's launch in the United States. (*See, e.g.*, Amended Compl. ¶¶ 11-53 (factual bases for the Attorney General's Compl.).) Because the false and misleading labeling was unfair and had the tendency to deceive, Defendants' conduct is actionable under SCUTPA. *See* S.C. Code Ann. § 39-5-20. Defendants' conduct with respect to the representations in the labeling was "willful" under the statute because it is merely necessary to show that Defendants knew or should have known that the labeling was unfair or deceptive. S.C. Code Ann. §§ 39-5-20, 39-5-110(c). And, most importantly for purposes of this discussion, Defendants had the opportunity to strengthen the warnings in the labeling at any time that they determined there was a reasonable association between Risperdal consumption and a serious hazard. *See* 21 C.F.R. § 201.57(e) (2006). But, Defendants continuously failed to take advantage of that regulatory self-help provision.

Accordingly, this Court rejected defendant's virtually identical arguments in *Lilly* "[b]ased on [defendant's] ability to make unilateral amendments to its labeling and the further facts concerning [its] marketing and labeling methods which have been demonstrated to this Court as being in controversy." Slip op. 22-23 (emphasis added) (Ex. A). The fact that the FDA had intermediately "approved" Zyprexa's labeling, therefore, did not absolve Lilly from its duty to update the labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *See* 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); *accord Wyeth v. Levine*, 129 S. Ct. 1187, 1197 (2009).

Further, Defendants cite no authority for the proposition that an FDA-approved label cannot constitute a SCUTPA violation, nor does it overcome controlling precedent distinguishing and rejecting this very proposition. See *Wyeth*, 129 S. Ct. at 1199; *Lilly*, slip op. at 22-23 (Ex. A). It is unquestionable that *Wyeth* rejected the argument that because the prescription drug labeling at issue was FDA-approved and regulated, the company could not comply with conflicting state law. And, this Court has found “as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA.” *Lilly*, slip op. at 23 (emphasis added) (Ex. A).

Additionally, Defendants essentially advocate for the application of the now-discarded “general activity” test in arguing that its labeling is exempted under SCUTPA. Defendants rely upon the very case that this Court distinguished as *inapposite* in *Lilly*, as well as a case decided prior to the abandonment of the “general activity” test by the South Carolina Supreme Court in *Ward v. Dick Dyer & Assocs., Inc.*, 403 S.E.2d 310, 312 (S.C. 1991), without more. (See Defs. Mot. at 21-23 (citing *InMed Diagnostic Servs., L.L.C. v. MedQuest Assocs., Inc.*, 594 S.E.2d 552, 555 (Ct. App. 2004); *Carr v. United Van Lines, Inc.*, 345 S.E.2d 734, 737 (Ct. App. 1986)).)

Rejecting a virtually identical argument in *Lilly*, the Court ruled as follows:

This Court does not find the InMed case to be particularly useful in this analysis. It is clear that when dealing with false information contained in an application document submitted directly to a state regulatory agency for the purpose of having that agency act upon that application, that such matters would be within the regulatory jurisdiction of that agency. The issues involved in this case revolve around. . . *consumer protection issues which are precisely the issues concerning which the South Carolina Legislature enacted SCUTPA.* *Ward* abandoned the “general activities” test, and subsequently adopted the language of a Tennessee case stating:

. . . . The purpose of the exemption is to insure that a business is not subjected to a lawsuit under the Act

when it does something required by law, or does something that would otherwise be a violation of the Act, but which is allowed under other statutes or regulations. It is intended to avoid conflict between laws, not to exclude from the Act's coverage every activity that is authorized or regulated by another statute or agency. Virtually every activity is regulated to some degree. The defendant's interpretation of the exemption would deprive consumers of a meaningful remedy in many situations. We find this reasoning persuasive and applicable to our statutory exemption . . .

Ward v. Dick Dyer and Associates, Inc., 304 S.C. 152, 156, 403 S.E.2d 310, 312 (S.C. 1991).

The FDA does not allow or authorize the illegal or deceptive activities that the Plaintiff alleges to have occurred in this case.

This Court does not interpret the SCUTPA to create a "safe harbor" for the alleged activities of [defendant] in the marketing and labeling of [its drug]. The exemption of § 39-5-40(a) does not bar this claim.

Slip op. at 24-26 (emphases added) (Ex. A).

Based on the foregoing, Defendant's contentions are plainly unmeritorious and do not comport with controlling decisions by this and higher Courts. Consistent with that controlling precedent, the Court should deny Defendants' Motion.

IV. CONCLUSION

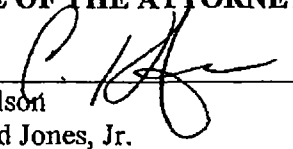
The Court should deny Defendants' Motion. In summary, Defendants' argument that because Risperdal labeling is intended for physicians and not consumers is at best immaterial and at worst wrong. In particular, not only is the labeling actionable under SCUTPA because it is

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deceptive, but the State may also seek penalties based on Defendants' willful, unfair conduct that violates the State's public interests and/or public policy. Also, the State's claim based on Risperdal labeling is not time-barred because the statute of limitations is not triggered by any general awareness or specific, anecdotal knowledge of Risperdal's side-effects alone. Indeed, this Court already decided that issue in the State's favor in the companion *Lilly* case. Similarly, the Court should refuse Defendants' argument—also dusted off and recycled from the *Lilly* rejects—that their unfair and deceptive conduct with respect to Risperdal's labeling somehow falls within SCUTPA's "safe harbor" provision. It simply does not. For all the foregoing reasons, Defendants' Motion must fail.

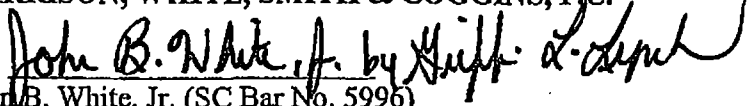
Respectfully submitted,

**STATE OF SOUTH CAROLINA
OFFICE OF THE ATTORNEY GENERAL**

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January 21, 2011

Spartanburg, South Carolina

Attorneys for the State of South Carolina

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STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.
Alan Wilson, in his capacity as
Attorney General of the State of South
Carolina,

Civil Action No. 2007-CP-42-1438

Plaintiff,

v.

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA INC.,
and/or JANSSEN, L.P. and
JOHNSON & JOHNSON, INC.,

Defendants.

**DEFENDANTS' MEMORANDUM OF LAW
IN OPPOSITION TO PLAINTIFF'S MOTION
TO EXCLUDE THE EXPERT TESTIMONY
OF DR. WILLIAM E. WECKER**

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Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby submit this Memorandum of Law in Opposition to Plaintiff's Motion To Exclude The Expert Testimony Of Dr. William E. Wecker ("Pl.'s Motion").

I. INTRODUCTION

Contrary to the impression Plaintiff would have the Court take from its brief, Dr. Wecker's expertise has been recognized by courts around the country, which have qualified him as an expert to assist the trier of fact in cases like this one where statistical analysis tends to support or, as here, refute a party's claims. Dr. Wecker has even been named as a court-appointed expert, helping a California court navigate statistical issues in a dispute between the State of California and Bank of America. See Affidavit of William E. Wecker ("Wecker Aff.") ¶ 4 (Ex. A). Dr. Wecker is an accomplished

statistician with superior qualifications. After graduating from the United States Air Force Academy in 1963 and serving in the Air Force as a fighter pilot in the Vietnam War, Dr. Wecker did his graduate study at the University of Michigan. He received a Ph.D. in statistics and management science in 1972 and began a teaching career that lasted almost two decades at the Graduate School of Business at the University of Chicago and the Graduate School of Management at the University of California at Davis. *Id.* ¶ 2.

In 1990, eager to put complex statistical theories to practical application on real-world problems, Dr. Wecker left teaching to start his own statistical and mathematical consulting company outside of San Francisco, California. His company employs approximately 20 mathematicians and statisticians who work with fifty different computer systems and more than 65 billion records on currently active projects. Wecker Associates works for a wide variety of businesses and government entities including automobile manufacturers, airplane manufacturers, airlines, banks, railroads, credit card companies, the United States government, local government agencies, and foreign countries. With his company, Dr. Wecker has also worked as a consulting and testifying expert in litigation. *Id.* ¶ 3.

In the present case, Dr. Wecker reviewed Plaintiff's allegations and identified evidentiary sources available for statistical analysis of Plaintiff's claim. As explained below, his expert opinions, which are based in part on a deposition survey of randomly identified antipsychotics prescribers and on observational data from Plaintiff's voluminous Medicaid claims database, go to the core issue of "deception" raised by Plaintiff's South Carolina Unfair Trade Practices Act ("SCUTPA") claim. His analysis

employs tools utilized by statisticians to form opinions that fall squarely within the scope of his expertise. See generally Expert Report of William E. Wecker (Dec. 3, 2010) ("Wecker Report") (attached as Ex. 1 to the Wecker Aff. (Ex. A)).

Seeking to exclude Dr. Wecker's testimony, Plaintiff mischaracterizes the work he has done in this case and raises arguments that ignore the statistical expertise that is directly relevant to evaluation of its claim. Plaintiff's unfounded arguments cannot obscure the conclusions that are clear from a review of Dr. Wecker's opinions in this case: his analysis will assist the trier of fact and is reliable; moreover, its probative value far outweighs any prejudicial effect it may have. For these reasons, Plaintiff's motion should be denied.

II. ARGUMENT

A. Applicable Standard.

"[A]ll expert testimony under Rule 702, SCRE, imposes on the trial courts an affirmative and meaningful gatekeeping duty." *State v. White*, 382 S.C. 265, 270, 676 S.E.2d 684, 686 (2009). In the discharge of this duty, the trial court must initially determine the admissibility of expert evidence by answering the threshold questions of qualification and reliability. *Id.* at 274, 676 S.E.2d at 688-89.

Thus, in order for expert evidence to be admissible under Rule 702, the trial judge must make three determinations: (1) the evidence will assist the trier of fact, (2) the expert witness is qualified, and (3) the underlying science is reliable. See *State v. Council*, 335 S.C. 1, 20, 515 S.E.2d 508, 518 (1999). If the evidence is admissible under Rule 702, the judge must still determine whether, under Rule 403, SCRE, its probative value outweighs any prejudicial effect. *Id.*

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B. The Court Should Deny Plaintiff's Motion.

1. Dr. Wecker's Statistical Survey Of South Carolina Physicians Is Admissible.

Plaintiff devotes the majority of its Motion to Dr. Wecker's design of a statistical survey of a randomly-identified sample of South Carolina physicians who prescribed Risperdal® and other antipsychotics to Medicaid patients. As the Court is aware, Defendants sought leave to depose 150 South Carolina physicians as part of the survey process, but Plaintiff opposed Defendants' request and the Court limited Defendants to 20 depositions. Now, Plaintiff seeks to use this limitation as a basis for excluding Dr. Wecker's testimony, arguing that a survey of 20 physicians will not "produce reliable 'survey' results" and asserting that Defendants "have admitted before this Court that such a number is inadequate." Pl.'s Motion at 12. Plaintiff's argument ignores the survey design and the results reported, which are clearly described in Dr. Wecker's expert report, and Plaintiff's contentions find no support in prior statements from Defendants.

Because the Court limited Defendants to surveying 20 physicians by deposition, Dr. Wecker's sample was randomly identified from the 101 physicians who prescribed antipsychotics most frequently. See Wecker Aff. ¶ 10. Generally speaking, physicians who prescribed antipsychotic medicines to greater numbers of patients can be expected to have more experience regarding the efficacy of Risperdal compared to other antipsychotics. See Wecker Report ¶ 16. Denied the opportunity to survey the number of physicians best suited for drawing conclusions about the entire population of South Carolina prescribers, therefore, Dr. Wecker focused on those with the most experience.

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Dr. Wecker's survey sought fact-based answers from physicians to questions about their experiences with antipsychotics, their knowledge about the benefits and risks of Risperdal and other antipsychotics, and other issues related to their prescribing decisions. *Id.* ¶ 20. Questions and answers were transcribed, providing a word-by-word record of each survey that allowed Dr. Wecker to confirm that the attorneys who took the depositions conducted the survey in a reliable and unbiased manner. Wecker Aff. ¶ 9. At the survey's conclusion, Dr. Wecker calculated population estimates with confidence intervals for the 101 most frequent prescribers – the group from which the sample size of 20 was drawn. Wecker Report ¶ 25. Thus, Dr. Wecker specifically worked from and reported results within the limited sample size urged by Plaintiff and ordered by the Court.

As fully explained below, the survey results are both relevant and reliable, Dr. Wecker is qualified to offer testimony about the results, and the probative value of the survey outweighs any possible prejudicial effect. Indeed, the only prejudicial effect of Dr. Wecker's testimony is harm to Plaintiff's case, which is not a basis for exclusion.

a. **Dr. Wecker's Testimony Will Assist The Jury Because It Is Directly Relevant to Plaintiff's SCUTPA Claim.**

In its Motion, Plaintiff alleges that Dr. Wecker's testimony is irrelevant to the State's "solitary claim" that Janssen violated SCUTPA by "deceptively communicating Risperdal health risk information in Risperdal labeling and other communications about the drug." Pl.'s Motion at 4. To recover under SCUTPA, Plaintiff must show that the Risperdal package insert and/or the November 2003 mailing were "deceptive" – i.e., that they were likely to deceive.

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Whether a given alleged practice or act was likely to deceive "depends upon the surrounding facts and the impact of the transaction on the marketplace." *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (Ct. App. 2000). The express provisions of SCUTPA make clear that it is to be construed consistent with the Federal Trade Commission Act ("FTCA"). See S.C. Code Ann. § 39-5-20(b); see also *Plowman v. Bagnol*, 316 S.C. 283, 287, 450 S.E.2d 36, 38 (1994) ("In section 39-5-20(b), the Legislature specifically instructs state courts to be guided by the decisions of the Federal Trade Commission (FTC) and the Federal Courts construing the Federal Trade Commission Act, 15 U.S.C. [§] 45(a)(1), in interpreting section 39-5-20(a)[.]"). In 1983, the Federal Trade Commission ("FTC") issued a Policy Statement on Deception, clarifying the FTC's approach to determinations of allegedly deceptive trade practices. Through this Policy Statement, the FTC established that the knowledge and sophistication of the relevant audience must be considered when determining whether a company's trade practice is likely to deceive. See 2 Fed. Trade Comm'n App. D-2 (2009). The Policy Statement explains that an allegedly deceptive practice is examined "from the perspective of a consumer acting reasonably in the circumstances. If the representation or practice affects or is directed primarily to a particular group, the Commission examines reasonableness from the perspective of the group." Thus, "a practice or representation directed to a well-educated group, such as a prescription drug advertisement to doctors, would be judged in light of the knowledge and sophistication of that group." *Id.* (emphasis added).

South Carolina prescribers are the relevant, intended audience for the materials Plaintiff says were "deceptive". The November 2003 mailing was sent to prescribers;

likewise, the Risperdal package insert was written for prescribers. See November 2003 mailing (Ex. B) (addressed, "Dear Healthcare Provider"); see also 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008) ("FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to healthcare practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."); *Morlino v. Med. Ctr. of Ocean Cnty.*, 152 N.J. 563, 580, 706 A.2d 721, 729-30 (1998) ("Drug manufacturers write explanations and warnings for doctors, not the general public."); *Martin v. Hacker*, 83 N.Y.2d 1, 9, 628 N.E.2d 1308, 1311 (1993) ("Warnings for prescription drugs are intended for the physician, whose duty it is to balance the risks against the benefits of various drugs and treatments and to prescribe them and supervise their effects."). What South Carolina prescribers knew or did not know about Risperdal and other antipsychotics and their benefits and risks – the context within which they would have considered the Risperdal package insert and the November 2003 mailing – therefore is undeniably relevant to the question of the materials' "impact on the marketplace" and the "likely to deceive" element of Plaintiff's claim.

Thus, the questions in Dr. Wecker's survey go directly to the core issues in this case. Physicians were asked whether they were aware of an association between antipsychotic medications and weight gain or risk of diabetes, whether they agreed that the 1993 package insert for Risperdal advised of an association between the drug and diabetes, and whether any Janssen sales representative ever represented anything inconsistent with the warnings about Risperdal that are provided on the FDA-approved

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package insert. See Wecker Report, Ex. 5. Physicians were also shown the November 10, 2003 letter from Janssen to healthcare providers that Plaintiff challenges as one of the centerpieces of its lawsuit and asked whether they had seen it before and, if so, whether it caused them to change their choice of antipsychotic medication for patients or their methods for monitoring patients for side effects. *Id.* These questions are squarely relevant to what Plaintiff contends its case is about: "whether Defendants violated SCUTPA by deceptively communicating Risperdal health risk information in Risperdal labeling and other communications about the drug." Pl.'s Motion at 4.

Dr. Wecker's testimony is relevant and will assist the trier of fact.

b. **Dr. Wecker Is Qualified To Render An Expert Opinion On The Physician Survey.**

Plaintiff does not challenge Dr. Wecker's expertise in the design of statistical surveys or the analysis of survey results. Plaintiff does, however, contend that Dr. Wecker is not qualified to analyze the results of a survey of physicians. Plaintiff cites no authority for the idea that a statistician should be barred from offering statistical analysis of a survey of physicians, and Plaintiff's unsupported contention does not withstand scrutiny.

An expert may offer opinion testimony if he has "acquired by study or practical experience such knowledge of the subject matter of his testimony as would enable him to give guidance and assistance to the jury in resolving a factual issue which is beyond the scope of the jury's good judgment and common knowledge." *State v. White*, 372 S.C. 364, 612, 642 S.E.2d 607, 612 (Ct. App. 2007). As discussed above, Dr. Wecker has spent years learning, teaching, and applying statistical methods and principles. He has extensive education in the subject matter, has taught statistics and applied

mathematics, and has worked as a statistician for 40 years. Wecker Aff. ¶¶ 2-4. He is highly qualified to assist the jury in understanding what statistical analysis shows about the experience of the most frequent South Carolina prescribers of antipsychotics and whether they were deceived or likely to be deceived about Risperdal's safety profile.

The theory and practice of statistical sampling, including sample surveys of human subjects, has been a fundamental topic within the science of statistics at least since the early twentieth century. Richard Johnson and Gouri Bhattacharyya recognized the importance of statistical sampling in their authoritative text *Statistics Principles and Methods*, observing that "the subject of statistics provides the methodology to make inferences about the population from the collection and analysis of sample data. These methods enable one to derive plausible generalizations and then assess the extent of uncertainty underlying these generalizations." Wecker Report ¶ 12 (quoting Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd edition, 1996, p. 14); see also Wecker Aff. ¶ 8.

Plaintiff asserts that the testimony should nevertheless be excluded because a statistician – not a medical doctor – purports to testify as to the out-of-Court medical opinions of 20 licensed South Carolina physicians" and "[t]here has been no showing whatsoever that Dr. Wecker is qualified to interpret the respondent physicians' medical opinions, or has received any training at all in medicine." Pl.'s Motion at 14. As an initial matter, Dr. Wecker's survey did not solicit opinions from the 20 South Carolina physicians. Rather, the physicians were asked factual questions about their experience using Risperdal and other antipsychotics and their exposure to Janssen promotional activity and communications. Wecker Aff. ¶ 9. Just as significantly, Dr. Wecker did not

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"interpret the respondent doctors' medical opinions," as Plaintiff charges. Pl.'s Motion at 14. Instead, a review of Dr. Wecker's expert report shows that he described the survey methodology and the steps taken to ensure that it complied with principles set out in leading statistics texts, reported what responses were given *without interpretation*, and then utilized statistical tools to calculate population estimates and confidence intervals based on the physicians' answers. Wecker Report ¶¶ 16-25 & Ex. 5.

Dr. Wecker's work is not simply analysis that is typically done by statisticians; rather, "[t]his methodology is one that *falls squarely within the province of statisticians*." Wecker Aff. ¶ 11 (emphasis added). Accordingly, even if Dr. Wecker's survey had sought medical opinions from physicians, he would properly be permitted to testify regarding the design of the survey, report the results obtained, and calculate population estimates and confidence intervals. *See, e.g., i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 855 (Fed. Cir.) (permitting Dr. Wecker to testify about the survey design, the results obtained, and his calculation of population estimates), *cert. granted*, 131 S.Ct. 647 (2010); *Kinetic Concepts, Inc. v. BlueSky Med. Corp.*, No. SA-03-CA-0832-2006 U.S. Dist. LEXIS 60187, *5-26 (W.D. Tex. Aug. 11, 2006) (allowing expert to testify about survey reflecting physicians' and nurses' opinions of defendants' allegedly false and misleading advertising materials). Were Plaintiff's contrary position to be adopted, it would never be possible to survey professionals from a population too broad to question exhaustively and offer statistical calculations showing the extent to which the views of those surveyed can be generalized to the broader population. Such a result would erroneously exclude valid statistical science from the courtroom.

c. Dr. Wecker's Expert Opinion Is Reliable.

To determine whether scientific testimony is reliable a trial judge should consider the following factors:

- (1) the publications and peer review of the technique;
- (2) prior application of the method to the type of evidence involved in the case; (3) the quality control procedures used to ensure reliability; and (4) the consistency of the method with recognized scientific laws and procedures.

State v. Jones, 383 S.C. 535, 549 n.5, 681 S.E.2d 580, 587 n.5 (2009) (quoting *Council*, 335 S.C. at 19-20, 515 S.E.2d at 517-18). "Once the evidence is admitted under these standards, the jury may give it such weight as it deems appropriate." *Id.* In an effort to support its argument that Dr. Wecker's opinions fail to meet this standard or exhibit bias, Plaintiff mischaracterizes the work performed and ignores Dr. Wecker's adherence to standards governing similar work on the part of statisticians.¹

For example, Plaintiff asserts that the fact that attorneys questioned physicians results in a risk of bias, but can identify no bias that resulted from this process. In the course of making this unfounded argument, Plaintiff ignores the crucial distinction between this case and the cases it cites – that any potential bias was eliminated by the fact that *Plaintiff's own attorneys* were also present at each deposition and were allowed

¹ Plaintiff cites case law and briefing from *Buell-Wilson v. Ford Motor Co.*, 141 Cal. App. 4th 525, 46 Cal. Rptr. 3d 147 (Cal. Ct. App. 2006), where the court found Dr. Wecker's statistical analysis of Fatal Accident Reporting Statistics (FARS) and similar state-level data in vehicle safety products liability cases inapposite to the issues ultimately set for trial in that case, see Pl.'s Motion at 16 n.12, but that ruling had nothing to do with the reliability of Dr. Wecker's work or his expertise as a statistician. On the contrary, the statistical evidence was excluded on the basis that "[a] manufacturer cannot defend a product liability action with evidence it met its industry's customs or standards on safety." *Buell-Wilson*, 141 Cal. App. 4th at 545, 46 Cal. Rptr. 3d at 164.

to, and in fact did, question each physician. Plaintiff also ignores the fact that the existence of a transcript of each physician's deposition, including the physician's responses given under oath to the survey questions, allowed Dr. Wecker and his staff to confirm that the physicians were questioned in an unbiased manner. See Wecker Aff. ¶ 9. And while Plaintiff contends that a key question for the Court is whether the results were "used in a statistically correct way," Pl.'s Motion at 5, Plaintiff does not identify any way in which Dr. Wecker's population estimates or confidence interval calculations, set out in Exhibit 5 to his expert report, are incorrect.

Plaintiff further argues that Dr. Wecker should not have limited his target population to the 101 most frequent South Carolina prescribers, but fails to acknowledge that Dr. Wecker chose the target population because the Court, at Plaintiff's insistence, limited Defendants to 20 depositions. Plaintiff also fails to note that in his report, Dr. Wecker only calculated population estimates for the target population, thus rendering Plaintiff's criticism of Dr. Wecker's methodology unfounded. That is, Plaintiff argues that Dr. Wecker's testimony should be excluded because he used a survey of 20 to calculate population estimates and confidence intervals for a population of more than 8,000, but Dr. Wecker made no such calculation. He calculated population estimates and confidence intervals for the 101 most frequent (and most experienced) prescribers from which the sample of 20 was randomly identified. Wecker Aff. ¶ 11.

Plaintiff's arguments, at best, go to the weight to be accorded the survey, not to its admissibility. See *Harolds Stores, Inc. v. Dillard Dep't Stores*, 82 F.3d 1533, 1546 n.9 (10th Cir. 1996) (court refused to consider the technical deficiencies in the survey, including the purportedly "slanted, leading, and ambiguous" questions because any

such problems were solely a matter of weight (emphasis added)); *i4i*, 598 F.3d at 855 (objections based on low response rate, and existence of other facts that could have been included, did not render survey inadmissible); *Kinetic Concepts, Inc.*, 2006 U.S. Dist. LEXIS 60187, at *14-15 (expert's use of a convenience sample that could not be statistically extrapolated to the entire universe did not render survey results inadmissible, but instead went to the weight to be assigned to the evidence by the jury); *Arner v. Sharper Image Corp.*, No. CV94-1713, 1995 WL 873730, at *8-9 (C.D. Cal. Oct. 5, 1995) (although attorney's handwritten notes were reflected on proposed questions, court found that objections to methodology properly went to weight of the evidence and not admissibility); *V. La Rosa & Sons, Inc. v. De Rosa Cheese & Macaroni Co.*, No. CV85-L-513, 1986 WL 8699, *4-5 (D. Neb. May 22, 1986) (despite objection to attorney involvement in phrasing and asking of questions, court held the surveys still had value and were admissible). Dr. Wecker's survey testimony is reliable and admissible.

d. **Dr. Wecker's Opinions Meet The Materiality And Trustworthiness Standards Plaintiff Cites In Its Motion As The Standards For Admission Of Survey Evidence.**

Plaintiff does not argue, nor could it, that survey results are inadmissible in South Carolina as a category of evidence. Instead, Plaintiff cites a number of federal cases for the proposition that survey evidence must be material and trustworthy. Pl.'s Motion at 13 (citing, e.g., *Harolds Stores, Inc.*, 82 F.3d at 1544; *Brunswick Corp. v. Spinit Reel Co.*, 832 F.2d 513, 522 (10th Cir. 1987); *Amstar Corp. v. Domino's Pizza, Inc.*, 615 F.2d 252, 264 (5th Cir. 1980)). Dr. Wecker's survey testimony meets these twin standards of materiality and trustworthiness. The survey results go to the core issue raised by

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Plaintiff's SCUTPA claim and were attained pursuant to a well-established methodology for statistical sampling and analysis.

Plaintiff's argument that all survey evidence should be excluded on hearsay grounds is therefore misplaced, and it is contrary to the case-by-case admissibility analysis undertaken by courts in South Carolina. See, e.g., *Harris v. Campbell*, 293 S.C. 85, 87-8, 358 S.E.2d 719, 720-21 (Ct. App. 1987) (affirming trial court's decision to allow testimony of an expert regarding a survey); *Welch Moving & Storage Co. v. Pub. Serv. Comm'n.*, 301 S.C. 259, 260-61, 391 S.E.2d 556, 557 (1990) (reversing a finding of public necessity and convenience, in part, *because* no expert testimony or statistical surveys had been presented); see also *John Walker & Sons, Ltd. v. Bethea*, 305 F. Supp. 1302, 1305-06 (D.S.C. 1969) ("[t]he results of three surveys conducted by" prominent statisticians who generalized the survey answers to reflect the answers that would have been given if answered by the entire population "competently and scientifically demonstrate[d] that many people [made] the association between" the defendant motel establishment operating as Johnny Walker Motel and the famous brand of Johnnie Walker whiskey and showed that there was likelihood of confusion between the products (footnote omitted)).

Plaintiff's efforts to exclude Dr. Wecker's opinions also fail for the practical reason that, if necessary, the survey results could be replicated at trial. In the event the Court were to decide that Dr. Wecker may not rely on the results of the twenty South Carolina prescriber depositions for hearsay reasons, the proper remedy would not be exclusion of his expert testimony. Instead, the appropriate course would be to allow Defendants to call all 20 physicians to testify live at trial, affirm what they have

previously stated under oath, and then call Dr. Wecker to offer opinions on statistical sampling and the specific population estimates and confidence interval calculations that can be made based on the testimony of the twenty randomly identified physicians.

e. **Dr. Wecker's Expert Opinion Does Not Unfairly Prejudice Plaintiff.**

Plaintiff's contention that Dr. Wecker's testimony will result in unfair prejudice to Plaintiff is equally unfounded. Without any context or adequate explanation, Plaintiff states simply that Dr. Wecker's testimony about the physician survey has "no probative value," will "confuse and mislead the jury," and "will lead to the needless and wasteful accumulation of [] irrelevant evidence." Pl.'s Motion at 17. Because Plaintiff must prove that Defendants' acts were likely to deceive, testimony from Dr. Wecker about the responses of surveyed physicians to relevant questions about their experience with Risperdal and other antipsychotics and their knowledge and understanding of the benefits and risks of antipsychotics provides highly probative evidence for the fact finder's consideration. Further, Plaintiff makes no attempt to illustrate how the proposed expert testimony – including statistical analysis of the survey responses of a randomly-selected sample of South Carolina prescribers on matters relevant to the "deception" element of Plaintiff's claim – would "confuse" a jury or result in "accumulation of irrelevant evidence."

The only discernible reason for Plaintiff's attempt to exclude Dr. Wecker's testimony on grounds of prejudice is the apparent concern that such testimony will refute Plaintiff's allegation that Defendants' conduct was "deceptive". Pl.'s Motion at 4, 17. But Plaintiff may not seek to exclude testimony simply because it is detrimental to its case. See, e.g., *Holmes v. Black River Elec. Coop., Inc.*, 274 S.C. 252, 259, 262

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S.E.2d 875, 878 (1980) (admitting evidence despite detriment to opposing party because its probative value greatly outweighed any prejudice). The Court should deny Plaintiff's motion.

2. **Dr. Wecker's Analysis Of Statistical Claims Data Produced By Plaintiff Is Admissible.**

In addition to designing a random statistical survey and performing statistical calculations based on survey results, Dr. Wecker performed three different types of statistical analysis of Medicaid and State Health Plan claims data produced by the State. In the first, he evaluated the incidence of side effects that Plaintiff alleges to be associated with Risperdal in three separate groups of patients: (1) patients who received Risperdal, (2) patients who received other second generation antipsychotics, and (3) patients who received only a first generation antipsychotic. In the second, he evaluated how time to discontinuation – the primary outcome measure of the CATIE study – in South Carolina Medicaid patients receiving Risperdal compared to patients receiving first generation antipsychotics. In the third, he determined whether Risperdal's market share in South Carolina changed over time, focusing on market share before and after events such as the November 10, 2003 mailing the Plaintiff challenges. Wecker Aff. ¶ 12; Wecker Report ¶¶ 26-41 & Exs. 6-9.

Plaintiff moves to exclude only the first type of analysis, arguing that the Court should exclude Dr. Wecker's testimony because "Dr. Wecker provides no analysis of how he analyzed or manipulated the State's claims data to obtain his results." Pl.'s Motion at 17. Plaintiff is wrong. Dr. Wecker's methodology is described in detail in his expert report, in the exhibits to the report, and in the electronic files provided to Plaintiff in support of his opinions. Wecker Aff. ¶ 13 & Exs. 1-2. Indeed, Dr. Wecker provided

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Plaintiff a step-by-step guide to his analyses that identifies what dataset each result is drawn from, the program used to analyze the data, all intermediate data results, and the electronic output file where the results are located, along with all datasets and programs required for Plaintiff to replicate his work and assess the impact of the parameters applied during the course of his analysis. Wecker Aff. Ex. 2.

Plaintiff also seeks to exclude Dr. Wecker's analysis on the ground that there is "no data 'cross-walk' to link" prescription data for patients treated at Department of Mental Health (DMH) facilities with separate Medicaid data for those patients showing diagnoses, arguing that this makes Dr. Wecker's analysis of DMH patients unreliable. Pl.'s Motion at 18. But Dr. Wecker excluded DMH claims produced by Plaintiff from his analysis for this precise reason, Wecker Aff. ¶¶ 6, 13, and Plaintiff's argument is therefore inapplicable to Dr. Wecker's work. In a related argument, Plaintiff urges exclusion on the basis that diagnoses for prescription drug claims in the South Carolina Medicaid database are not recorded consistently, citing Dr. Wecker's testimony in the Louisiana Risperdal trial to argue that the absence of diagnoses with prescription claims somehow renders the work unreliable. Pl.'s Motion at 19. But Plaintiff omitted the complete transcript of Dr. Wecker's sworn testimony from Louisiana and specifically ignores Dr. Wecker's explanation that he accounted for the absence of a diagnosis code in prescription claims records by looking for diagnosis codes in other records. See La. Tr. at 98:1-98:7 (Oct. 12, 2010) (Ex. C) ("So when I look for the diagnosis, I don't look for it in the prescription record. I look for it in the doctor record or the hospital record or some other record. I have no problem finding the diagnosis. I just don't find it in the prescription record.") The same is true in South Carolina. Dr. Wecker reviewed

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complete patient claims histories, including professional and hospital claims where diagnoses are routinely recorded, for his analysis. Wecker Aff. ¶ 13.

Plaintiff separately charges that parameters Dr. Wecker used for his analysis are "arbitrary", Pl.'s Motion at 19, but leaves its charge in conclusory form without any explanation of how the parameters impacted results or rendered them unreliable. Plaintiff's arguments are unfounded and, as with Plaintiff's arguments concerning Dr. Wecker's survey, at best go to the weight to be accorded the statistical analysis, not to its admissibility.

3. **Dr. Wecker's Statistical Analyses Of Epidemiological Studies And The CATIE Trial Are Admissible.**

As noted, Dr. Wecker also reviewed and analyzed the statistical conclusions contained in the eight epidemiological studies Janssen cited in its November 10, 2003 mailing to healthcare providers ("the eight studies") and the statistical implications of the design of the CATIE trial, which Plaintiff contends "proved . . . that Risperdal is no more effective in treating schizophrenia" and "is no safer . . . than the less expensive atypical antipsychotics." Second Am. Compl. ¶ 52. Plaintiff argues that Dr. Wecker is not qualified to give these opinions because "[h]e has no medical training" and "is not a pharmacologist or toxicologist." Pl.'s Motion at 20. Again, Plaintiff is wrong. Dr. Wecker is well-qualified to offer the opinions in his expert report.

As Dr. Wecker specifically indicated in the report, he limited his analysis to (1) the statistical conclusions in the eight studies, Wecker Report ¶ 44, (2) whether South Carolina-specific statistical analysis supports or contradicts the conclusions in the CATIE study, *id.* ¶¶ 49-50, and (3) whether the CATIE study's design impacted the statistical calculations that are presented as study outcomes, *id.* ¶¶ 52-53. For

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example, addressing one of the eight studies (the "Buse study"), Dr. Wecker examined the hazard ratios reported by the study authors for subgroups of patients taking individual first generation antipsychotics, as opposed to all first generation patients combined. Dr. Wecker formed an opinion on whether the study's reported confidence intervals and p-values represent statistically significant results for the subgroup analysis, as opposed to an analysis of the full population studied. He concluded:

There are several formulaic ways to assess statistical significance for a subgroup analysis. The most common and easiest method to apply is the method of Bonferroni. In the case of the haloperidol subgroup analysis and the p-value of 0.040, which is a part of that analysis, the Bonferroni p-value is 0.16 (= 4 x 0.040) *which is not a statistically significant result.*

Id. ¶ 46 n.20 (emphasis added) (citation omitted). Dr. Wecker's opinions are based on fundamental concepts within the science of statistics, see Wecker Aff. ¶¶ 16-17, and Plaintiff's contention that this statistical analysis should be excluded is without merit.

4. **Plaintiff Was Not Prejudiced By The Timing Of Dr. Wecker's Expert Report.**

As its final argument, Plaintiff asserts that Dr. Wecker's expert testimony should be precluded in its entirety because the timing of the submission of the expert report of Dr. Wecker resulted in "significant prejudice." Pl.'s Motion at 20-21. The claim of "prejudice" is meritless. Plaintiff has known that Dr. Wecker would testify as Defendants' expert on statistical analysis for more than a year and a half. Moreover, Dr. Wecker's expert report was submitted nearly three months before the current trial date and promptly after it was prepared. All of the electronic files underlying the report were provided a few days later. Not only was the report submitted just after it was completed, but it could not have been completed earlier, because the prescriber

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depositions on which Dr. Wecker's survey opinions and calculations are based were not completed until mid-November 2010 and the final transcript not completed by the court reporter until November 30, 2010. Wecker Aff. ¶ 11.

Under well-settled South Carolina law, "the sanction of exclusion of a witness should never be lightly invoked" See *Laney v. Hefley*, 262 S.C. 54, 60, 202 S.E.2d 12, 14 (1974) (citation omitted). Thus, the failure of a party to comply with a previously-entered scheduling order is not a sufficient basis for exclusion. *Jumper v. Hawkins*, 348 S.C. 142, 152, 558 S.E.2d 911, 916 (Ct. App. 2001). Rather, in determining whether to exclude a witness, "even in the face of a pre-trial order mandating the disclosure of a witness by a certain date, a trial judge is required to consider and evaluate the following factors . . . : (1) the type of witness involved; (2) the content of the evidence emanating from the proffered witness; (3) the nature of the failure or neglect or refusal to furnish the witness' name; (4) the degree of surprise to the other party, including the prior knowledge of the name of the witness; and (5) the prejudice to the opposing party." *Id.*

In *Jenkins v. Few*, __ S.E.2d __, No. 4763, 2010 WL 5071603 (S.C. Ct. App. Dec. 8, 2010), the defendant argued that the trial court erred when it refused to exclude the plaintiff's expert for failure to identify the expert in a timely manner. *Id.* at *4. The Court of Appeals of South Carolina, however, affirmed the trial court, finding, among other things, that the degree of prejudice was "low" because the expert intended to testify consistent with his deposition testimony and defendant's counsel had an opportunity to cross-examine the expert prior to his trial testimony. *Id.* at *4. Compare *Jenkins*, 2010 WL 5071603, at *4, and *Kirkland v. Peoples Gas Co.*, 269 S.C. 431, 436, 237 S.E.2d 772, 774 (1977) ("In light of the prior knowledge of the existence and

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testimony of the witness, exclusion was not justified[.]"), *with Bryson v. Bryson*, 378 S.C. 502, 508-09, 662 S.E.2d 611, 614 (Ct. App. 2008) (affirming exclusion of expert who was identified on the morning of trial because it "left the [opponent] with an insufficient amount of time to adequately prepare for an examination of [the witness] and eliminated the [opponent's] opportunity to depose [the witness]"), and *Arthur v. Sexton Dental Clinic*, 368 S.C. 326, 339-41, 628 S.E.2d 894, 901-02 (Ct. App. 2006) (affirming exclusion of fact and expert witnesses who were identified after the end of discovery because the opponent was not able to depose them).

The cases cited by Plaintiff are inapposite. *See Samples v. Mitchell*, 329 S.C. 105, 112, 115, 495 S.E.2d 213, 216, 218 (Ct. App. 1997) (reversing because the trial court did not consider the *Laney* factors, which are similar to the *Jumper* factors); *see also Adalman v. Baker, Watts & Co.*, 807 F.2d 359, 368-70 (4th Cir. 1986) (affirming, under federal law, the trial court's exclusion of an expert witness who was identified for the first time after the trial had already begun and whose testimony was cumulative of other witnesses).

Consideration of the *Jumper* factors, as well as long-standing South Carolina law rejecting preclusion based simply on the timing of expert disclosures, leads clearly to the conclusion that the Court should reject Plaintiff's request for preclusion of Dr. Wecker's testimony. With respect to the first and second factors, as explained in more detail above, Dr. Wecker is an accomplished statistician with superior qualifications. Dr. Wecker's testimony will relate directly to Plaintiff's SCUTPA claim.

With respect to the remaining factors, Plaintiff's claim of surprise or prejudice rings particularly hollow. As early as *May 2009*, Defendants raised the need for

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prescriber depositions for purposes of a statistical analysis with the Court. See Tr. of Status Conference (May 4, 2009) at 40:16-46:12 (Ex. D). A month later, in June 2009, Defendants filed their motion seeking leave to depose South Carolina physicians *for the purpose of preparing the precise statistical survey challenged by Plaintiff*. See Defs.' Mem. of Law in Support of Motion for Leave to Depose a Statistically Significant Sample of Prescribing Physicians and Institutions (Ex. D to Pl.'s Motion). As part of that motion, Defendants submitted a detailed affidavit from Dr. Wecker outlining the need for the depositions for purposes of his expert report. *Id.* (Ex. D to Pl.'s Motion (Ex. A)). By Order dated June 26, 2009, the Court granted Defendants' motion, in part, and permitted Defendants to take 20 depositions for purposes of Dr. Wecker's statistical analysis. See Order (June 26, 2009) (Ex. E).

On more than one occasion, Plaintiff asked that the Court put a premature end to the prescriber depositions. On May 11, 2010, during a hearing before the Court on a motion filed by Plaintiff seeking to limit the number of prescriber depositions, Defendants' counsel again specifically argued the importance of the prescriber depositions for purposes of conducting analysis of South Carolina prescribers. See Tr. of Oral Arg. (May 11, 2010) at 23:25-24:3 (Ex. F) ("We wanted to look at the universe of doctors in South Carolina, taking a . . . sample of that universe . . . regarding what was said to them, what they understood."). The Court permitted the depositions to proceed. *Id.* at 29:12-29:15.

The depositions were not completed by May 14, 2010, the date set by the Preliminary Scheduling Order for the exchange of expert reports, in part due to Plaintiff's efforts to stop the process before 20 depositions had been taken. Although

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his report could not yet be completed, Defendants specifically identified Dr. Wecker as an expert witness on May 14, 2010. In the May 14 letter to Plaintiff's counsel serving expert reports, Defendants' counsel specifically advised Plaintiff that: "Defendants will produce the expert report of William Wecker, Ph.D. once the remaining prescribing physicians' depositions have been completed and the report is generated." Letter from Kenneth A. Murphy to Fletcher V. Trammell and John B. White, Jr. (May 14, 2010) (Ex. G). Plaintiff cannot plausibly claim that it was surprised by the Wecker report or that it suffered "significant prejudice."

The last prescriber deposition was not completed until November 19, 2010, and the transcript of the deposition was completed and provided to Dr. Wecker on November 30, 2010. See James Liddell Elmore, M.D. Dep. Tr. (Nov. 19, 2010) (Ex. H); Wecker Aff. ¶ 11. Two and a half weeks later, on December 17, 2010, Dr. Wecker's expert report was provided to Plaintiff. See Letter from Steven J. Pugh to John B. White (Dec. 17, 2010) (Ex. I). On December 22, 2010, Defendants provided all of the electronic files supporting Dr. Wecker's opinion to Plaintiff. See Letter from Steven J. Pugh to John S. Simmons (Dec. 22, 2010) (Ex. J). On January 6, 2011, Plaintiff received Dr. Wecker's deposition. See Pl.'s Notice To Take Videotaped Oral Dep. Of William Wecker (Jan. 6, 2011) (Ex. K). Accordingly, the State has not been "prevented from deposing Dr. Wecker," as it claims in its Motion, Pl.'s Motion at 20; in fact, Dr. Wecker's deposition is currently scheduled, at Plaintiff's request, for January 27, 2011.

As in *Few*, the *Jumper* factors clearly weigh in favor of allowing Dr. Wecker to testify at the trial of this matter. This simply is not a case like *Bryson* or *Arthur* where a party was surprised by the identification of a witness on the eve of or during trial,

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resulting in incurable prejudice. Here, excluding Dr. Wecker as a witness would not "serve to protect the rights of discovery provided by the rules." *Orlando v. Boyd*, 320 S.C. 509, 511, 466 S.E.2d 353, 355 (1996). Plaintiff has known that Dr. Wecker would be identified as an expert witness for more than a year and a half. In addition, Plaintiff will have had Dr. Wecker's report for nearly three months prior to trial and will have deposed Dr. Wecker more than one month before trial begins.

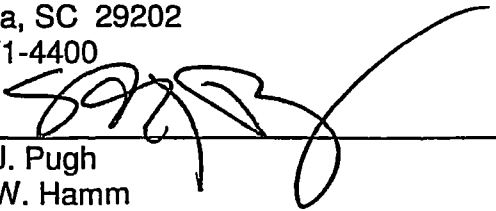
Plaintiff has suffered no surprise or prejudice, and its Motion should be denied.

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III. CONCLUSION

For all the foregoing reasons, Defendants respectfully request that this Court deny Plaintiff's Motion in its entirety.

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January 21, 2011

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EXHIBIT A

STATE OF SOUTH CAROLINA)
COUNTY OF SPARTANBURG)
STATE OF SOUTH CAROLINA)
ex rel. Alan Wilson, in his capacity)
as Attorney General of the State of)
South Carolina,)
Plaintiff,)
v.)
ORTHO-McNEIL-JANSSEN)
PHARMACEUTICALS, INC., f/k/a)
JANSSEN PHARMACEUTICA INC.,)
and/or JANSSEN, L.P. and)
JOHNSON & JOHNSON, INC.,)
Defendants.)

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT
CIVIL ACTION NO.: 2007-CP-42-1438

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STATE OF CALIFORNIA §
COUNTY OF MARIN §

AFFIDAVIT OF WILLIAM E. WECKER, Ph.D.

BEFORE ME, the undersigned authority, personally appeared William E. Wecker, who upon his oath did depose and state:

1. I am the President of William E. Wecker Associates, a statistical and mathematical consulting company in Novato, California. I am over the age of twenty-one (21) years old. I have never been convicted of a crime involving moral turpitude. I have personal knowledge of each fact set forth herein and each is true and correct. I am competent to testify about the matters set forth herein because I have either personally observed such matters or have formed opinions within my areas of professional expertise concerning such matters.
2. I graduated from the United States Air Force Academy in 1963. After serving as a fighter pilot in the United States Air Force, I received a Ph.D. in statistics and management

science from the University of Michigan in 1972. Thereafter, I worked as a professor of statistics and applied mathematics at the Graduate School of Business at the University of Chicago from 1973-1985 and at the Graduate School of Management at the University of California at Davis from 1985-1989.

3. In 1990, I founded William E. Wecker Associates, Inc. We currently employ approximately 20 mathematicians and statisticians who work with fifty different computer systems and more than 65 billion data records on our active projects. We perform statistical and mathematical consulting work for a wide variety of businesses and government entities, including automobile manufacturers, airplane manufacturers, airlines, banks, railroads, credit card companies, the United States Department of Interior, the Environmental Protection Agency, the City of Chicago, and the Czech Republic.

4. I am a member of the American Statistical Association, the Institute of Mathematical Statistics, and the Society for Risk Analysis. I have served as associate editor of the *Journal of the American Statistical Association* for four years and of the *Journal of Business and Economic Statistics* for eighteen years. I have been qualified by state and federal courts around the country to provide expert testimony on statistics, including the design and results of statistical surveys. I have also been retained as a court-appointed expert to help a California court in a dispute between the State of California and Bank of America regarding the treatment of dormant accounts.

5. I have performed statistical analysis of data sources available for evaluation of plaintiff's claims in the above-captioned case. My opinions are set out in my expert report of December 3, 2010, which is attached hereto as Exhibit 1, and the electronic files that are a part of and document the statistical analysis that I undertook. Those files, including the data sets,

programs and output files used in my analysis and provided to plaintiff, are listed in Exhibit 2 to this Affidavit. It is my understanding that Exhibit 2 was previously provided to plaintiff with my electronic files.

6. I specifically performed the following statistical analyses, as more fully explained in my expert report: I designed and analyzed the results from a statistical survey of South Carolina doctors; I analyzed patient claims data produced by the plaintiff from the HMO, Fee-for-Service (FFS) and State Health Plan (SHP) databases (but not the Department of Mental Health database, for reasons explained below); and I reviewed and analyzed the statistical conclusions presented in the eight peer-reviewed epidemiological studies existing as of November 2003 that compared the risk of diabetes in schizophrenia patients treated with Risperdal to the risk in untreated schizophrenia patients, patients treated with conventional antipsychotics, or patients treated with other second generation antipsychotics, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

Statistical Survey of South Carolina Doctors

7. Given the size of the relevant population, it would be prohibitively time-consuming and expensive to interview each prescriber of Risperdal in South Carolina concerning his or her experience with Risperdal and other antipsychotic medications. However, a properly representative sample of South Carolina doctors provides an economically feasible, reasonably accurate approximation of the same information. It is generally accepted among professional statisticians as well as scientists and scholars in related fields that statistical sampling is the only generally applicable, scientifically valid method for creating a representative sample from a universe that is too large to process exhaustively. By means of statistical sampling it is possible to produce unbiased, reasonably accurate approximations, having a known degree of potential

error, to questions whose exact answers would be impracticably expensive or burdensome to obtain. I therefore obtained information about the experience of South Carolina doctors from legal depositions of randomly identified doctors who treated FFS and SHP beneficiaries in the State.

8. The theory and practice of statistical sampling, including sample surveys of human subjects, has been a fundamental topic within the science of statistics at least since the early twentieth century and is addressed in authoritative statistical textbooks such as *Statistics Principles and Methods* by Richard Johnson and Gouri Bhattacharyya and *Sampling Techniques* by leading statistician William Cochran. During the decades of my education and career as a professional statistician in academia and consulting, I have acquired extensive experience with numerous aspects of sampling theory, sample and survey design, sample and survey implementation, and the analysis of sample and survey data.

9. The questions posed to doctors in deposition asked doctors about their experience with Risperdal and other antipsychotic medications and their specific exposure to Janssen promotional activity and communications. I sought fact-based answers from doctors in response to questions about whether Janssen had marketed Risperdal to them for off-label uses, whether they had received specific correspondence from Janssen, and how their patients fared while taking Risperdal and other antipsychotics. Obtaining survey responses through depositions taken by attorneys for defendants does not impact the reliability of the responses provided. Responses were given by doctors under oath, subject to penalty of perjury. Each of the depositions was transcribed and the questions and answers were reviewed by myself and my staff. In addition, counsel for plaintiff was allowed to and did attend each deposition and ask the surveyed doctors questions.

10. It is my understanding that the Court limited defendants to surveying only 20 doctors through deposition. For that reason, my survey sample was randomly identified from the 101 doctors who prescribed *antipsychotics* most frequently to patients in the Fee-for-Service or State Health Plan databases produced by the plaintiff. I did not limit my survey to the most frequent *Risperdal* prescribers, because doing so would have resulted in the omission of doctors who preferred other medications to Risperdal for patients requiring antipsychotic medications. As explained in my expert report, I used a random process to identify the sample members from a list of all doctors eligible for selection.

11. After the transcript from the final deposition, taken November 19, 2010, was completed and available for my review on November 30, 2010, I utilized commonly-used and accepted statistical methods to calculate population estimates for the 101 most frequent prescribers. Those estimates, including confidence intervals, are listed in Exhibit 5 to my expert report. The methodology I employed is a well-established one that allows statisticians to reach conclusions about a population from the collection and analysis of sample data. This methodology is one that falls squarely within the province of statisticians.

Statistical Analysis of Claims Data

12. I performed three different analyses of claims data produced by plaintiff in this case. First, I was able to utilize claims data produced by the State to compare the incidence of side effects alleged by plaintiff to be risks from Risperdal use to the incidence of the same side effects in untreated patients suffering from psychotic disorders, patients treated with first generation (conventional) antipsychotics, and patients treated with other second generation (atypical) antipsychotics. Second, I was able to utilize claims data to compare time to discontinuation—the primary outcome measure of the CATIE study—in Risperdal patients to

patients using first generation antipsychotics. Third, I was able to determine Risperdal use as a percentage of all antipsychotic use by patients in the HMO, FFS or SHP programs over time.

13. My work is described in detail in my expert report. As set out there, in order to analyze the incidence of side effects that plaintiff alleges are associated with Risperdal use, I first identified patients who, based on their HMO, FFS or SHP claims, were receiving only Risperdal, only first generation antipsychotics, or only other second generation antipsychotics. I excluded DMH claims from my analysis because there was no way to link DMH prescription claims by patient identification number to claims for other Medicaid services. I then examined all claims, including full patient histories with professional and hospital claims where diagnoses were routinely recorded in the claims data, in the 36 months after their first antipsychotic drug prescription for diagnoses indicating an alleged side effect. To attempt to ensure that the first antipsychotic drug prescription recorded in the State claims data was a patient's first use of the drug, I required a minimum of 12 months of uninterrupted eligibility prior to the first antipsychotic drug prescription. To attempt to ensure that I was comparing patients with similar histories with respect to each side effect, I required that there be no diagnosis indicating the side effect prior to the first antipsychotic drug prescription, again including full patient claims histories in my analysis. To analyze untreated patients, I separately identified patients with uninterrupted eligibility for a period of at least 48 months prior to their first antipsychotic drug prescription and no diagnosis indicating the side effect prior to the final 36 months of the eligibility period. I then examined all claims in that 36 month period for diagnoses indicating an alleged side effect. I analyzed full patient claims histories, not just prescription claims, in this process. The results are contained in my expert report and electronic files.

14. As noted, I also performed a statistical analysis of claims contained in the FFS and SHP data to determine all-cause discontinuation times in the South Carolina population of State beneficiaries. Using the claims data, I analyzed the comparative time to discontinuation for South Carolina patients treated with different antipsychotics. In order to be confident that I was measuring the first use of a drug, or first use after a substantial period of time in which the patient had not taken the drug for which I was measuring time to discontinuation, I identified those claims that were preceded by a minimum of 12 months of uninterrupted eligibility with no claims for the drug in question. I then measured time to discontinuation following the first prescription by tracking patient claims histories for 18 months, as the CATIE study does. To determine discontinuation, I looked for periods of time without refills that followed the expiration of a patient's last prescription for the drug using three different, alternative time periods without refills to define discontinuation: 15 days, 30 days and 60 days. For example, if a patient received a prescription for a 30-day supply of Risperdal on April 1, but did not obtain another prescription until May 28, the patient would be deemed to have discontinued Risperdal use under the 15 days period, but not the 30 day or 60 day periods, because there was a 28 day period without a Risperdal refill prescription following the expiration of the 30 days supply prescribed on April 1. There is support in the peer-reviewed medical literature for each of the time periods I use to define discontinuation for my statistical analysis. The results are contained in my expert report and electronic files.

15. The third type of analysis of the claims data analyzed Risperdal prescriptions as a percentage of all antipsychotic prescriptions paid for by the State through the FFS or SHP benefits programs to determine whether the comparative frequency of Risperdal prescriptions changed following events that plaintiff cites in its Complaint: the November 10, 2003 and July

21, 2004 mailings from Janssen to health care providers, the April 2005 FDA advisory and subsequent black box warning for geriatric use, or the publication of the CATIE trial results in September 2005. The results of this statistical analysis are contained in my expert report and electronic files.

Statistical Analysis of Peer-Reviewed Literature and the CATIE Study

16. In my expert report, I also disclosed my opinions based on my analysis of the statistical conclusions presented in the eight peer-reviewed epidemiological studies addressing the risk of diabetes in patients taking Risperdal compared to untreated patients, patients taking conventional antipsychotics, and patients taking other atypical antipsychotics that existed as of November 10, 2003 and were cited by Janssen in a mailing to health care providers that is challenged by plaintiff. My analysis, contained in my expert report, is squarely within my expertise as a statistician. In particular, the concepts of statistical significance, hazard ratios, confidence intervals, p-values, and subgroup analysis, including p-value calculations using the Bonferroni method, are fundamental concepts within the science of statistics.

17. Likewise, my analysis of the CATIE study is based on my expertise as a statistician, including my assessment as a statistician of the implications of the CATIE study design for the statistical results reported in Table 2 to the CATIE trial results, as published in September 2005.

FURTHER AFFIANT SAYETH NOT.

W^W Wecker

William E. Wecker

State of California

County of Marin

Subscribed and sworn to (or affirmed) before me on this 19 day of January, 2011, by

William E. Wecker, personally known to me or proved to me on the basis of

satisfactory evidence to be the person(s) who appeared before me.

[Signature]

Signature of Notary Public

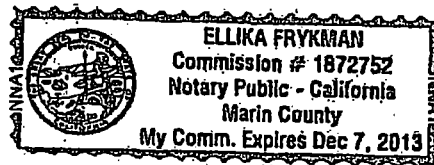


Exhibit 1

STATE OF SOUTH CAROLINA

COUNTY OF SPARTANBURG

STATE OF SOUTH CAROLINA,
ex rel. HENRY McMASTER, in his
capacity as Attorney General of the State
of South Carolina,

PLAINTIFF,

VERSUS

JANSSEN PHARMACEUTICA, INC., et al.

DEFENDANTS.

) IN THE COURT OF COMMON PLEAS

) FOR THE SEVENTH JUDICIAL CIRCUIT

) Case No.: 2007-CP-42-1438

EXPERT REPORT OF WILLIAM E. WECKER, PH.D.

DECEMBER 3, 2010

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R. 8380

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- Exhibit 2: William E. Wecker, Deposition and Trial Testimony
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- Exhibit 4: Deposition Questions and Responses of 20 Doctors
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- Exhibit 7: Antipsychotic Drugs and Alleged Side Effects (Data as of Nov. 10, 2003)
- Exhibit 8: Antipsychotic Drugs and Time to Discontinuation
- Exhibit 9: Antipsychotic Prescriptions by Month
Percent Risperdal Prescriptions by Month

1. My name is William E. Wecker. I am a statistician and applied mathematician. I received the Bachelor of Science degree (Basic Sciences) from the United States Air Force Academy in 1963. I received both the Master of Science degree (Operations Research, 1970) and Doctor of Philosophy degree (Statistics and Management Science, 1972) from the University of Michigan. I have served on the faculties of the University of Chicago, the University of California, Davis, and Stanford University where I taught statistics and applied mathematics at the graduate level. I have performed research in statistical theory, statistical methods, and applied mathematics since 1972. I am currently President of William E. Wecker Associates, Inc., an applied mathematics consulting firm located in Novato, California. I am a member of the American Statistical Association, the Institute of Mathematical Statistics, and the Society for Risk Analysis. I have served as associate editor of the *Journal of the American Statistical Association* for four years and of the *Journal of Business and Economic Statistics* for eighteen years. These qualifications and a list of my professional publications are shown in my curriculum vitae, which is appended to this report as Exhibit 1.

2. A list of all cases in which I have testified as an expert at trial or by deposition since January 1, 2006, is appended to this report as Exhibit 2. The billing rate for my time working on this matter is \$650 per hour.

3. My report consists of three primary sections that follow this introduction. First, in Section I, I identify and cite some of the primary allegations made by plaintiff of purportedly unlawful conduct by Janssen. Also in Section I, I identify the central questions that plaintiff's allegations raise for my expert analysis in this case and the data sources that are available for statistical analysis and evaluation of plaintiff's allegations. The available data include statistical surveys of South Carolina doctors, patient claims data produced by the

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plaintiff, and peer-reviewed epidemiological and experimental studies. The results of my statistical survey of South Carolina doctors and analysis of patient claims data are presented in Section II. In Section III, I review and analyze the eight peer-reviewed epidemiological studies existing as of November 2003 that compared the risk of diabetes in patients treated with Risperdal to the risk in untreated schizophrenia patients, patients treated with conventional antipsychotics, or patients treated with other second generation antipsychotics. Also in Section III, I discuss the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

4. In forming my opinions, I have considered the documents listed on Exhibit 3 and the data and electronic files provided to the plaintiff in conjunction with this report. It is my understanding that plaintiff has thus far provided reports from only two of the three experts it intends to present at trial in this case: Dr. Laura Plunkett and Dr. William Wirshing. I reserve the right to conduct further analysis of plaintiff's allegations and the work of plaintiff's experts, and further reserve the right to review and offer opinions on additional material as it becomes available.

5. I am providing electronic files that document my work and are a part of this report.

**I. Plaintiff's Allegations and Available Data Sources
for Analysis of Plaintiff's Allegations**

6. In plaintiff's Second Amended Complaint ("2d Am. Compl."), plaintiff alleges that Janssen made misrepresentations about Risperdal's safety and effectiveness and marketed Risperdal for off-label uses. In particular, plaintiff alleges:

a. Defendants made "false and misleading misrepresentations of fact regarding Risperdal's risk profile, including but not limited to misrepresenting the likelihood and severity of the side effects associated with Risperdal, including diabetes, stroke, high blood pressure, weight gain, and other serious and potentially life-threatening conditions." (2d Am. Compl. ¶ 57(a).)

b. Defendants "misrepresent[ed] that Risperdal is safer and more effective than less expensive first generation 'typical' antipsychotics." (2d Am. Compl. ¶ 57(c).)

c. Defendants "heavily marketed Risperdal for multiple non-approved purposes." (2d Am. Compl. ¶ 23.)

d. A November 10, 2003 mailing from defendant Janssen to health care providers misled doctors concerning the risk of diabetes with Risperdal. (2d Am. Compl. ¶ 46.)

e. "[T]he CATIE study proved what Defendants knew since launching Risperdal: (1) that Risperdal is no more effective in treating schizophrenia; (2) that Risperdal is no safer; and (3) that Risperdal has intolerable side effects making it no more desirable than the less expensive atypical antipsychotics." (2d Am. Compl. ¶ 52.)

7. Plaintiff's allegations raise several questions for my analysis. At a broad level, the question for analysis is whether the allegations of wrongful conduct by Janssen are valid. On a more specific level, plaintiff's allegations raise the questions of how Risperdal's safety and efficacy compare to first generation antipsychotics and other second generation antipsychotics, how Janssen marketed Risperdal to doctors in South Carolina, and how South Carolina patients responded when treated with Risperdal, as compared to alternative medications. Plaintiff's allegations concerning Janssen's November 10, 2003 mailing to health

care providers raise the question of whether data and literature—in the form of South Carolina patient claims data and the eight peer-reviewed epidemiological studies cited by Janssen—support the statements Janssen made in the cover letter that accompanied the revised Risperdal package insert that Janssen sent to South Carolina doctors. Finally, plaintiff's allegations regarding the CATIE study raise the question of whether the conclusions reached by the study or those that plaintiff attempts to draw from it are valid.

8. I have identified three primary, available data sources that provide information related to the fundamental questions raised by plaintiff's allegations:

a. Documented South Carolina physician experience, such as may be found from South Carolina doctors who treat patients with Risperdal, including the doctors' experience with Risperdal's efficacy, experience with the potential side effects of antipsychotic medications, the circumstances in which off-label use is regarded by the physician as appropriate, and Janssen promotional practices.

b. Observational data, such as the claims data produced by plaintiff from the State Fee-for-Service ("FFS") and State Health Plan ("SHP") benefits programs.

c. Published experimental and epidemiological studies.

9. My analysis of physician experience and observational data is explained in Section II, below. I address published experimental and epidemiological studies in Section III. The explanations provided here are supplemented by the presentation of results in the tables and charts at the end of this report and in the electronic files that are being produced with this report and are a part of my expert work in this case.

II. Statistical Analysis of Plaintiff's Allegations

A. Documented Physician Experience

10. Given the size of the relevant prescriber population, it would be prohibitively time-consuming and expensive to interview each prescriber of Risperdal in South

Carolina concerning his or her experience with Risperdal and other antipsychotic medications. However, a properly representative sample of South Carolina doctors provides an economically feasible, reasonably accurate approximation of the same information. It is generally accepted among professional statisticians as well as scientists and scholars in related fields that statistical sampling is the only generally applicable, scientifically valid method for creating a representative sample from a universe that is too large to process exhaustively. By means of statistical sampling it is possible to produce unbiased, reasonably accurate approximations, having a known degree of potential error, to questions whose exact answers would be impracticably expensive or burdensome to obtain. I therefore obtained information about the experience of South Carolina doctors from legal depositions of randomly identified doctors who treated FFS and SHP beneficiaries in the State.

11. The theory and practice of statistical sampling, including sample surveys of human subjects, has been a fundamental topic within the science of statistics at least since the early twentieth century. During the decades of my education and career as a professional statistician in academia and consulting, I have acquired extensive experience with numerous aspects of sampling theory, sample and survey design, sample and survey implementation, and the analysis of sample and survey data.

12. Richard Johnson and Gouri Bhattacharyya recognized the importance of statistical sampling in their text *Statistics Principles and Methods*: "The subject of statistics provides the methodology to make inferences about the population from the collection and

analysis of sample data. These methods enable one to derive plausible generalizations and then assess the extent of uncertainty underlying these generalizations.”¹

13. Leading statistician William Cochran has also recognized the importance of statistical sampling for decision-makers in his book *Sampling Techniques*.²

14. Johnson and Bhattacharyya emphasize that “[s]tatistical concepts are also essential during the planning stage of an investigation when decisions must be made as to the mode and extent of the sampling process,” thus the “design of the sampling process is an important step” and “[a] good design for the process of data collection permits efficient inferences, often with a straightforward analysis.”³

15. In this case, the population sampled consists of doctors who prescribed antipsychotic drugs for South Carolina patients in the Fee-for-Service (FFS) or State Health Plan (SHP) claims databases.

16. Generally speaking, physicians who prescribed antipsychotic drugs to greater numbers of patients can be expected to have more experience regarding the efficacy of Risperdal and more experience regarding marketing and promotional activities of Janssen than physicians with fewer such patients. Because the Court limited Janssen to surveying 20 doctors through deposition, my survey sample was randomly identified from the 101 doctors who prescribed antipsychotics most frequently.⁴

¹ Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd edition, 1996, 14.

² Cochran, William G., *Sampling Techniques*, John Wiley & Sons, New York, 1977.

³ Johnson and Bhattacharyya, *op. cit.*, 14.

⁴ The population to be sampled was the top 100 prescribers. Two doctors tied for 100th place, so the sample was drawn from a population of 101 prescribers.

17. From the 101 most frequent prescribers, I selected, at random, with equal probability of selection, a sample of 20.⁵ I used a random process—a sequence of random numbers generated by a computer—to identify the final sample members from a list of all doctors eligible for selection.⁶ This random selection procedure guarantees a statistically representative sample because it rules out any purposive or inadvertent selection bias that could skew the composition of the sample towards any favored subgroup of doctors. Random sampling of this kind is a standard procedure in scientific survey research.

18. Counsel for Janssen endeavored to contact the selected doctors in the deposition sample to arrange for and conduct their depositions. Certain of the selected doctors were not available for deposition.⁷ In each of those instances, the next member in the random selection sequence was designated as a replacement.

19. The specific questions posed to the 20 doctors who were deposed are set forth in Exhibit 4 together with the doctors' responses. Exhibit 4 also shows the percent of doctor-deponents answering "yes" or "probably yes" to each question.

20. The questions to doctors in deposition asked doctors about their experience with Risperdal and other antipsychotic medications and their specific exposure to Janssen promotional activity and communications. I sought fact-based answers from doctors in response to questions about whether Janssen had marketed Risperdal to them for off-label uses,

⁵ "Equal probability samples" are also called "simple random samples."

⁶ I employed the following standard procedure for selecting the sample. Let N denote the population size, and n the designated sample size. I used the SAS statistical software package to assign independently to each of the N population members a decimal-fraction random number between zero and one, equally likely to fall within either of any given pair of subintervals of equal length within the overall interval from zero to one. I then sorted the list of N population members in order of these assigned random numbers, and selected the first n members of the sorted list as the sample.

⁷ One doctor was unavailable due to terminal illness; one had moved to California; one refused to be deposed; and three could not be located. See Wecker electronic file "sample list.xls".

whether they had received specific correspondence from Janssen, and how their patients fared while taking Risperdal and other antipsychotics.

21. As noted, the methodology I employed is a well-established one that allows statisticians to reach conclusions about a population from the collection and analysis of sample data. Exhibit 5 shows the conclusions that can be derived from the responses of 20 doctor-deponents about the entire population of the 101 most frequent prescribers. In aggregate, those 101 doctors wrote 33 percent of the antipsychotic prescriptions paid for through the FFS and SHP programs.⁸

22. The depositions regarding the actual experience of South Carolina doctors prescribing Risperdal and other antipsychotics yield results that contradict the plaintiff's allegations. For example, the great majority of physicians affirmed the following statements based on their experience: Risperdal is generally effective for treating the positive symptoms of schizophrenia; Risperdal is generally effective for treating the negative symptoms of schizophrenia; Risperdal typically has a more moderate side effect profile than first generation antipsychotics; both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently; and patients who consistently take their antipsychotic medications are less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications.

23. Plaintiff's allegations are also contradicted by the result that no doctors affirmed that: any Janssen sales representative ever promoted to them any off-label use of Risperdal in children or geriatric patients; or that any Janssen sales representative ever promoted to them any off-label use of Risperdal at all. No Janssen sales representative ever represented

⁸ See Wecker electronic file "ffs_top_101.apd_pct.lst".

anything inconsistent with the warnings about Risperdal that are provided on the FDA-approved package insert, and no Janssen sales representative ever misrepresented information about the potential side effects associated with Risperdal use to a deposed doctor.

24. Only a small number of physicians recall seeing Janssen's November 10, 2003 mailing to health care professionals. Of those, almost none changed their choice of antipsychotic medication based on the mailing. These responses are consistent with the history of the frequency with which doctors prescribed Risperdal, discussed below, which showed almost no change in Risperdal sales as a percentage of overall antipsychotic prescriptions after the mailing was sent to South Carolina doctors.

25. The commonly-used and accepted statistical tools that allow me to draw conclusions about the entire population of frequent South Carolina prescribers to FFS and SHP patients based on the answers provided in the survey show that the experience of South Carolina doctors contradicts plaintiff's allegations. The sample size of 20 allows me to reach reliable population estimates for the 101 most frequent prescribers, as shown in Exhibit 5.

B. Observational Data

26. Claims data produced by the plaintiff from South Carolina State databases is also useful for analyzing plaintiff's allegations.⁹ I performed three different analyses. First, I was able to utilize claims data produced by the State to compare the incidence of side effects alleged by plaintiff to be risks from Risperdal use to the incidence of the same side effects in untreated patients suffering from psychotic disorders; patients treated with first generation (conventional) antipsychotics; and patients treated with other second generation (atypical)

⁹ For my analyses of plaintiff's claims data, I combined HMO claims data with the FFS claims data. The two programs use a common patient identification code and some patients had claims records in both data bases.

antipsychotics. Second, I was able to utilize claims data to compare time to discontinuation—the primary measure of efficacy of the CATIE study—in Risperdal patients to patients using first generation antipsychotics. Third, I was able to determine Risperdal use as a percentage of all antipsychotic use by patients in the FFS or SHP programs over time.

B.1. Incidence of Alleged Side Effects

27. I analyzed the claims data to calculate the incidence of side effects that plaintiff alleges are caused by Risperdal, and to compare the incidence of those side effects in patients receiving Risperdal to the incidence of those side effects in untreated patients suffering from psychotic disorders; patients treated with first generation (conventional) antipsychotics; and patients treated with other second generation (atypical) antipsychotics.

28. In order to perform this analysis, I first identified patients who, based on their FFS or SHP claims, were receiving only Risperdal, only first generation antipsychotics, or only other second generation antipsychotics. I then examined all claims in the 36 months after their first antipsychotic drug prescription for diagnoses indicating an alleged side effect. To attempt to ensure that the first antipsychotic drug prescription recorded in the State claims data was a patient's first use of the drug, I required a minimum of 12 months of uninterrupted eligibility prior to the first antipsychotic drug prescription. To attempt to ensure that I was comparing patients with similar histories with respect to each side effect, I required that there be no diagnosis indicating the side effect prior to the first antipsychotic drug prescription. To analyze untreated patients, I separately identified patients with uninterrupted eligibility for a period of at least 36 months prior to their first antipsychotic drug prescription and no diagnosis indicating the side effect prior to the 36 month period. I then examined all claims in that 36 month period for diagnoses indicating an alleged side effect. I analyzed two time periods: the

full claims data base, providing data for 1994–2007 and the period limited to claims on or before November 10, 2003.¹⁰

29. The results of a direct comparison of the side effects reported in the claims database, for patients treated with different antipsychotic drugs, is shown in Exhibits 6 and 7. The percents of South Carolina patients with first alleged side effect diagnosis during the 36 months after their first antipsychotic drug prescription (treated patients) or before their first antipsychotic drug prescription reflect elevated side effect rates compared to Risperdal. Statistically significant differences from Risperdal are indicated by asterisks.

30. My analysis shows that:

a. Diabetes. Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and untreated patients had a statistically significantly elevated risk of diabetes compared to patients treated with Risperdal, whether measured based on analysis of all data or data existing as of November 10, 2003.

b. Metabolic adverse events.¹¹ Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and untreated patients had a statistically significantly elevated risk of metabolic adverse events compared to patients treated with Risperdal based on analysis of all data. Patients treated with other atypical antipsychotics had a statistically significantly elevated risk of metabolic adverse events compared to patients treated with Risperdal based on analysis of data existing as of November 10, 2003.

c. Increased prolactin secretion. Patients treated with conventional antipsychotics, patients treated with other atypical antipsychotics, and

¹⁰ I do not believe it is proper to limit analysis to data existing as of November 10, 2003 when seeking to determine whether the South Carolina claims data supports statements made by Janssen about Risperdal in the November 10, 2003 mailing. Instead, statisticians and other scientists should look at all available evidence, regardless of when it became available, to evaluate whether Janssen's statements were true or false. I have nevertheless included analysis of data as of November 10, 2003, in case plaintiff or any of its experts take the position that the truth or falsity of Janssen's communications should be evaluated without reference to anything that occurred after Janssen sent the November 10, 2003 mailing.

¹¹ Includes diabetes mellitus, secondary diabetes mellitus, abnormal glucose, abnormal weight gain, obesity, and other hyperalimentation.

untreated patients had a statistically significantly elevated risk of increased prolactin secretion compared to patients treated with Risperdal based on analysis of all data.¹²

31. The data for South Carolina patients contradicts the opinion of plaintiff's expert Dr. William Wirshing that "risperidone elevates prolactin more than any marketed antipsychotic except the more recently marketed Janssen product paliperidone, a metabolite of risperidone." (Wirshing Report, p. 7). Dr. Wirshing's criticism of Janssen for "believ[ing] that the FDA mandated class labeling change and to a slightly lesser extent the consensus guidelines painted all of the medications with the same toxic brush" (Wirshing Report, p. 8) is similarly contradicted by the experience of South Carolina patients, because patient experience demonstrates differences in risk for Risperdal compared to other antipsychotics.

B.2. Time to Discontinuation

32. Plaintiff alleges in its Petition that the authors of the CATIE study "concluded that Risperdal is no more effective than the first generation, 'typical' antipsychotic, perphenazine, in treating schizophrenia. In addition, the time to discontinuation because of intolerable side effects, including movement disorders, were similar among all groups." (2d Am. Compl., ¶ 52.)

33. The CATIE study used "all-cause discontinuation" as the primary outcome measure of efficacy, meaning that the "failure" of a drug was attributed to the patient's discontinuation of the drug for any reason. The longer a patient took a drug in the CATIE trial, the more effective it was deemed to be by the study authors. I will return to the question of what the CATIE study shows, or does not show, about "all-cause discontinuation" times. But first, I

¹² The November 10, 2003 mailing did not discuss increased prolactin secretion.

will describe my analysis of all-cause discontinuation times in the South Carolina population of State beneficiaries.

34. I have performed a statistical analysis of claims contained in the FFS and SHP data to determine all-cause discontinuation times in the South Carolina population of State beneficiaries. Using the claims data, I analyzed the comparative time to discontinuation for South Carolina patients treated with different antipsychotics. In order to be confident that I was measuring the first use of a drug, or first use after a substantial period of time in which the patient had not taken the drug for which I was measuring time to discontinuation, I identified those claims that were preceded by a minimum of 12 months of uninterrupted eligibility with no claims for the drug in question.

35. I then measured time to discontinuation following the first prescription by tracking patient claims histories for 18 months, as the CATIE study does. To determine discontinuation, I looked for periods of time without refills that followed the expiration of a patient's last prescription for the drug using three different, alternative time periods without refills to define discontinuation: 15 days, 30 days and 60 days. For example, if a patient received a prescription for a 30-day supply of Risperdal on April 1, but did not obtain another prescription until May 28, the patient would be deemed to have discontinued Risperdal use under the 15 days period, but not the 30 day or 60 day periods, because there was a 28 day period without a Risperdal refill prescription following the expiration of the 30 days supply prescribed on April 1. There is support in the medical literature for each of the time periods I use to define discontinuation: 15 days,¹³ 30 days,¹⁴ and 60 days.¹⁵

¹³ Mullins, C. Daniel, *et al.*, *Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia*, Schizophrenia Research, Vol. 98 (2008), § 2.3.1.1 p. 9; Ren, X. S., *et al.*, *An alternative approach to*

36. My results show that Risperdal has a longer time to discontinuation compared to first generation antipsychotics in the FFS and SHP population under each of the three definitions of time to discontinuation. The complete results are set out in Exhibit 8. My analysis shows that:

a. Defining discontinuation as a 60-day period. Average time to discontinuation was 211 days for Risperdal, 133 days for perphenazine, 130 days for Haldol, and 58 days for all other first generation antipsychotics considered as a group.

b. Defining discontinuation as a 30-day period. Average time to discontinuation was 166 days for Risperdal, 107 days for perphenazine, 99 days for Haldol, and 44 days for all other first generation antipsychotics considered as a group.

c. Defining discontinuation as a 15-day period. Average time to discontinuation was 126 days for Risperdal, 83 days for perphenazine, 78 days for Haldol, and 35 days for all other first generation antipsychotics considered as a group.

B.3. Risperdal Use Over Time

37. Using the claims data, I was also able to analyze Risperdal prescriptions as a percentage of all antipsychotic prescriptions paid for by the State through the FFS or SHP benefits programs and determine whether the comparative frequency of Risperdal prescriptions changed following events that plaintiff cites in its Complaint: the November 10, 2003 and July 21, 2004 mailings from Janssen to health care providers; the April 2005 FDA advisory and

measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration, Neuropsychiatric Disease and Treatment, Vol. 3, No. 2 (2007), p. 279; Ren, X. S., et al., Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents, J. Clin. Pharm. and Therap., Vol. 31 (2006), p. 59.

¹⁴ Ren, X. S., et al., *An alternative approach to measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration, Neuropsychiatric Disease and Treatment, Vol. 3, No. 2 (2007), p. 279.*

¹⁵ Kilzieh, Nael, et al., *Time to Discontinuation and Self-Discontinuation of Olanzapine and Risperidone in Patients With Schizophrenia in a Naturalistic Outpatient Setting, J. Clin. Psychopharmacol., Vol 28, No. 1 (Feb. 2008), p. 75; Zhu, Baojin, et al., Time to Discontinuation of Depot and Oral First-Generation Antipsychotics in the Usual Care of Schizophrenia, Psychiatric Services, Vol. 59, No. 3 (Mar. 2008), p. 316.*

subsequent black box warning for geriatric use; or the publication of the CATIE trial results in September 2005.

38. In order to determine the percentage of all antipsychotic prescriptions that Risperdal accounts for, I first eliminated claims that were reversed and duplicate claims within the database, so that each prescription for an antipsychotic medication would be counted only once. I then counted Risperdal prescriptions for each month from January 2003–December 2005. I separately counted all antipsychotic prescriptions in the same months. It was then straightforward to determine the number of Risperdal prescriptions as a percentage of all antipsychotic prescriptions paid for by the State through the FFS and SHP programs.

39. The results of my analysis are presented numerically and graphically in Exhibit 9. As the graph in Exhibit 9 shows, I was able to specifically analyze whether the events cited in the Complaint were followed by any change in the frequency with which South Carolina doctors prescribed Risperdal to patients in the FFS or SHP programs, as compared to all antipsychotic prescriptions.

40. In particular, I found no change in Risperdal prescribing frequency following Janssen's November 10, 2003 mailing to health care providers. If, as plaintiff contends, Janssen misled doctors about Risperdal's safety compared to other antipsychotics, I would expect to see an increase in the frequency with which doctors prescribed Risperdal compared to other antipsychotics. There was no such increase.

41. There was likewise no change in Risperdal prescribing frequency following July 2004, when Janssen sent its "correction" letter to South Carolina doctors at the request of the DDMAC division of FDA. The data also demonstrates that Risperdal use did not decline after the FDA issued its April 2005 advisory and subsequently required a black box

warning for risk of death in geriatric patients or in the time period following the publication of the CATIE study results in September 2005. If, as plaintiff contends, these events mark times when doctors were exposed to information previously withheld or when “the public perception of Risperdal created by Defendants was dealt a crushing blow” (2d Am. Compl. ¶ 50), I would expect to see a decline in the frequency with which doctors prescribed Risperdal compared to other antipsychotics. That did not occur.

III. Analysis of Peer-Reviewed Literature

A. The Eight Studies Cited by Janssen in Its November 10, 2003 Mailing

42. Plaintiff alleges that a November 10, 2003 mailing from Janssen to doctors in South Carolina contained misleading information about the risk of diabetes in patients taking Risperdal. As shown in Exhibits 4–7 and addressed above, the experience of South Carolina doctors and South Carolina patients supports the statements that Janssen made in the mailing:

Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiological research¹⁻⁸ suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

Janssen’s statements are also supported by the eight then-existing peer-reviewed epidemiological studies addressing the risk of diabetes in patients taking Risperdal compared to untreated patients, patients taking conventional antipsychotics and patients taking other atypical antipsychotics.

43. The eight studies cited by Janssen, which collectively analyze data from 6 million patients,¹⁶ are:

¹⁶ See Wecker electronic file “eight studies patient counts.xls”.

- a. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003; 56: 164-170.
- b. Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002; 63:1135-1139.
- c. Fuller MA, Shermock KM, Secic M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003; 23(8): 1037-1043.
- d. Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003; 23(4): 328-335 ("Gianfrancesco 1").
- e. Gianfrancesco F, Grogg AL, Mahmoud RA et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003; 25(4): 1150-1171 ("Gianfrancesco 2").
- f. Gianfrancesco F, Grogg AL, Mahmoud RA et al. Differential effect of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database. *J Clin Psychiatry* 2002; 63: 920-930 ("Gianfrancesco 3").
- g. Koro CE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; 325: 243-245.
- h. Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002; 159: 561-566.

44. I have reviewed and analyzed the statistical conclusions presented in the eight studies. Four of the eight studies contain results comparing patients treated with Risperdal to untreated patients: Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3 and Koro. All four of these studies find "that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients"

45. Six of the eight studies contain results comparing patients treated with Risperdal to patients treated with conventional antipsychotics: Buse, Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3, Koro and Sernyak. All six of these studies find “that RISPERDAL is not associated with an increased risk of diabetes when compared to ... patients treated with conventional antipsychotics.”

46. Buse warrants additional attention. Buse found overall that the incidence of diabetes mellitus for patients treated with Risperdal was lower than for patients treated with conventional antipsychotics. The hazard ratio for Risperdal was also lower than the hazard ratio for conventional antipsychotics.¹⁷ Buse separately reported results for a subgroup analysis that compared each of the four atypical antipsychotics, including Risperdal, to the haloperidol cohort.¹⁸ As a part of his subgroup analysis, Buse calculated that Risperdal’s hazard ratio compared to haloperidol was 1.23, with a 95% confidence interval of 1.01–1.50 and a p-value of 0.040. A p-value of 0.040 would indicate a statistically significant result for a primary endpoint of a study, but it does not indicate a statistically significant result for a secondary, subgroup analysis. Subgroup p-values need to be interpreted based on the number of comparisons made in subgroups that are analyzed—at least four in this case.¹⁹ Properly interpreted, the p-value of 0.040, which is part of the haloperidol subgroup analysis is not a statistically significant result.²⁰

¹⁷ Buse at 168, Table 3.

¹⁸ Buse at 168, Table 4.

¹⁹ Walsh, Bruce. *Multiple Comparisons: Bonferroni Corrections and False Discovery Rates*, Lecture notes for EEB 581, 2004.

²⁰ There are several formulaic ways to assess statistical significance for a subgroup analysis. The most common and easiest method to apply is the method of Bonferroni. (See Walsh, *op. cit.*) In the case of the haloperidol subgroup analysis and the p-value of 0.040, which is a part of that analysis, the Bonferroni p-value is 0.16 (= 4 x 0.040) which is not a statistically significant result.

47. All eight studies contain results comparing patients treated with Risperdal to patients treated with another atypical antipsychotic, and four of those eight found statistically significant results: Ward, Fuller, Gianfrancesco 2, and Gianfrancesco 3. All four of these studies find “that RISPERDAL is associated with a [statistically significantly] lower risk of diabetes than some other studied atypical antipsychotics.”

48. Taken together, the results of the eight studies, like the experience of South Carolina doctors and patients, contradict the contention of plaintiff’s expert Laura Plunkett, that “the language of the November 2003 ‘Dear Health Care Provider’ letter was not an accurate reflection of the risks posed by Risperdal.” (Plunkett Report, ¶ 50.) Contrary to Dr. Plunkett’s opinion, Janssen’s statement in the mailing was an accurate reflection of the risks posed by Risperdal, whether judged by the then-existing body of published peer-reviewed epidemiological literature or the data from South Carolina doctors and patients.

B. The CATIE Study

49. As described above, the experience of South Carolina doctors with Risperdal and other antipsychotic medications contradicts plaintiff’s interpretation of the CATIE study:

[T]he CATIE study proved what Defendants knew since launching Risperdal: (1) that Risperdal is no more effective in treating schizophrenia; (2) that Risperdal is no safer; and (3) that Risperdal has intolerable side effects making it no more desirable than the less expensive atypical antipsychotics. (2d Am. Compl. ¶ 52.)

In the experience of South Carolina doctors, Risperdal is more effective; has a more moderate side effect profile; and is better tolerated than first generation antipsychotics.

50. The experience of South Carolina patients also contradicts plaintiff’s interpretation of the CATIE study. Time to discontinuation of Risperdal, for South Carolina

patients, is longer than time to discontinuation of perphenazine, Haldol, or other first generation antipsychotics.

51. It takes no deep statistical analysis to show that the CATIE study itself demonstrates that Risperdal is more effective than and safer than perphenazine, the first generation drug included in the CATIE study. The study protocol states that perphenazine is "contraindicated" for patients with a prior history of tardive dyskinesia.²¹ This contraindication alone is sufficient to show that Risperdal is more effective than and safer than perphenazine for at least this large segment of the patient population.

52. Any direct comparisons of results from the perphenazine group to other treatment groups in the CATIE study will produce only ambiguous results, because the perphenazine group excluded patients with tardive dyskinesia while the other groups did not. Thus, the perphenazine group differs from the other groups in two ways: a difference in treatment and a difference in the patients treated. Because the perphenazine group differs from the other groups in more than one way, it is not valid to claim that any difference in outcomes for the perphenazine group versus any of the other treatment groups is due to the difference in treatment alone.

53. In an apparent attempt to cure the problem caused by the difference in patients treated with perphenazine compared to patients who received other treatments, the CATIE study chose to ignore results from patients with a prior history of tardive dyskinesia when making certain comparisons between treatment groups. But ignoring patients with a prior history of tardive dyskinesia is not a cure, because perphenazine, which is contraindicated for such patients, can be expected to have a differential and less satisfactory outcome for such

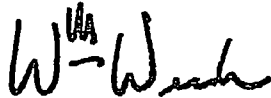
²¹ Protocol, Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia, 26-27.

patients. Ignoring outcomes for patients for whom perphenazine is expected to be ineffective or harmful amounts to ignoring an important difference in treatment results that will occur in the general population, which makes such comparisons inapplicable to the general population.

IV. Conclusion

54. In summary, for the reasons I have explained, statistical analysis of the primary data sources that provide information related to the central questions at issue refutes plaintiff's allegations.

December 3, 2010

A handwritten signature in dark ink, appearing to read 'W. E. Wecker', with a horizontal line drawn underneath it.

William E. Wecker

December 2010

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EMPLOYMENT

1963-1967 Fighter pilot, U.S. Air Force
1968-1969 Chief of Protocol, U.S. Air Force, Berlin, Germany
1970-1972 Graduate Student, University of Michigan
1973-1976 Assistant Professor, Graduate School of Business, University of Chicago
1977-1983 Associate Professor, Graduate School of Business, University of Chicago
1984-1985 Associate Professor, Graduate School of Management, University of California, Davis
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1994-1998 Consulting Professor of Law, School of Law, Stanford University
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ACTIVITIES

1977-1981 Associate Editor (Theory and Methods), Journal of the American Statistical Association
1981-1999 Associate Editor, Journal of Business and Economic Statistics
1990-1992 Management Committee, Journal of Business and Economic Statistics
1976-1994 Seminar Leader, NSF/NBER Seminar on Time Series Analysis
1993-1994 National Advisory Council on Environmental Policy and Technology
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PUBLICATIONS

- "A Nonparametric Approach to the Construction of Prediction Intervals for Time Series Forecasts" (with W. A. Spivey), Proceedings of the Business and Economic Statistics Section--American Statistical Association, 1972.
- "Regional Economic Forecasting: Concepts and Methodology" (with W. A. Spivey), The Regional Science Association Papers, Vol. 28, 1972, pp. 257-276.
- "On the Weighted Average Cost of Capital" (with R. R. Reilly), Journal of Financial and Quantitative Analysis, January 1973, Vol. VIII, pp. 123-126.
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- "The Prediction of Turning Points," Proceedings of the Business and Economic Statistics Section-- American Statistical Association, 1976.
- "Bounds on Absorption Probabilities for the m-Dimensional Random Walk" (with T. Morton), Journal of the American Statistical Association, March 1977.
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Exhibit 2

William E. Wecker
Deposition and Trial Testimony
January 1, 2006 – December 3, 2010

1. Carla P. Cox v. Ford Motor Company and Mullinax Ford South, Inc. Circuit Court, Broward County, Florida, No. 02012391.
2. Cook, et al., v. Rockwell International Corp., et al. USDC, Denver, Colorado, No. 90-K-181.
3. Misty Arias, et al. v. Award Homes, Inc., et al. Superior Court, Monterey County, California, No. M54183.
4. Marjorie Rosenthal, et al. v. Ford Motor Company, et al. USDC, Connecticut, No. 3:05-cv-478(JCH).
5. Karen Jean Hubbard, et al. v. Ford Motor Company, et al. Superior Court, Macon County, Georgia, No. 2003CV-283-P.
6. Ronene J. Bracken, et al. v. Ford Motor Company, et al. USDC, Nevada, No. CV-S-04-1543-RLH(RJJ).
7. Thelma Byrd, et al. v. Ford Motor Company, et al. Circuit Court, Copiah County, Mississippi, No. 2002-0446.
8. Yolanda Adams v. Ford Motor Company. District Court of the Virgin Islands, Division of St. Croix.
9. Ford Explorer Cases, Coordination Proceeding (Gray; Tompkins; Katz; Montoya and McLachlan v. Ford Motor Company). Superior Court, Sacramento County, California, JCCP Nos. 4226 and 4270.
10. State of California ex rel. Barakat Consulting Incorporated and Samir F. Barakat v. Los Angeles Department of Water and Power. Superior Court, San Bernardino County, California, No. SCVSS 100293.
11. Hohnbaum, et al. v. Brinker Restaurant Corporation, et al. Superior Court, San Diego County, California, No. GIC834348.
12. Leslie J. Whiteley and Leonard Whiteley v. Raybestos-Manhattan, Inc., et al. Superior Court, San Francisco, California, No. 303184.

13. Dallas R. Maxwell and Angela J. Maxwell v. U-Haul International, Inc., Ford Motor Company, et al. Circuit Court, Jackson County, Missouri, No. 04CV226516.
14. Lindsay Rae Burnett, et al. v. Pirelli North America, Inc., Ford Motor Company, et al. District Court, Clark County, Nevada, No. A476187.
15. Rodrigo Ibarra, et al. v. Goodyear Tire and Rubber Company, Ford Motor Company, et al. District Court, Clark County, Nevada, No. A485304.
16. National Economic Research Associates, Inc. and Marsh & McLennan Companies, Inc. v. David S. Evans, LECG Corporation and LECG, LLC. Superior Court Department of the Trial Court, Suffolk, Massachusetts, No. 04-2618.
17. Michael Gutzler, et al. vs. General Motors Corporation. Circuit Court, Jackson County, Missouri, No. 03CV208786.
18. Self-Insurers' Security Fund v. Gallagher Bassett Services, Inc. USDC, Northern District of California, San Francisco Division, No. C 06-02828 JSW/JCS.
19. Autry Petroleum Company and McDonald Oil Company v. BP Products North America, Inc. USDC, Middle District of Georgia, Columbus Division, No. 4:05-CV-113 (CDL).
20. Wyeth v. Impax Laboratories, Inc. USDC, Delaware, No. C.A. 06-222 (JJF).
21. Discover Financial Services, DFS Services LLC, and Discover Bank v. Visa, U.S.A. Inc., Visa International Services Association, Mastercard Incorporated and Mastercard International Incorporated. USDC, Southern District of New York, No. 04-CV-7844 (BSJ).
22. In re: New Motor Vehicles Canadian Export Antitrust Litigation. USDC, Maine, MDL No. 03-md-1532.
23. Lyle Verry and Carla Verry v. General Motors Corporation. USDC, Eastern District of California, No. 2:06-CV-01566-LKK-PAN.
24. Equal Employment Opportunity Commission v. University of Phoenix, Inc. and Apollo Group, Inc. USDC, Arizona, No. CV06-2303-PHX-MHM.
25. Charles Foti, Attorney General *ex rel*, State of Louisiana v. Janssen Pharmaceutica, Inc. et al. Judicial District Court, Parish of St. Landry, Louisiana, No. 04-C-3967-D.
26. Sabrina Black Manuel v. Ford Motor Company, et al. Beverly Barber-Crouse v. Ford Motor Company, et al. Eugene Manuel, Jr. v. Ford Motor Company, et al. USDC, North District of Illinois, Eastern District, Nos. 07C5320, 07C5324, 07C5325.

27. i4i Limited Partnership v. Microsoft Corporation. USDC, Eastern District of Texas, Tyler Division, No. 6:07-CV-113-LED.
28. Wyeth v. Apotex Inc. and Apotex, Corp. USDC, Southern District of Florida, No. 1:2008cv22308.
29. Steven Wirsz v. Nissan North America, Inc., et al. Superior Court, Los Angeles County, California, No. BC 377417.
30. L-3 Communications Integrated Systems, LP v. Lockheed Martin Corporation. USDC, Northern District of Texas, Dallas Division, No. 3-07CV0341-B.
31. Zurn PEX Plumbing Products Liability Litigation. USDC Minnesota, MDL 08-MD-1958.
32. Network-1 Security Solutions, Inc. v. Cisco Systems, Inc. USDC, Eastern Division of Texas, Tyler Division, No. 6:08cv030-LED.
33. In Re Payment Card Interchange Fee and Merchant Discount Antitrust Litigation. USDC, Eastern District of New York, No. 1:05-MD-1720 (JG)(JO).
34. In Re: Tobacco Litigation (Individual Personal Injury Cases). Circuit Court, Ohio County, West Virginia, No. 00-C-5000.
35. City of St. Louis, et al. v. American Tobacco Company, et al. Circuit Court, City of St. Louis, Missouri, No. 982-9652.

Exhibit 3

List of Materials Considered

Datasets and Electronic Files:

South Carolina Fee For Service, State Health Plan, and HMO claims data produced by plaintiff (including eligibility data).

Cover letters, data dictionaries, correspondence between plaintiff and defense counsel regarding data production.

Depositions:

Millard Clinton Trott
Delfin Valite
Eugene F. Smith
Andrew W. Hedgepath
Balbir Coshal
William H. Bragdon
Rosen J. Lawsin
Glenn Hooker
Anil Juneja
James Frank Riddle
Lori W. Barwick
Laurel A. Weston
Sallie Amanda Carter
Kathy Marie Waggett
Kenneth G. Kassebaum
Ricardo J. Fermo
Evan L. Vogel
Michael J. Wood
Paul P. Lowe
James L. Elmore

Books, Articles and Papers:

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Sernyak MJ, Leslie DL, Alarcon RD et al. *Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia*, Am. J. Psychiatry 2002, 159:561-566.

Lieberman, J., et al., *Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia (CATIE)*, New Eng. J. Med., 353(12) (Sept. 2005).

Rosenheck, R., et al., *Cost Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia*, Am. J. of Psych., 163(12) (2006).

Rosenheck RA, et al. (2006), Supplemental table A, Patient characteristics at the time of random assignment by initial treatment, available at <http://ajp.psychiatryonline.org/>.

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Pleadings, Court Filings and Discovery:

Second Amended Complaint.

July 1, 2009 Order (a ruling on Janssen's request to take doctor depositions).

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Expert Report of Laura M. Plunkett, Ph.D., DABT, July 7, 2009.

Declaration of Lon S. Schneider, M.D., July 10, 2009,

Expert Report of John Abramson, M.D., July 10, 2009.

Supplemental Expert Report of Laura M. Plunkett, Ph.D., DABT; August 4, 2010.

Other documents:

Janssen November 10, 2003 mailing to health care providers.

Risperdal package inserts and drug labels.

Protocol, Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia (Rev. Oct. 15, 2001).

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Dont Recall	Dont Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Have you ever treated pediatric patients, meaning patients 0 through 12 years old?	19		1												20	95%
Have you ever treated adolescent patients, meaning patients 13 through 17 years old?	20														20	100%
Have you ever treated non-geriatric adult patients, meaning patients 18 through 64 years old.	20														20	100%
Have you ever treated geriatric patients, meaning patients 65 or older?	19		1												20	95%
Have you ever prescribed Risperdal® for any of your patients?	20														20	100%
Have you ever prescribed Risperdal® for a pediatric patient?	14		2		1	3									20	70%
For an adolescent patient?	14		2			4									20	70%
For a non-geriatric adult patient?	20														20	100%
For a geriatric patient?	16	1	2			1									20	85%
For a South Carolina Medicaid patient?	20														20	100%
For a South Carolina State Health Plan patient?	8	3	2			2	5								20	55%
Have you ever prescribed antipsychotic medications other than Risperdal® for any of your patients?	20														20	100%
Have you ever prescribed antipsychotic medications other than Risperdal® for a pediatric patient?	14	2	2		1	1									20	80%
For an adolescent patient?	17	1	1			1									20	90%
For a non-geriatric adult patient?	20														20	100%
For a geriatric patient?	17	2	1												20	95%
Have you ever prescribed first generation antipsychotics for any of your patients?	20														20	100%
Have you ever prescribed second generation antipsychotics other than Risperdal® for any of your patients?	19													1	20	95%
In your experience, is Risperdal® generally effective for treating the positive symptoms of schizophrenia?	20														20	100%
In your experience, is Risperdal® generally effective for treating the negative symptoms of schizophrenia?	13	1	1				2						3		20	70%

R. 8414

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
In your experience, do patients who take Risperdal® have better overall outcomes more frequently than patients who take a first generation antipsychotic?	12	1	3				1	2					1		20	65%
In your practice, for patients requiring antipsychotic medications, do you generally prefer to use first generation antipsychotics, or, second generation antipsychotics? [Percent shown is for "second generation".]								1	1	14			4		20	70%
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience extrapyramidal and anticholinergic side effects than patients who take second	20														20	100%
generation antipsychotics, such as Haldol and Thorazine, more likely to experience tardive dyskinesia than patients who take second generation antipsychotics?	18						2								20	90%
In your experience, does Risperdal® typically have a more moderate side effect profile than first generation antipsychotics?	14						1	4					1		20	70%
In your experience, is Risperdal® typically better tolerated than first generation antipsychotics?	17							1					2		20	85%
In your experience with antipsychotic medications, are both efficacy and tolerability important considerations in the choice of which antipsychotic to prescribe?	19												1		20	95%
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	19													1	20	95%
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not	19						1								20	95%
In your experience, are patients who consistently take their antipsychotic medications less likely, to require costly follow-up treatment, such as emergency room care, than patients who do not	17						1							2	20	85%
In your experience, does increased patient compliance with antipsychotic prescriptions result in overall conservation, as opposed to consumption, of healthcare resources?	17		1				2								20	85%
In your experience, does the use of Risperdal® typically conserve healthcare resources as compared to first generation antipsychotics?	9		1				4	2					4		20	45%
In your experience, does increased patient compliance with antipsychotic prescriptions typically decrease the human consequences of psychiatric illnesses?	20														20	100%
In your experience, does compliance taking antipsychotic medications typically make patients less likely to experience recurrence of	20														20	100%
Less likely to be violent?	17	1					2								20	90%

R. 8415

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Dont Recall	Dont Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Less likely to be an extreme burden on family members?	20														20	100%
Less likely to experience worsening of their conditions?	19						1								20	95%
Overall, in your experience, is Risperdal® a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	19												1		20	95%
Overall, in your experience, is Risperdal® a safer and more effective medication for treating schizophrenia and other psychotic disorders than the first generation medications?	11		1				3	2			1	2			20	55%
In your experience, are there circumstances when the off-label use of medications is appropriate?	20														20	100%
In your experience, is it fair to say that off-label use of medications is not an uncommon practice?	18												2		20	90%
In your experience, are there circumstances when the off-label use of antipsychotic medications is appropriate?	18			1									1		20	90%
In your experience, is it fair to say that off-label use of antipsychotic medications is not an uncommon practice?	18						1						1		20	90%
Have you ever prescribed a medication for off-label use?	19					1									20	95%
In those circumstances, did you expect your patients to benefit from the off-label use of the medication?	19													1	20	95%
Have you ever prescribed an antipsychotic medication for off-label use?	18		1			1									20	90%
Have you ever prescribed Risperdal® for off-label use?	16	2	1			1									20	90%
Did you expect your patients to benefit from the off-label use of Risperdal®?	18													2	20	90%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in children?			19			1									20	0%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in geriatric patients?			19										1		20	0%
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® at all?			19										1		20	0%
Have you ever received or seen any communication from Janssen promoting the off-label use of Risperdal®?			20												20	0%
Based on your training and experience, is it common for medications to have both benefits and risks?	20														20	100%

R. 8416

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Don't Recall	Don't Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Based on your training and experience, is it your understanding that all antipsychotic medications – both first generation and second generation - have potential side effects?	20														20	100%
Are you aware of an association between antipsychotic medications and weight gain?	20														20	100%
Are you aware of an association between antipsychotic medications and risk of diabetes?	19													1	20	95%
When you prescribe antipsychotic medications, including Risperdal®, do you monitor your patients for weight gain?	20														20	100%
If you see or learn of rapid weight gain in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	12		2					6							20	60%
If you see or learn of a change in blood glucose level in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	12		2					6							20	60%
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and weight gain?	20														20	100%
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and diabetes?	20														20	100%
Would you agree that the 2004 package insert for Risperdal® incorporated a class warning of hyperglycemia and diabetes?	20														20	100%
Were you aware of an association between second generation antipsychotics, and weight gain or a risk of diabetes, prior to the 2004 revision to the package insert for Risperdal®?	16					2	2								20	80%
Did the change to the package insert for Risperdal® in 2004 cause you to change the circumstances in which you prescribe Risperdal® for patients?	2	1	15				1						1		20	15%
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal® that are provided on the package insert?			19			1									20	0%
Has any Janssen sales representative ever represented to you that there is no association between Risperdal® and increased mortality in the elderly?			20												20	0%
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal® use?			19											1	20	0%
Have you ever seen this letter before? [November 10, 2003]	1	3	2			10	4								20	20%
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	1		4			1	1							13	20	5%

Exhibit 4

Deposition Questions and Responses of 20 Doctors

Question	Yes	Probably Yes	No	Probably No	Refills Only	Dont Recall	Dont Know	It Depends	First Generation Antipsychotic	Second Generation Antipsychotic	More Effective	Safer	Other Answers	Not Asked	Total	Percent Responding "Yes" or "Probably Yes"
Did it cause you to change your choice of which antipsychotic to prescribe?		1	4										1	14	20	5%
Did it cause you to change your methods for monitoring for side effects in your patients on antipsychotic medications?	1		4			1								14	20	5%
Prior to the deposition today, have you had any communications with any of the attorneys for the Plaintiff in this case?	3		15											2	20	15%

See Wecker electronic file summary.deps.xls.

R. 8418

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Have you ever treated pediatric patients, meaning patients 0 through 12 years old?	95.0%	(77.2% , 99.0%)
Have you ever treated adolescent patients, meaning patients 13 through 17 years old?	100.0%	(85.1% , 100.0%)
Have you ever treated non-geriatric adult patients, meaning patients 18 through 64 years old.	100.0%	(85.1% , 100.0%)
Have you ever treated geriatric patients, meaning patients 65 or older?	95.0%	(77.2% , 99.0%)
Have you ever prescribed Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed Risperdal® for a pediatric patient?	70.0%	(48.5% , 86.1%)
For an adolescent patient?	70.0%	(48.5% , 86.1%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	85.0%	(64.4% , 95.0%)
For a South Carolina Medicaid patient?	100.0%	(85.1% , 100.0%)
For a South Carolina State Health Plan patient?	55.0%	(33.7% , 74.3%)
Have you ever prescribed antipsychotic medications other than Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed antipsychotic medications other than Risperdal® for a pediatric patient?	80.0%	(59.4% , 93.1%)
For an adolescent patient?	90.0%	(71.3% , 98.0%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	95.0%	(77.2% , 99.0%)
Have you ever prescribed first generation antipsychotics for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed second generation antipsychotics other than Risperdal® for any of your patients?	95.0%	(77.2% , 99.0%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, is Risperdal® generally effective for treating the positive symptoms of schizophrenia?	100.0%	(85.1% , 100.0%)
In your experience, is Risperdal® generally effective for treating the negative symptoms of schizophrenia?	70.0%	(48.5% , 86.1%)
In your experience, do patients who take Risperdal® have better overall outcomes more frequently than patients who take a first generation antipsychotic?	65.0%	(43.6% , 82.2%)
In your practice, for patients requiring antipsychotic medications, do you generally prefer to use first generation antipsychotics, or, second generation antipsychotics? [Percent shown is for "second generation".]	70.0%	(48.5% , 86.1%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience extrapyramidal and anticholinergic side effects than patients who take second generation antipsychotics?	100.0%	(85.1% , 100.0%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience Tardive Dyskinesia than patients who take second generation antipsychotics?	90.0%	(71.3% , 98.0%)
In your experience, does Risperdal® typically have a more moderate side effect profile than first generation antipsychotics?	70.0%	(48.5% , 86.1%)
In your experience, is Risperdal® typically better tolerated than first generation antipsychotics?	85.0%	(64.4% , 95.0%)
In your experience with antipsychotic medications, are both efficacy and tolerability important considerations in the choice of which antipsychotic to prescribe?	95.0%	(77.2% , 99.0%)
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely, to require costly follow-up treatment, such as emergency room care, than patients who do not consistently take their medications?	85.0%	(64.4% , 95.0%)
In your experience, does increased patient compliance with antipsychotic prescriptions result in overall conservation, as opposed to consumption, of healthcare resources?	85.0%	(64.4% , 95.0%)
In your experience, does the use of Risperdal® typically conserve healthcare resources as compared to first generation antipsychotics?	45.0%	(25.7% , 66.3%)

R. 8420

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, does increased patient compliance with antipsychotic prescriptions typically decrease the human consequences of psychiatric illnesses?	100.0%	(85.1% , 100.0%)
In your experience, does compliance taking antipsychotic medications typically make patients less likely to experience recurrence of psychosis?	100.0%	(85.1% , 100.0%)
Less likely to be violent?	90.0%	(71.3% , 98.0%)
Less likely to be an extreme burden on family members?	100.0%	(85.1% , 100.0%)
Less likely to experience worsening of their conditions?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a safer and more effective medication for treating schizophrenia and other psychotic disorders than the first generation medications?	55.0%	(33.7% , 74.3%)
In your experience, are there circumstances when the off-label use of medications is appropriate?	100.0%	(85.1% , 100.0%)
In your experience, is it fair to say that off-label use of medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
In your experience, are there circumstances when the off-label use of antipsychotic medications is appropriate?	90.0%	(71.3% , 98.0%)
In your experience, is it fair to say that off-label use of antipsychotic medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
Have you ever prescribed a medication for off-label use?	95.0%	(77.2% , 99.0%)
In those circumstances, did you expect your patients to benefit from the off-label use of the medication?	95.0%	(77.2% , 99.0%)
Have you ever prescribed an antipsychotic medication for off-label use?	90.0%	(71.3% , 98.0%)
Have you ever prescribed Risperdal® for off-label use?	90.0%	(71.3% , 98.0%)
Did you expect your patients to benefit from the off-label use of Risperdal®?	90.0%	(71.3% , 98.0%)

R. 8421

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in children?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in geriatric patients?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® at all?	0.0%	(0.0% , 11.9%)
Have you ever received or seen any communication from Janssen promoting the off-label use of Risperdal®?	0.0%	(0.0% , 11.9%)
Based on your training and experience, is it common for medications to have both benefits and risks?	100.0%	(85.1% , 100.0%)
Based on your training and experience, is it your understanding that all antipsychotic medications -- both first generation and second generation -- have potential side effects?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and weight gain?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and risk of diabetes?	95.0%	(77.2% , 99.0%)
When you prescribe antipsychotic medications, including Risperdal®, do you monitor your patients for weight gain?	100.0%	(85.1% , 100.0%)
If you see or learn of rapid weight gain in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
If you see or learn of a change in blood glucose level in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and weight gain?	100.0%	(85.1% , 100.0%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and diabetes?	100.0%	(85.1% , 100.0%)
Would you agree that the 2004 package insert for Risperdal® incorporated a class warning of hyperglycemia and diabetes?	100.0%	(85.1% , 100.0%)
Were you aware of an association between second generation antipsychotics, and weight gain or a risk of diabetes, prior to the 2004 revision to the package insert for Risperdal®?	80.0%	(59.4% , 93.1%)
Did the change to the package insert for Risperdal® in 2004 cause you to change the circumstances in which you prescribe Risperdal® for patients?	15.0%	(5.0% , 35.6%)

Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal® that are provided on the package insert?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever represented to you that there is no association between Risperdal® and increased mortality in the elderly?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal® use?	0.0%	(0.0% , 11.9%)
Have you ever seen this letter before? [November 10, 2003]	20.0%	(6.9% , 40.6%)
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	5.0%	(1.0% , 22.8%)
Did it cause you to change your choice of which antipsychotic to prescribe?	5.0%	(1.0% , 22.8%)
Did it cause you to change your methods for monitoring for side effects in your patients on antipsychotic medications?	5.0%	(1.0% , 22.8%)
Prior to the deposition today, have you had any communications with any of the attorneys for the Plaintiff in this case?	15.0%	(5.0% , 35.6%)

See Wecker electronic file, confidence_limits.nb.

Exhibit 6

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims
Antipsychotic Drugs and Alleged Side Effects

Excess Side Effect Risk
Relative to Risperdal

		Alleged Side Effect		
		Diabetes	Metabolic Adverse Events	Increased Prolactin Secretion
Antipsychotic Drug Prescribed:	1st Generation	1.62% (*)	1.46% (*)	3.64% (*)
	Other 2nd Generation	2.33% (*)	4.47% (*)	1.82% (*)
	Untreated	1.29% (*)	0.99% (*)	2.22% (*)

Notes: 1. Percent of Patients with First Alleged Side Effect Diagnosis within 36 Months from First Antipsychotic Drug Prescription.

2. Treated patients excluded if prescribed more than one type of antipsychotic drug; if less than 12 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; if diagnosis of alleged side effect occurs prior to their first antipsychotic drug prescription; or if less than 36 months of uninterrupted eligibility following their first antipsychotic drug prescription.

3. Untreated patients excluded if less than 48 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; or if diagnosis of alleged side effect occurs prior to 36 months before their first antipsychotic drug prescription.

4. Asterisk (*) indicates value is statistically significantly different from Risperdal value at 95% confidence level.

See Wecker electronic files side.effect.diab.lst, side.effect.mae.lst, and side.effect.prlc.lst.

Exhibit 7

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims
Antipsychotic Drugs and Alleged Side Effects
Data as of November 10, 2003

Excess Side Effect Risk
Relative to Risperdal

		Alleged Side Effect	
		Diabetes	Metabolic Adverse Events
Antipsychotic Drug Prescribed:	1st Generation	1.17% (*)	0.65%
	Other 2nd Generation	1.84% (*)	3.02% (*)
	Untreated	1.32% (*)	0.78%

Notes: 1. Percent of Patients with First Alleged Side Effect Diagnosis within 36 Months from First Antipsychotic Drug Prescription.

2. Treated patients excluded if prescribed more than one type of antipsychotic drug; if less than 12 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; if diagnosis of alleged side effect occurs prior to their first antipsychotic drug prescription; or if less than 36 months of uninterrupted eligibility following their first antipsychotic drug prescription.

3. Untreated patients excluded if less than 48 months of uninterrupted eligibility prior to their first antipsychotic drug prescription; or if diagnosis of alleged side effect occurs prior to 36 months before their first antipsychotic drug prescription.

4. Asterisk (*) indicates value is statistically significantly different from Risperdal value at 95% confidence level.

5. The November 10, 2003 mailing did not discuss increased prolactin secretion.

See Wecker electronic files side.effect.diab.lst, side.effect.mae.lst, and side.effect.prlc.lst.

Exhibit 8

Analysis of South Carolina Fee for Service, State Health Plan, and HMO Claims Antipsychotic Drugs and Time to Discontinuation

Average Days to Discontinuation

		Patient Count	"Treatment Discontinuation" Defined as X or More Days without Drug Supply		
			X=15 Days	X=30 Days	X=60 Days
Antipsychotic Drug Prescribed:	Risperdal	27,197	125.59	166.00	211.23
	Perphenazine	976	82.70 (*)	106.50 (*)	132.84 (*)
	Haldol	7,071	77.86 (*)	98.96 (*)	130.43 (*)
	Other 1st Generation	18,531	34.81 (*)	44.40 (*)	58.14 (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

Notes: Patients are followed up for 18 months.

Patients excluded if less than 12 months of uninterrupted eligibility prior to start of treatment, or
less than 18 months of uninterrupted eligibility after start of treatment.

See Wecker electronic file time_to_discontinuation.lst.

Exhibit 9

South Carolina Fee for Service, State Health Plan, and HMO Claims Data
Antipsychotic Prescriptions by Month

Month and Year	Risperdal	First Generation Antipsychotics	Other Second Generation Antipsychotics	Total	Percent Risperdal
Jan 2003	6,945	3,798	13,034	23,777	29.21%
Feb 2003	6,518	3,503	12,415	22,436	29.05%
Mar 2003	7,068	3,606	13,569	24,243	29.15%
Apr 2003	7,254	3,696	13,742	24,692	29.38%
May 2003	7,199	3,601	14,082	24,882	28.93%
Jun 2003	6,906	3,464	13,916	24,286	28.44%
Jul 2003	7,179	3,669	14,593	25,441	28.22%
Aug 2003	7,111	3,564	14,341	25,016	28.43%
Sep 2003	7,131	3,490	14,820	25,441	28.03%
Oct 2003	7,603	3,558	15,278	26,439	28.76%
Nov 2003	6,809	3,230	14,067	24,106	28.25%
Dec 2003	7,648	3,644	15,918	27,210	28.11%
Jan 2004	7,073	3,272	14,546	24,891	28.42%
Feb 2004	6,954	3,107	14,254	24,315	28.60%
Mar 2004	7,811	3,505	16,540	27,856	28.04%
Apr 2004	7,653	3,336	15,607	26,596	28.78%
May 2004	7,429	3,177	15,276	25,882	28.70%
Jun 2004	7,884	3,345	16,177	27,406	28.77%
Jul 2004	7,721	3,266	15,901	26,888	28.72%
Aug 2004	7,886	3,273	16,447	27,606	28.57%
Sep 2004	7,764	3,234	16,312	27,310	28.43%
Oct 2004	7,809	3,233	16,184	27,226	28.68%
Nov 2004	8,047	3,314	16,852	28,213	28.52%
Dec 2004	8,090	3,373	17,011	28,474	28.41%
Jan 2005	7,460	3,094	16,041	26,595	28.05%
Feb 2005	7,199	2,947	15,516	25,662	28.05%
Mar 2005	7,975	3,266	17,410	28,651	27.83%
Apr 2005	7,748	3,152	16,995	27,895	27.78%
May 2005	7,970	3,175	17,483	28,628	27.84%
Jun 2005	7,918	3,300	17,641	28,859	27.44%
Jul 2005	7,549	2,970	16,632	27,151	27.80%
Aug 2005	8,625	3,296	18,350	30,271	28.49%
Sep 2005	8,204	3,294	17,616	29,114	28.18%
Oct 2005	8,336	3,246	17,614	29,196	28.55%
Nov 2005	8,471	3,221	18,037	29,729	28.49%
Dec 2005	8,227	3,108	17,102	28,437	28.93%

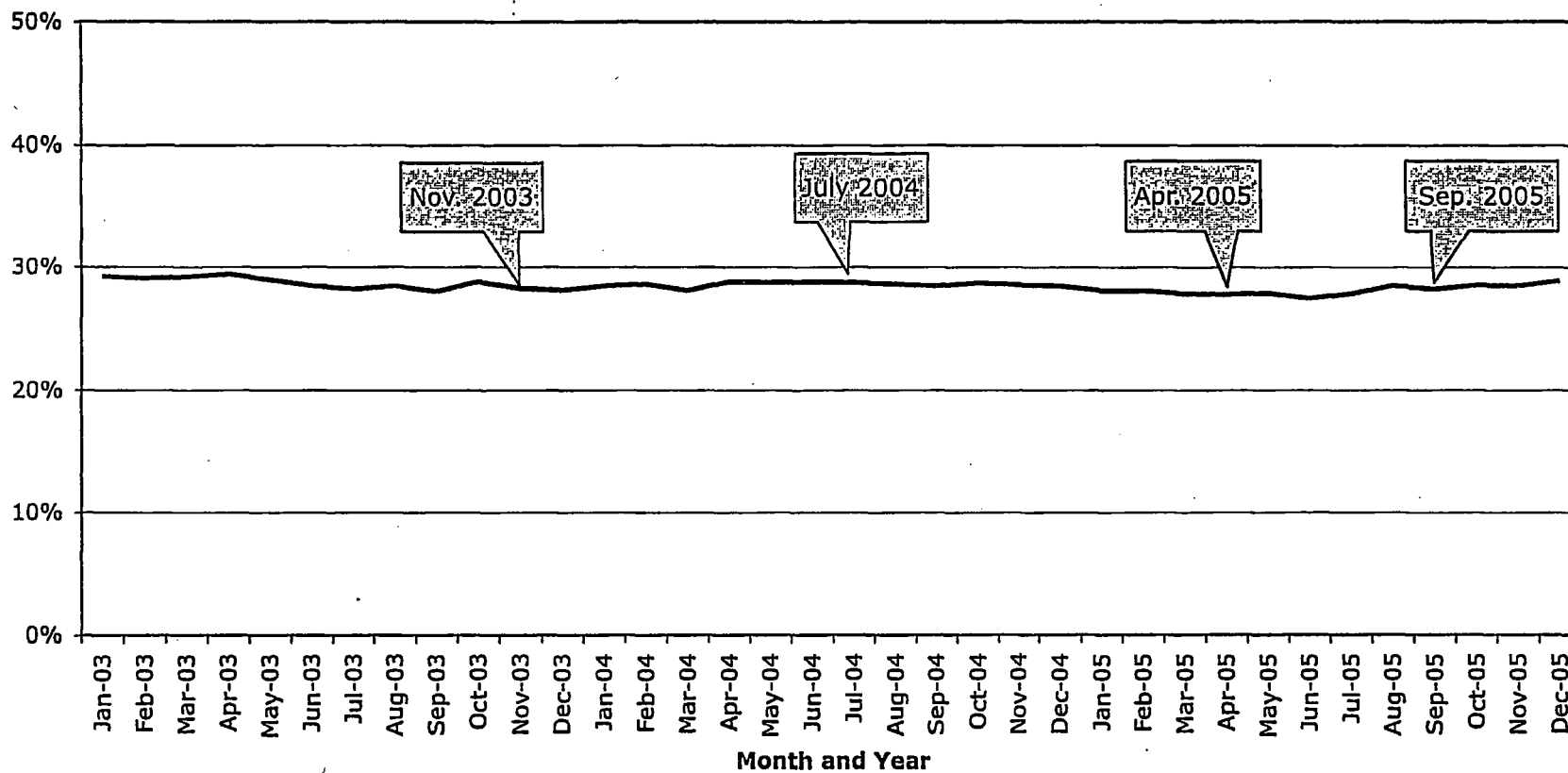
Notes: 1. Percent=Risperdal/Total x 100

2. Claims counts are net of reversals.

See Wecker electronic file risp.percent.lst.

Exhibit 9 (cont.)

**South Carolina Fee for Service, State Health Plan, and HMO Claims Data
Percent Risperdal Prescriptions by Month**



Notes: Percent=Risperdal/(Antipsychotic Prescriptions Total) x 100

November 2003: Janssen's November 10, 2003 mailing to health care providers.

July 2004: Janssen's "correction" letter.

April 2005: FDA advisory.

September 2005: publication of the CATIE trial results in N Engl J Med.

See Wecker electronic file risp.percent.lst.

Exhibit 2

Report of William E. Wecker, Ph.D., December 3, 2010
Notes for Electronic Files

Step	Inputs	Program	Outputs	Notes
1	claimsdata/SC-ALL-VOL.2/drugs95.csv ... claimsdata/SC-ALL-VOL.2/drugs07.csv claimsdata/SC-ALL-VOL.9/Data dictionary Updated.docx	dir01/readin_data.shp.drugs.95_07.sas	sasdata/drugs95.sas7bdat ... sasdata/drugs07.sas7bdat	Create annual SAS datasets of SHP drug claims for 1995-2007.
2	claimsdata/SC-ALL-VOL.12/SC-ALL-12 part 1.xls claimsdata/SC-ALL-VOL.12/SC-ALL-12 part 2.xls claimsdata/SC-ALL-VOL.15/SC-ALL-15 - xls data.xls	Microsoft Excel - open file in Excel, save as CSV (comma delimited) file	sasdata/SC_ALL_12_part_1.csv sasdata/SC_ALL_12_part_2.csv sasdata/SC_ALL_15_data.csv	Convert SHP prescriber names lookup tables from spreadsheets to text files.
3	sasdata/SC_ALL_12_part_1.csv sasdata/SC_ALL_12_part_2.csv sasdata/SC_ALL_15_data.csv	dir02/readin_data.shp.12_15.sas	sasdata/prescriber_12_1.sas7bdat sasdata/prescriber_12_2.sas7bdat sasdata/prescriber_15.sas7bdat	Convert SHP prescriber names lookup tables to SAS datasets.
4	sasdata/drugs00.sas7bdat ... sasdata/drugs07.sas7bdat	dir03/prescribers_summary.shp.sas	sasdata/shp_prescribers.sas7bdat	Create a summary of SHP APD-prescribing physicians.
5	sasdata/prescriber_12_1.sas7bdat sasdata/prescriber_12_1.sas7bdat sasdata/prescriber_15.sas7bdat	dir04/name_multiplicitiy_fix.shp.sas	sasdata/shp_prescriber_names.sas7bdat	Combine all SHP prescribers with the same prescriber ID.
6	sasdata/shp_prescribers.sas7bdat sasdata/shp_prescriber_names.sas7bdat	dir05/prescribers_printlist.shp.sas	sasdata/prescribers_printlist.shp.csv	Combine names with SHP prescriber data. Create summary of SHP APD-prescribing physicians
7	claimsdata/SC-ALL-VOL.6/clms_new1994 ... claimsdata/SC-ALL-VOL.4/clms_new2007 claimsdata/SC-ALL-VOL.4/Data Dictionary for Medicaid Claims and Eligibility Files.xls	dir06/readin_data.ffi.claims.94_07.sas	sasdata/clms_new1994.sas7bdat ... sasdata/clms_new2007.sas7bdat	Create annual SAS datasets of FFS claims for 1994-2007.
8	claimsdata/SC-ALL-VOL.17/prov2001 ... claimsdata/SC-ALL-VOL.17/prov2007 claimsdata/SC-ALL-VOL.17/Provider and Prescriber Data Dictionary (Updated 10 Nov).xls	dir07/readin_data.ffi.prov.sas	sasdata/prov2001.sas7bdat ... sasdata/prov2007.sas7bdat	Create annual SAS datasets of FFS prescription provider data for 2001-2007

R. 8430

Step	Inputs	Program	Outputs	Notes
9	claimsdata/SC-ALL-VOL.23/admding_procdates1994 ... claimsdata/SC-ALL-VOL.23/admding_procdates2007 claimsdata/SC-ALL-VOL.23/Admit Diag - Secondary Proc Date - License num Data Dictionary.xls	dir08/readin_admding_procdates.ffs.sas	sasdata/admding_procdates1994.sas7bdat ... sasdata/admding_procdates2007.sas7bdat	Create annual datasets of FFS admit diagnosis/procedure date data
10	sasdata/clms_new2001.sas7bdat ... sasdata/clms_new2007.sas7bdat sasdata/prov2001.sas7bdat ... sasdata/prov2007.sas7bdat	dir09/create_prescriptions_dataset.ffs.sas	sasdata/ffs_prescriptions_01_07.sas7bdat	Combine FFS claim data and FFS provider data for 2001-2007.
11	sasdata/ffs_prescriptions_01_07.sas7bdat	dir10/prescribers_printlist.ffs.fixnpi.sas	sasdata/ffs_prescribers.sas7bdat sasdata/prescribers_printlist.ffs.fixnpi.csv	Reformat prescriber IDs. Create summary of FFS APD-prescribing physicians
12		dir12/rand_101.sas	dir12/rand_101.lst	Create list of 101 random numbers.
13	sasdata/prescribers_printlist.shp.csv sasdata/prescribers_printlist.ffs.fixnpi.csv dir12/rand_101.lst http://www.llr.state.sc.us/pol/medical/	Microsoft Excel Adobe Acrobat	dir13/sample list.xls dir13/sample 20 info.pdf, school list.pdf, specialty code list.pdf, profession code list.pdf, basis code list.pdf	Create doctor sample of 20 (Report §§15- 18). Add information from South Carolina Board of Medical Examiners.
14		Microsoft Excel	dir14/script.xls	Create list of deposition questions.
15	dir14/script.xls	Stat/Transfer	sasdata/script.sas7bdat	Convert from Excel to SAS (deposition questions).
16	deptxt/ 20 deposition transcript files *.ptx	RealLegal E-transcript Viewer	deptxt/ 20 text files *.txt	Convert deposition transcripts from ptx to text format.
17	deptxt/ 20 text files *.txt	Microsoft Excel	decoded/ 20 Excel files *_coded.xls	Convert deposition transcripts from text to Excel format and code deponent responses.
18	decoded/ 20 Excel files *_coded.xls sasdata/script.sas7bdat	dir15/sum.deps.1_20.sas	dir15/summary.deps.xls sasdata/summary_deps.sas7bdat	Summarize deponent responses. Create data sets for further analysis, reference, and Exhibits (Report Ex. 4).
19	sasdata/summary_deps.sas7bdat sasdata/script.sas7bdat	dir16/sc.md.dep.data.sas	dir16/sc.md.dep.data.xls	Prepare input data for Mathematica 7 program.
20	dir16/sc.md.dep.data.xls	Mathematica 7 dir16/confidence_limits.nb	dir16/confidence_limits.nb	Estimate percent responding "Yes" or "Probably Yes" and calculate confidence limits (Report Ex. 5).

Step	Inputs	Program	Outputs	Notes
21	sasdata/ffs_prescribers.sas7bdat	dir20/create_ffs_top_101.sas	sasdata/ffs_top_101_sample.sas7bdat	Create list of top 101 FFS APD prescribers
22	sasdata/shp_prescribers.sas7bdat sasdata/ffs_prescribers.sas7bdat sasdata/ffs_top_101_sample.sas7bdat sasdata/prescriber_12_1.sas7bdat sasdata/prescriber_12_1.sas7bdat sasdata/prescriber_15.sas7bdat	dir21/ffs_top_101.apd_pct.sas	dir21/ffs_top_101.apd_pct.lst	Calculate percentage of prescriptions written in FFS and SHP by top 101 FFS APD prescribers and number of top 101 FFS APD prescribers who also prescribed under SHP (Report J21)
23	claimsdata/SC-ALL-VOL.7/clms_hmo1997 ... claimsdata/SC-ALL-VOL.7/clms_hmo2007 claimsdata/SC-ALL-VOL.4/Data Dictionary for Medicaid Claims and Eligibility Files.xls	dir22/readin_data.hmo.claims.97_07.sas	sasdata/clms_hmo1997.sas7bdat ... sasdata/clms_hmo2007.sas7bdat	Create annual SAS datasets of HMO claims for 1997-2007.
24	claimsdata/SC-ALL-VOL.23/admdiag_procdates_hmo1997 ... claimsdata/SC-ALL-VOL.23/admdiag_procdates_hmo2007 claimsdata/SC-ALL-VOL.23/Admit Diag - Secondary Proc Date - License num Data Dictionary.xls	dir23/readin_admdiag_procdates.hmo.sas	sasdata/ admdiag_procdates_hmo1997.sas7bdat, ... admdiag_procdates_hmo2007.sas7bdat	Create annual datasets of HMO admit diagnosis/procedure date data for 1997-2007.
25	sasdata/drugs95.sas7bdat ... sasdata/drugs07.sas7bdat	dir24/create_drug_stratum.shp.sas	sasdata/shp_drug_stratum.sas7bdat	Create drug stratum for SHP patients.
26	claimsdata/SC-ALL-VOL.25/Disc 1/claims95.sas7bdat ... claimsdata/SC-ALL-VOL.25/Disc 5/claims07.sas7bdat sasdata/shp_drug_stratum.sas7bdat	dir25/create_claims_dataset.shp.sas	sasdata/shp_claims_dataset_9507.sas7bdat	Create SAS dataset of SHP claims for 1995-2007
27	sasdata/drugs95.sas7bdat ... sasdata/drugs07.sas7bdat sasdata/shp_drug_stratum.sas7bdat sasdata/shp_prescriber_names.sas7bdat	dir26/create_drug_dataset.shp.sas	sasdata/shp_drug_dataset_9507.sas7bdat	Create SAS dataset of SHP prescription claims for 1995-2007
28	claimsdata/SC-ALL-VOL.2/mental_aps.csv sasdata/shp_drug_stratum.sas7bdat claimsdata/SC-ALL-VOL.9/Data dictionary Updated.docx	dir27/create_mental_dataset.shp.sas	sasdata/shp_mental_dataset_0207.sas7bdat	Create SAS dataset of SHP mental claims for 2002-2007
29	sasdata/shp_drug_dataset_9507.sas7bdat sasdata/shp_claims_dataset_9507.sas7bdat sasdata/shp_mental_dataset_0207.sas7bdat	dir28/create_age_stratum.shp.sas	sasdata/shp_age_stratum.sas7bdat	Create age stratum for SHP patients

Step	Inputs	Program	Outputs	Notes
30	sasdata/shp_drug_dataset_9507.sas7bdat sasdata/shp_age_stratum.sas7bdat	dir29/create_apd_dataset.shp.sas	sasdata/shp_apd_dataset_9507.sas7bdat	Create SAS dataset of SHP APD prescription claims for 1995-2007
31	claimsdata/SC-ALL-VOL.9/elig2.sas7bdat	dir30/create_eligibility_data.shp.sas dir30/elig_macro.sas	sasdata/shp_eligibility_bymonth.sas7bdat	Create SAS dataset of SHP eligibility by month and year
32	sasdata/clms_new1994.sas7bdat ... sasdata/clms_new2007.sas7bdat	dir31/create_drug_stratum.ffs.sas	sasdata/ffs_drug_stratum.sas7bdat	Create drug stratum for FFS patients.
33	sasdata/clms_new1994.sas7bdat ... sasdata/clms_new2007.sas7bdat sasdata/admdiag_procdates1994.sas7bdat ... sasdata/admdiag_procdates2007.sas7bdat sasdata/ffs_drug_stratum.sas7bdat	dir32/create_claims_dataset.ffs.sas	sasdata/ffs_claims_dataset_9407.sas7bdat	Create SAS dataset of FFS claims for 1994-2007
34	sasdata/ffs_claims_dataset_9407.sas7bdat	dir33/create_age_stratum.ffs.sas	sasdata/ffs_age_stratum.sas7bdat	Create age stratum for FFS patients
35	sasdata/ffs_claims_dataset_9407.sas7bdat sasdata/ffs_age_stratum.sas7bdat	dir34/create_apd_dataset.ffs.sas	sasdata/ffs_apd_dataset_9407.sas7bdat	Create SAS dataset of FFS APD prescription claims for 1994-2007
36	claimsdata/SC-ALL-VOL.4/elg_new claimsdata/SC-ALL-VOL.4/Data Dictionary for Medicaid Claims and Eligibility Files.xls	dir35/create_eligibility_data.ffs.sas dir35/elig_macro.sas	sasdata/ffs_eligibility_bymonth.sas7bdat	Create SAS dataset of FFS eligibility by month and year
37	sasdata/clms_hmo1997.sas7bdat ... sasdata/clms_hmo2007.sas7bdat	dir36/create_drug_stratum.hmo.sas	sasdata/hmo_drug_stratum.sas7bdat	Create drug stratum for HMO patients.
38	sasdata/clms_hmo1997.sas7bdat ... sasdata/clms_hmo2007.sas7bdat sasdata/admdiag_procdates_hmo1997.sas7bdat ... sasdata/admdiag_procdates_hmo2007.sas7bdat sasdata/hmo_drug_stratum.sas7bdat	dir37/create_claims_dataset.hmo.sas	sasdata/hmo_claims_dataset_9707.sas7bdat	Create SAS dataset of HMO claims for 1997-2007
39	sasdata/hmo_claims_dataset_9707.sas7bdat	dir38/create_age_stratum.hmo.sas	sasdata/hmo_age_stratum.sas7bdat	Create age stratum for HMO patients
40	sasdata/hmo_claims_dataset_9707.sas7bdat sasdata/hmo_age_stratum.sas7bdat	dir39/create_apd_dataset.hmo.sas	sasdata/hmo_apd_dataset_9707.sas7bdat	Create SAS dataset of HMO APD prescription claims for 1997-2007

Step	Inputs	Program	Outputs	Notes
41	claimsdata/SC-ALL-VOL.10/elg_hmo claimsdata/SC-ALL-VOL.10/HMO Provider and Eligibility Data Dictionary.xls	dir40/create_eligibility_data.hmo.sas dir40/elig_macro.sas	sasdata/hmo_eligibility_bymonth.sas7bdat	Create SAS dataset of HMO eligibility by month and year
42	sasdata/shp_claims_dataset_9507.sas7bdat sasdata/shp_mental_dataset_0207.sas7bdat	dir41/ create_sideeffects_diagnosis_dataset.shp.sas	sasdata/shp_claims_se_diag.sas7bdat	Create dataset of SHP claims which contain a diagnosis of diabetes, metabolic adverse effect or increased prolactin secretion.
43	sasdata/shp_apd_dataset_9507.sas7bdat sasdata/shp_eligibility_bymonth.sas7bdat	dir42/create_eligdrug_dataset.shp.sas dir42/eligibility.sc.shp.sas	sasdata/shp_elig_1stapd.sas7bdat	Calculate number of eligibility months each SHP patient has before and after the first APD prescription.
44	sasdata/shp_apd_dataset_9507.sas7bdat sasdata/shp_eligibility_bymonth.sas7bdat	dir43/create_eligdrug_dataset.shp.031110.sas dir43/eligibility.sc.shp.031110.sas	sasdata/shp_elig_1stapd_0311.sas7bdat	Calculate number of eligibility months each SHP patient has before and after the first APD prescription as of 11/10/03.
45	sasdata/ffs_claims_dataset_9407.sas7bdat	dir44/ create_sideeffects_diagnosis_dataset.ffs.sas	sasdata/ffs_claims_se_diag.sas7bdat	Create dataset of FFS claims which contain a diagnosis of diabetes, metabolic adverse effect or increased prolactin secretion.
46	sasdata/hmo_claims_dataset_9707.sas7bdat	dir45/ create_sideeffects_diagnosis_dataset.hmo.sas	sasdata/hmo_claims_se_diag.sas7bdat	Create dataset of HMO claims which contain a diagnosis of diabetes, metabolic adverse effect or increased prolactin secretion.
47	sasdata/ffs_eligibility_bymonth.sas7bdat sasdata/hmo_eligibility_bymonth.sas7bdat	dir46/create_eligibility_data.ffs.hmo.sas	sasdata/ ffs_hmo_eligibility_bymonth.sas7bdat	Combine FFS and HMO eligibility files, eliminating duplicates.
48	sasdata/ffs_apd_dataset_9407.sas7bdat sasdata/hmo_apd_dataset_9707.sas7bdat sasdata/ffs_hmo_eligibility_bymonth.sas7bdat	dir47/create_eligdrug_dataset.ffs.hmo.sas dir47/eligibility.sc.ffs.hmo.sas	sasdata/ffs_hmo_elig_1stapd.sas7bdat	Calculate number of eligibility months each FFS or HMO patient has before and after the first APD prescription.
49	sasdata/ffs_apd_dataset_9407.sas7bdat sasdata/hmo_apd_dataset_9707.sas7bdat sasdata/ffs_hmo_eligibility_bymonth.sas7bdat	dir48/ create_eligdrug_dataset.ffs.hmo.031110.sas dir48/eligibility.sc.ffs.hmo.031110.sas	sasdata/ffs_hmo_elig_1stapd_0311.sas7bdat	Calculate number of eligibility months each FFS or HMO patient has before and after the first APD prescription as of 11/10/03.
50	sasdata/shp_claims_se_diag.sas7bdat sasdata/ffs_claims_se_diag.sas7bdat sasdata/hmo_claims_se_diag.sas7bdat sasdata/shp_elig_1stapd.sas7bdat sasdata/ffs_hmo_elig_1stapd.sas7bdat	dir49/ diabetes_sideeffects.ffs.hmo.shp.createds.sas	sasdata/ffs_hmo_shp_se_diab.sas7bdat	Create SAS dataset for diabetes side effect analysis.

Step	Inputs	Program	Outputs	Notes
51	sasdata/shp_claims_se_diag.sas7bdat sasdata/ffs_claims_se_diag.sas7bdat sasdata/hmo_claims_se_diag.sas7bdat sasdata/shp_elig_1stapd_0311.sas7bdat sasdata/ffs_hmo_elig_1stapd_0311.sas7bdat	dir50/ diabetes_sideeffects.ffs.hmo.shp.created.sas 110.sas	sasdata/ffs_hmo_shp_se_diab_0311.sas7bdat	Create SAS dataset for diabetes side effect analysis as of 11/10/03.
52	sasdata/shp_claims_se_diag.sas7bdat sasdata/ffs_claims_se_diag.sas7bdat sasdata/hmo_claims_se_diag.sas7bdat sasdata/shp_elig_1stapd.sas7bdat sasdata/ffs_hmo_elig_1stapd.sas7bdat	dir51/ metabolic_sideeffects.ffs.hmo.shp.created.sas s	sasdata/ffs_hmo_shp_se_metab.sas7bdat	Create SAS dataset for metabolic adverse effects side effect analysis.
53	sasdata/shp_claims_se_diag.sas7bdat sasdata/ffs_claims_se_diag.sas7bdat sasdata/hmo_claims_se_diag.sas7bdat sasdata/shp_elig_1stapd_0311.sas7bdat sasdata/ffs_hmo_elig_1stapd_0311.sas7bdat	dir52/ metabolic_sideeffects.ffs.hmo.shp.created.sas 031110.sas	sasdata/ ffs_hmo_shp_se_metab_0311.sas7bdat	Create SAS dataset for metabolic adverse effects side effect analysis as of 11/10/03.
54	sasdata/shp_claims_se_diag.sas7bdat sasdata/ffs_claims_se_diag.sas7bdat sasdata/hmo_claims_se_diag.sas7bdat sasdata/shp_elig_1stapd.sas7bdat sasdata/ffs_hmo_elig_1stapd.sas7bdat	dir53/ prolactin_sideeffects.ffs.hmo.shp.created.sas s	sasdata/ffs_hmo_shp_se_prlc.sas7bdat	Create SAS dataset for increased prolactin secretion side effect analysis.
55	sasdata/ffs_hmo_shp_se_diab.sas7bdat, ffs_hmo_shp_se_diab_0311.sas7bdat	dir55/side.effect.diab.sas	dir55/side.effect.diab.lst	Calculate diabetes excess risk relative to Risperdal (Report §§27-30; Ex.6-7)
56	sasdata/ffs_hmo_shp_se_metab.sas7bdat, ffs_hmo_shp_se_metab_0311.sas7bdat	dir56/side.effect.mae.sas	dir56/side.effect.mae.lst	Calculate "metabolic adverse events" excess risk relative to Risperdal (Report §§27-30; Ex.6-7)
57	sasdata/ffs_hmo_shp_se_prlc.sas7bdat	dir57/side.effect.prlc.sas	dir57/side.effect.prlc.lst	Calculate "adverse events related to increased prolactin secretion" excess risk relative to Risperdal (Report §§27-30; Ex.6-7)
58	sasdata/ffs_eligibility_bymonth.sas7bdat, hmo_eligibility_bymonth.sas7bdat, shp_eligibility_bymonth.sas7bdat, ffs_apd_dataset_9407.sas7bdat, hmo_apd_dataset_9707.sas7bdat, shp_apd_dataset_9507.sas7bdat	dir58/time_to_discontinuation.sas Macros: runlength01.sas, eligibility.sc.sas, ttestwil.sas, finaltable.sas	dir58/time_to_discontinuation.lst	Analyze the comparative time to discontinuation by APD type (Report §§34-36; Ex.8)
59	sasdata/ffs_apd_dataset_9407.sas7bdat sasdata/shp_apd_dataset_9507.sas7bdat sasdata/hmo_apd_dataset_9707.sas7bdat	dir59/risp.percent.sas	dir59/risp.percent.lst	Calculate number of Risperdal prescriptions as a percentage of all antipsychotic prescriptions by month from Jan. 2003–Dec. 2005 (Report §§37-41; Ex.9)

Step	Inputs	Program	Outputs	Notes
60	dir15/summary.deps.xls dir16/confidence_limits.nb dir55/side.effect.diab.lst dir56/side.effect.mae.lst dir57/side.effect.pric.lst dir58/time_to_discontinuation.lst dir59/risp.percent.lst	Microsoft Excel	dir60/exhibits 101203.xls	Create Exhibits 4-9.
61		Microsoft Excel	dir61/eight studies patient counts.xls	Calculate number of patients analyzed in 8 studies cited in Janssen's November 10, 2003 mailing (Report J43).
62			dir62/Walsh 2004.pdf	Walsh, Bruce, <i>Multiple Comparisons: Bonferroni Corrections and False Discovery Rates</i> , Lecture notes for EEB 581, 2004 (Report fn. 19).

R. 8436

EXHIBIT B

JANSSEN



PHARMACEUTICA INC.

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca - Seroquel® (quetiapine)
Bristol-Myers Squibb - Abilify™ (aripiprazole)
Eli Lilly and Company - Zyprexa® (olanzapine)
Novartis - Clozaril® (clozapine)
Pfizer - Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research¹⁻⁶ suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

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JJRE 06838042

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D-351.5

R. 8438

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1. Buse JB, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.
2. Caro JJ, Ward A, Levinton G and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.
3. Fuller MA, Shermook KM, Secle M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.
4. Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.
5. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.
6. Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: Findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.
7. Koro GE, Fedder DO, L'Italien GJ et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.
8. Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

JJRE 06838043

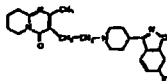
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D-351.6

RISPERDAL® (RISPERIDONE) TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8-tetrahydro-2-methyl-4H-pyrido[1,2-b]pyrimidin-4-one. Its molecular formula is $C_{24}H_{27}FN_4O$ and its molecular weight is 410.43. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are available in 0.5 mg, 1.0 mg, and 2.0 mg strengths and are light coral in color.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, silmethylsiloxane, carboxymethyl sodium hydroxide, aspartame, red ferric oxide, and peppermint.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of RISPERDAL®.

Risperidone is a selective monoamine receptor antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1A}, 5HT_{1B}, and 5HT_{1C} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma sites, and no affinity (when tested at concentrations >10⁻⁶ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB™ Orally Disintegrating Tablets are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α₁-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/mL), warfarin (10 µg/mL), and carbamazepine (10 µg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquine hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=79) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ¹⁴C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α₁-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

RISPERDAL® M-TAB™ (RISPERIDONE) ORALLY DISINTEGRATING TABLETS

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed: these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 8-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 18 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 8 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 18 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a BID schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (>20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a long-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinemia), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If antipsychotic treatment is withdrawn, antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

It signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketonacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of

JJRE 06838038

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an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular diseases (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent. In vivo, a factor of potential importance is the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when administered by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 18% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, these drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28-year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdosage.

Use in Patients With Concomitant Illnesses

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advised in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarketing testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylalanine

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains

0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone (titrated to 8 mg/day for 3 weeks), followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C8, 3A4, and 3A5, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m ² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (2.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.8 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.33-10 mg/kg or 0.4 to 6 times the maximum recommended human dose (MRHD) on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment II and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment II study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams.

regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agnathia of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL[®] therapy is unknown.

RISPERDAL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL[®] on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL[®] did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL[®] (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL [®]	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL[®]-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL[®] compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL[®]-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL[®] groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL[®] at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL[®]-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL[®]-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL[®] doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigations. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1 Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials^a

Body System/ Preferred Term	RISPERDAL [®]		Placebo (N=142)
	≤10 mg/day (N=324)	16 mg/day (N=77)	
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	25%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms ^b	17%	34%	15%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Tsushache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seronegia	1%	0%	0%

Table 1 (continued) Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials^a

Body System/ Preferred Term	RISPERDAL [®]		
	≤10 mg/day (N=324)	16 mg/day (N=77)	Placebo (N=142)
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

^a Events reported by at least 1% of patients treated with RISPERDAL[®] ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL[®] 16 mg/day and placebo are provided as well. Events for which the RISPERDAL[®] incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

^b Includes tremor, dystonia, hypokinesia, hyperkinesia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyperreflexia, akathisia, and extrapyramidal disorders. Although the incidence of "extrapyramidal symptoms" does not appear to differ for the 10 mg/day group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.8
EPS incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL[®] (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, asthenia/asthenia-increased fatigue, and increased pigmentation.

Vital Sign Changes

RISPERDAL[®] is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL[®] and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL[®] (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL[®]/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL[®]/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL[®] administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL[®] doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenic trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL[®]

During its premarketing assessment, multiple doses of RISPERDAL[®] (risperidone) were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL[®] varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL[®] who experienced an event of the type cited on at least one occasion while receiving RISPERDAL[®]. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL[®], they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. **Infrequent:** impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. **Rare:** emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. **Infrequent:** dysarthria, vertigo, stupor, paresthesia, confusion. **Rare:** aphasia, cholinergic syndrome, hypoaesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. **Infrequent:** flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. **Rare:** fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. **Infrequent:** edema, rigors, malaise, influenza-like symptoms. **Rare:** pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. **Rare:** asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation, photosensitivity. Infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis, lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal refraction.

Metabolic and Nutritional Disorders

Infrequent: hypokalemia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hypophosphatemia, hyperglycemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia. Infrequent: urinary incontinence, hematuria, dysuria. Rare: urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. Rare: arthralgia, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia, organic dysfunction, dry vagina. Infrequent: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginitis, hemerhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. Rare: normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction. Infrequent: ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on clinical reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL[®]. A causal relationship with RISPERDAL[®] has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL[®] (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL[®] has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL[®] misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL[®] (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia, and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL[®] overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL[®] overdosage, include torsade de pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bromocriptine might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL[®]. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose

RISPERDAL[®] (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL[®] was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL[®]; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 8 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use

Safety and effectiveness of RISPERDAL[®] in pediatric patients have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL[®] than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Directions for Use of RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets

RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablet on the tongue. The RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to spit or to chew the tablet.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL[®] should remain on it, the effectiveness of RISPERDAL[®] 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL[®] was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL[®], the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL[®], or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL[®] therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

HOW SUPPLIED

RISPERDAL[®] (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "1", and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-05, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-08, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-08, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-08, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL[®] (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL[®] (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either tea or lemonade.

RISPERDAL[®] M-TAB[™] (risperidone) Orally Disintegrating Tablets are etched on one side with R0.5, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, bingo card of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, bingo card of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling

RISPERDAL[®] tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

RISPERDAL[®] 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.

Keep out of reach of children.

RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).

Keep out of reach of children.

7503225

US Patent 4,804,663

Revised October 2003

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RISPERDAL[®] tablets are manufactured by:

JOLLG, Gurabo, Puerto Rico or

Janssen-Cilag, SpA, Latina, Italy

RISPERDAL[®] oral solution is manufactured by:

Janssen Pharmaceutica N.V.,

Beerse, Belgium

RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets are manufactured by:

JOLLG, Gurabo, Puerto Rico

RISPERDAL[®] tablets, RISPERDAL[®] M-TAB[™] Orally Disintegrating Tablets,

and oral solution are distributed by:

Janssen Pharmaceutica Products, L.P.,

Titussville, NJ 08560



EXHIBIT C

October 12, 2010

Page 1

TWENTY-SEVENTH JUDICIAL DISTRICT COURT

FOR THE PARISH OF ST. LANDRY
STATE OF LOUISIANA

CHARLES FOTI, ATTORNEY GENERAL
EX REL, STATE OF LOUISIANA

CIVIL DOCKET
NO. 04-C-3967-D

VERSUS

JANSSEN PHARMACEUTICA, INC., ET AL

--- CONSOLIDATED WITH ---

CHARLES FOTI, ATTORNEY GENERAL
EX REL, STATE OF LOUISIANA

NO. 04-3977-D

VERSUS

JANSSEN PHARMACEUTICA, INC., ET AL

* * *

UNOFFICIAL TRANSCRIPT OF THE
PROCEEDINGS HELD BEFORE THE HONORABLE DONALD W.
HEBERT in the 27th Judicial District Court,
Division D, Opelousas, Louisiana, on October
12th, 2010.

1 way. Is that, -- Look at the next -- the next
2 page, page 29 in your report. You say that

3 "There was no requirement that a diagnosis be
4 recorded for prescription drug claims in the
5 Medicaid claims database prior to August,
6 2005. Indeed, only 5.4 percent of Risperdal
7 prescription claims in the Medicaid database
8 have a diagnosis recorded in the period 1995
9 to 2005." Do you see that?

10 A. Sure.

11 Q. Okay. I asked you before, have you
12 ever criticized the database, the Medicaid
13 database for any reason, and you say -- I
14 understood you to say you couldn't recall. Is
15 that correct?

16 A. Yeah. I don't think this is a
17 criticism of the database.

18 Q. All right. How can you -- Do you
19 agree that you're stating there that the
20 Louisiana Medicaid database did not even have
21 a requirement that somebody put in a diagnosis
22 until the year 2005?

23 A. No, that's not true at all. It says
24 they didn't have a requirement they put it in
25 the prescription record, but they had

1 requirements they put it in other records. So
2 when I look for the diagnosis, I don't look
3 for it in the prescription record. I look for
4 it in the doctor record or the hospital record
5 or some other record. I have no problem
6 finding the diagnosis. I just don't find it
7 in the prescription record.

8 Q. All right. We can agree that the
9 prescription records for Risperdal do not
10 contain a medical diagnosis up until the year
11 2005, or a requirement of it. Can we agree
12 with that?

13 A. Right. We do.

14 Q. Okay. And your opinions on whether
15 somebody does or does not get diabetes is
16 based on diagnosis codes; correct?

17 A. Yes. For the results I presented,
18 that's what I did.

19 Q. If only 5.4 percent of the Risperdal
20 prescription claims had a diagnosis code, then
21 that means that almost 95 percent had no
22 diagnosis code at all.

23 A. That doesn't mean that. It means if
24 you look for the diagnosis in the prescription
25 claim, you won't find it there because that's

EXHIBIT D

STATE OF SOUTH CAROLINA

COURT OF COMMON PLEAS

COUNTY OF SPARTANBURG

2007-CP-42-1438

Ex Rel HENRY MCMASTER, in his capacity
as ATTORNEY GENERAL of THE STATE of
SOUTH CAROLINA,

Plaintiff,

-VS-

JANSSEN PHARMACEUTICA, INC., JANSSEN,
LP, and JOHNSON & JOHNSON, INC.,

Defendants.

TRANSCRIPT OF RECORD

May 4, 2009

Spartanburg, South Carolina

Ordered: May 4, 2009

Delivered: May 8, 2009

B E F O R E:

THE HONORABLE ROGER E. COUCH, Presiding Judge.

RECEIVED

MAY 12 2009

BY: _____

Pamela Faucette
Circuit Court Reporter

PAMELA FAUCETTE, CVR - (864) 574-9534 or (336) 260-2864

1 MR. TRAMMELL: Sure.

2 THE COURT: As to whether or not -- he'll -- he'll go
3 over the Lily procedure with you. And, if that works, fine.
4 If not, then, I would get involved then and see if we can't
5 resolve it.

6 MR. TRAMMELL: And just to be clear, I said, what I want
7 him to do was respond to my question, which he did. So, I --
8 I needed to get a response to my motion. And I think this is
9 the -- I'll talk -- talk about the procedure with him, but I
10 think this is the way forward.

11 THE COURT: All right. Let's -- let's see if that can't
12 be resolved in that fashion. And -- and I think it's a
13 workable solution. It wasn't all my idea, but it seems to be
14 working.

15 (Brief Pause)

16 THE COURT: All right. Now, there's apparently a
17 Janssen's proposed stipulated order governing discovery from
18 prescribing physicians?

19 MR. MURPHY: That's correct, Your Honor.

20 THE COURT: Yes, sir.

21 MR. MURPHY: We had -- I had had sent to Mr. Trammell a
22 proposed protocol for taking depositions of one hundred and
23 fifty (150) prescribers in the State of South Carolina.

24 THE COURT: Yes, sir.

25 MR. MURPHY: You'll recall, when we initially appeared

1 before you, we explained how we brought kind of towards --
2 would seek to move forward in regard to statistics --

3 THE COURT: Uh-huh (affirmative).

4 MR. MURPHY: --- atypical statistics and the like and we
5 identified that procedure.

6 Mr. Trammell responded, or his office responded, in a
7 -- in about ten (10) days with a counter proposal. And where
8 I proposed one hundred and fifty (150), they proposed ten
9 (10).

10 That, however, just isn't going to work. In -- in the
11 State of South Carolina, there are not less than seventy-eight
12 hundred (7,800) prescribers of atypicals in the fee-for-
13 service Medicaid program, another twenty-five hundred (2,500)
14 in the -- the State Health Plan.

15 And, so, that is even greater -- that's even a greater
16 pool than what we've seen in Louisiana.

17 But, still our experts says, "I won't need any more than
18 one hundred, fifty (150)." Now --

19 THE COURT: Well, let me -- let me hear what Mr.
20 Trammell has to say about the --

21 MR. MURPHY: Sure.

22 MR. TRAMMELL: Well, this again is an area where I
23 think will benefit from our experience in the Lily case.

24 If you recall, the first hearing probably -- well, maybe
25 the first hearing in the Zyprexa case before the board, I

1 talked for hours about what would happen when you launch into
2 a discovery program like this.

3 And the Lily program was based on the program Janssen got
4 in Louisiana, where they got to do a hundred and fifty (150
5 doctors' depositions.

6 They got a bunch of medical records. And they convinced
7 the judge to do that and the judge ended up getting reversed
8 twice.

9 So, then, they desisted and they said, "Well, we don't --
10 we don't want to do that anymore." So, what they've asked to
11 do here is go depose a bunch of these doctors for reasons I
12 can't imagine.

13 I've acknowledged to the Court and to the Defendant that,
14 to the extent they want to get some testimony from doctors
15 about, you know, what information doctors consider when they
16 prescribe drugs, what do they think of Risperdal, what kinds
17 of patients it's good for, to play for a jury, I think that's
18 fine.

19 It becomes cumulative very quickly. Lily asked for I'm
20 sure as many as -- as Janssen has asked for. Lily has noticed
21 zero and all fact -- fact deposition cut off is in five (5)
22 weeks.

23 So, they're obviously prepared to go to trial not having
24 done any of those depositions. And I think the reason is,
25 when they know there are real deadlines, and when the case is

1 not about manufacturing reasons for discovery, they realize
2 they really don't need those depositions.

3 There is really no use for them. When you try to get the
4 Defendants to explain how their experts are going to rely on
5 them, they can't. I mean, there's just nothing they can do
6 with them.

7 You can't extrapolate those depositions out into a
8 statewide model. There's just nothing you can do except play
9 that yes, for the jury, that yes, doctors like Risperdal.
10 Yes, doctors realize there are risks with every drug, and that
11 sort of thing.

12 That's fine if they want to go take those depositions. I
13 agree that they can. But it just has to be limited.

14 Obviously, a hundred and fifty (150) is a number that
15 they've just come up with, and I don't think it has anything
16 to do with the litigation. It's interesting to me they know
17 how many prescribers we have but they don't know anything
18 about KOLs.

19 But, nevertheless, we would oppose this -- this
20 deposition program, on the same grounds, that we opposed the
21 Lily program and Court denied Lily's request for it.

22 They can do some depositions. Incidentally, there's no
23 motion pending, so, there's really nothing for the Court to
24 rule on.

25 I think the Defense is just trying to get the Court to

1 agree that this is a good number. They should start noticing
2 depositions when they're ready and notice ---

3 THE COURT: Well, you know, what I'd like to -- what I'd
4 like to see happen is that they begin to take depositions.

5 Obviously, if you're generating new information from --
6 as you take a few, if you're generating new information, then,
7 certainly you could come back to the Court and ask to extend
8 times or whatever is necessary to get -- to get them done.

9 But I would suspect, just from my -- my suspicions that,
10 if you are asking them about prescribing decisions or
11 information they based it on or their results that they --
12 that they received in using it or whatever -- you know, you
13 have a right to ask about whatever you want to ask them, but
14 at some point in time, it would become cumulative.

15 MR. MURPHY: And -- yes, sir.

16 THE COURT: And, you know, I just kind -- I -- if -- if
17 we've done twenty-five (25) and -- and you're generating new
18 information each time you take one, then, I'll be glad to hear
19 about that.

20 But ---

21 MR. TRAMMELL: Sure. Especially -- especially because,
22 Your Honor, the State will stipulate that doctors want to
23 treat their patients the best way they can. Doctors know that
24 drugs have side effects. Doctors consider risks and benefits.

25 Doctors know Risperdal has side effects. I mean, the

1 State will stipulate to everything that they're going to try
2 to establish in these depositions.

3 It is just a waste of time. I think ----

4 THE COURT: Well, I'm not -- I'm not sure you'd
5 stipulate to everything, but....

6 MR. TRAMMELL: Not to everything, but to most
7 everything. I take that back.

8 MR. MURPHY: Well, what we have in reality, Your
9 Honor ---

10 THE COURT: Yes, sir.

11 MR. MURPHY: --- the questions that are prepared for
12 these doctors are -- are prepared in conjunction with our
13 expert. And the questions go along the lines of, "Doctor, in
14 your experience," and tracks things such as not only to the
15 allegation related to off-label promotion, but also the
16 efficacy of the medicine.

17 THE COURT: Well --

18 MR. MURPHY: And how from experience ---

19 THE COURT: Well, before I would order that many
20 depositions to be taken, you're going to have to make a
21 motion.

22 MR. MURPHY: Okay.

23 THE COURT: And, then, number two, there's going to have
24 to be something from your expert indicating a direct need for
25 that.

1 And I'll give them an opportunity to respond to that
2 particular position because it would seem to me that a hundred
3 and fifty (150) depositions, of similarly situated
4 practitioners, about one particular drug might be cumulative.

5 So, I would -- I'm not -- I'm not going to order that at
6 this time. There's not a motion in front of me right now.

7 MR. MURPHY: Understood, Your Honor. And we will be
8 filing a motion and we will have a ---

9 THE COURT: Well, I would have to have something to base
10 that decision on. And right now I haven't -- I haven't heard
11 that yet. And I have my suspicions about that. I've
12 explained that part.

13 One thing that I noticed in the -- in the information I
14 received, discovery issues where motion practice is
15 anticipated, identities of and production of and production of
16 documents related -- relative to Janssen's sales directors.

17 MR. TRAMMELL: Sure. This is hard. It's vague. And
18 I'll explain it to you ---

19 THE COURT: It is vague. I had a hard time reading it.
20 Go ahead.

21 MR. TRAMMELL: Yeah. Well, we've -- we -- in the last
22 couple or few weeks, we've sent them more discovery requests.
23 They've given us their call notes.

24 We have identified certain sales reps that we want to
25 depose. It'll probably not be more than ten (10).

EXHIBIT E

STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA
ex rel. Henry McMaster, in his capacity
as Attorney General of the State of
South Carolina,

Civil Action No. 07-CP-42-1438

Plaintiff,

ORDER

v.

JANSSEN PHARMACEUTICA INC.,
JANSSEN, L.P. and
JOHNSON & JOHNSON, INC.,

Defendants.

This matter comes before me on Defendants', Ortho-McNeil-Janssen, Inc. and Johnson & Johnson (collectively, "Janssen"), Motion to Compel Responses To Its First Set of Requests For Production And Interrogatories, Plaintiff The State of South Carolina's ex rel. Henry McMaster, in his capacity as Attorney General of The State of South Carolina, (the "State"), Motion to Compel Documents Responsive to the State's Seventh Set of Requests for Production Directed to Defendants, and Defendants' Motion For Leave to Depose 150 Prescribing Physicians and Institutions: hearing was held on June 15, 2009 in Spartanburg, South Carolina. Fletcher V. Trammell of Bailey Perrin and Bailey, and John B. White, Jr., of Harrison, White, Smith & Coggins, P.C. represented the State. Kenneth A. Murphy of Drinker Biddle & Reath LLP, and Steven J. Pugh of Richardson Plowden & Robinson, P.A., represented Janssen. Upon consideration of the above-described Motions, the Memoranda and Responses of the parties filed therewith, and the oral arguments of counsel, I hereby order as follows:

[Signature]
#7

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SPARTANBURG COUNTY
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MALE KITCHENS

I. The State's Motion To Compel Documents Responsive to the State's Seventh Set of Requests for Production is Denied Without Prejudice

By its Motion, the State has requested the entry of an Order to Compel Defendants' Responses To the State's Seventh Set of Requests for Production. Among other things, the State's Seventh Set of Requests sought all Field Conference Reports generated in the State of South Carolina, all Call Plans implemented by Defendants' sales representatives in the State of South Carolina, and all documents produced by Defendants in the New Jersey lawsuit styled Lynn Powell v. Janssen Pharmaceutica, Inc., et al. The Court is satisfied that Defendants have commenced the process required to locate, process and produce documents responsive to those requests. Defendants expect to produce responsive documents by July 15, 2009. To the extent the State deems the production incomplete, the State may renew its Motion at that time.

II. Defendants' Motion To Compel Responses To Its First Set of Requests For Production And Interrogatories Is Denied Without Prejudice

By its Motion to Compel, Defendant Janssen has sought an Order compelling the State to produce and/or identify, among other things, 1.) documents and information reflecting articles, studies and other information the State contends Defendants misrepresented or concealed from South Carolina physicians — as alleged in the Complaint; 2.) the identity of South Carolina physicians who contend that Defendants' sales representatives encouraged the prescription of Risperdal for off-label purposes; 3.) the amount of money the State contends it spent to purchase Risperdal and/or underwrite the cost of Risperdal prescriptions.

In response, the State argues that the documents requested are part and parcel of expert reports and analyses that are not yet due. The State argues that Defendants'

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requests in this regard are premature and improper. The Court will not require the State to produce these documents and information at this time. However, the State shall produce all responsive documents and information well in advance of the relevant expert(s) deposition(s), to allow Defendants adequate time to prepare for the deposition and to conduct any follow up discovery Defendants may deem necessary. Defendants may renew their Motion should the State fail to produce responsive documents in advance of any relevant expert deposition.

In addition, Defendants seek various documents and files related to Drug Utilization Review activities performed on behalf of the State by third-party contractors. As to these documents, the Court accepts the representations of the State's counsel, and is satisfied that the State has produced all Drug Utilization Review-related documents within its custody and control.

III. Defendants' Motion For Leave to Depose 150 Prescribing Physicians and Institutions Is Denied in Part.

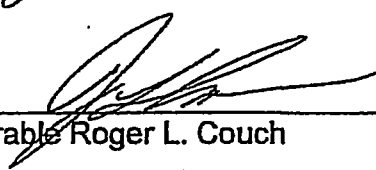
By its Motion For Leave To Depose 150 Prescribing Physicians and Institutions, Defendant Janssen seeks leave to depose a statistically significant sample of universe of South Carolina physicians who prescribed Risperdal and other antipsychotic medicines to South Carolina residents. The Court will grant the Defendant leave to depose twenty (20) prescribing physician depositions to be conducted. The Court will allow the Defendant to renew the motion after these twenty (20) depositions if necessity of additional depositions is shown.

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SPRINGFIELD COUNTY
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IT IS FURTHER ORDERED, that by July 6, 2009, the State shall fully comply with this Court's Order dated March 19, 2009, with regard to the personnel files of Messrs. Martin Brecher and Wayne Macfadden.

IT IS SO ORDERED this 20th day of June, 2009.



Honorable Roger L. Couch

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SPARTANBURG COUNTY
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MARC KITCHENS

A CERTIFIED COPY



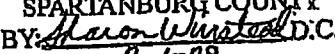
CLERK OF COURT
SPARTANBURG COUNTY
BY:  D.C.
DATED 7-1-09

EXHIBIT F

1 STATE OF SOUTH CAROLINA

2 COUNTY OF SPARTANBURG

) COURT OF COMMON PLEAS NONJURY

3
4 STATE OF SOUTH CAROLINA, EX REL.
5 HENRY McMASTER, IN HIS CAPACITY
6 AS ATTORNEY GENERAL OF THE STATE
OF SOUTH CAROLINA,

7 PLAINTIFF,

8 VS.

9 JANSSEN PHARMACEUTICA,

10 DEFENDANT.

TRANSCRIPT

OF

RECORD

07-CP-42-1438

11
12 May 11th, 2010
13 Spartanburg, South Carolina

14
15 B E F O R E :

16 THE HONORABLE ROGER L. COUCH, Judge.

17 A P P E A R A N C E S :

18 FLETCH TRAMMELL, DONALD COGGINS, JOHN WHITE, and JOHN
19 SIMMONS
ESQ.
Attorneys for the Plaintiff

20
21 KENNETH MURPHY and STEVEN PUGH
22 ESQ.
Attorneys for the Defendant

23
24
25 **RECEIVED**
MAY 18 2010
BY: _____

PAMELA E. GREEN
Circuit Court Reporter
Seventh Judicial Circuit

1 in a particular place is wholly irrelevant. But, but the
2 Court granted them leave to take 20. We have cooperated
3 with that, stand ready to cooperate through the, the balance
4 of the 20, but beyond that---

5 THE COURT: You said they're 17 at this point in time?

6 MR. COGGINS: We, we have taken 16.

7 THE COURT: Sixteen.

8 MR. COGGINS: And we have the others scheduled I
9 believe. There was one that had to be rescheduled and I'm
10 not quite sure if it has gotten back on the calendar. But I
11 believe we have them scheduled.

12 THE COURT: All right. Mr. Murphy, Mr. Pugh, I don't
13 know who's gonna---

14 MR. MURPHY: I'd address it, Your Honor.

15 THE COURT: All right.

16 MR. MURPHY: The first thing, Your Honor, is with

17 regard to, to the language, Mr. Coggins acknowledges that
18 South Carolina is to look to the FTC for guidance with
19 regard to the SCUTPA claim because SCUTPA is really in many
20 FTC statutes, and one thing the FTC has made clear is that
21 the analysis is not whether there is a tendency to deceive,
22 but whether it is likely to deceive, and that is one of the
23 things that we made clear to the Court when we came and we
24 asked for this statistically significant number of doctors.

25 okay. We wanted to look at the universe of doctors in

1 south Carolina, taking a statistically significant sample of
2 that universe and determine certain things regarding what
3 was said to them, what they understood. And as the FTC has
4 also made clear, when answering the question whether, in a
5 particular audience, was deceived or mislead, what you have
6 to understand is the knowledge base and sophistication of
7 that audience, and here the audience is prescribing
8 physicians in South Carolina. And I think in the papers
9 that we submitted before on that point there was a case
10 directly on point talking about physicians and how they're
11 impacted by advertising.

12 So, when I came---

13 THE COURT: Well, I think my question though here is if
14 we've taken 16 and we're---

15 MR. MURPHY: Well, let me address that.

16 THE COURT: Are we getting consistent responses or are
17 we---

18 MR. MURPHY: You've heard Mr. Coggins say that they're
19 consistent responses, but there's a difference in the, the
20 that Your Honor allowed us to take.

21 THE COURT: Uh-huh. (Affirmative).

22 MR. MURPHY: And we want to take the 20 to maintain the
23 integrity of this statistical sampling.

24 THE COURT: Yes, sir.

25 MR. MURPHY: But there are six other doctors that we

1 THE COURT: Who, who would of been there for the
2 plaintiffs?

3 MR. SIMMONS: Your Honor, I know I've attended at least
4 one that Mr. Murphy took in Columbia, and I've, and I've
5 also attended I believe a couple of the other ones out of
6 the group that Mr. Coggins has. It's my recollection that,
7 that the format is generally the same with the additional
8 questions of these six that, that Mr. Pugh and Mr. Murphy
9 have identified containing questions regarding the HID
10 letter. So, it's -- so, I believe it's in addition to.
11 That's, that's the way that I recall.

12 THE COURT: All right. Well, here's, here's how I'm
13 gonna resolve it. I'm gonna let you take the depositions

14 of -- I'm gonna let you use at trial 20 in the vein that I
15 talked about, up to 20. We'll talk about that once we see
16 them. I don't know if we're gonna use all 20 or not. But

17 we'll, we'll take a look at it and see what they've, they've
18 produced.

19 As to the HID letters, that's a different issue. I'll
20 let you take depositions from those who responded to those
21 letters. So -- but when we get to trial, now, we're not
22 gonna use that to expand the universe.

23 Do you follow what I'm saying?

24 MR. PUGH: I do, Your Honor.

25 THE COURT: If you also ask those HID people the same

EXHIBIT G

Law Offices

One Logan Square, Ste. 2000
Philadelphia, PA
19103-6996
215-988-2700 phone
215-988-2757 fax
www.drinkerbiddle.com

CALIFORNIA
DELAWARE
ILLINOIS
NEW JERSEY
NEW YORK
PENNSYLVANIA
WASHINGTON DC
WISCONSIN

May 14, 2010

Via Federal Express

Fletcher V. Trammell, Esq.
Bailey, Perrin Bailey LLP
The Lyric Centre
440 Louisiana, Suite 2100
Houston, TX 77002

John B. White, Jr., Esq.
Harrison, White, Smith & Coggins, P.A.
178 W. Main Street
Spartanburg, SC 29306

Re: **State of South Carolina v. Janssen, et al.**
Case No. 2007-CP-1438

Dear Counsel:

Pursuant to the Preliminary Scheduling Order in this case, enclosed please find expert reports generated by the following witnesses, on behalf of the Defendants:

1. Janet B. Arrowsmith, M.D.
2. Vivan Fonseca, M.D.
3. Ellen L. Gandle, M.D.
4. Ira D. Glick, M.D.
5. Dr. Eric S. Johnson
6. Ramy Mahmoud, M.D.
7. Herbert Y. Meltzer, M.D.
8. John W. Newcomer, M.D.
9. Joseph M. Palumbo, M.D.
10. Peter V. Rabins, M.D.
11. Denese Shervington, M.D.

DrinkerBiddle&Peath

Fletcher V. Trammell, Esq.

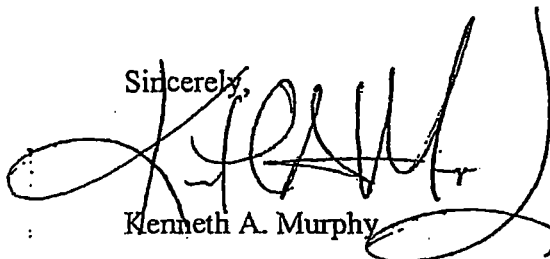
John B. White, Jr., Esq.

Page 2

May 14, 2010

Defendants reserve the right to supplement these reports and to submit others, once the State provides full and complete responses to Defendants' outstanding discovery requests. Further, Defendants will produce the expert report of William Wecker, Ph.D. once the remaining prescribing physicians' depositions have been completed and the report is generated.

Sincerely,

A handwritten signature in black ink, appearing to read "Ken Murphy", with a large, sweeping flourish extending from the end of the signature.

Kenneth A. Murphy

KAM/cms

Enclosures

cc: Steven J. Pugh, Esq. (w/o encls.)
John S. Simmons, Esq. (w/o encls.)
Thomas F. Campion, Esq. (w/o encls.)

EXHIBIT H

STATE OF SOUTH CAROLINA	)	IN THE COURT OF COMMON PLEAS
	)	
COUNTY OF SPARTANBURG	)	C.A. NO.: 2007-CP-42-1438
State of South Carolina, Ex	)	
rel. Henry McMaster, in his	)	
Capacity as Attorney General	)	
of the State of South Carolina)	)	
	)	
Plaintiff,	)	
	)	
vs.	)	VIDEO DEPOSITION OF
	)	JAMES LIDDELL ELMORE, M.D.
Janssen Pharmaceutica, Inc.;	)	November 19, 2010
Janssen, L.P. and Johnson	)	
and Johnson, Inc.,	)	
	)	
Defendants.	)	
	)	

Video Deposition on oral examination of JAMES LIDDELL ELMORE, M.D., reported by Betty M. Washington, Verbatim Court Reporter and Notary Public in and for the State of South Carolina; said deposition taken pursuant to notice and in accordance with the South Carolina Rules of Civil Procedure, at the Offices of Santee-Wateree Mental Health Center, Adult Outpatient Clinic, 215 N. Magnolia Street, Sumter, South Carolina, on Friday, the 19th day of November, 2010, scheduled for 8:30 a.m. and commencing the hour of 8:42 a.m.

EXHIBIT I



COLUMBIA P.O. Drawer 7788• Columbia, SC 29202
1900 Barnwell St., Columbia, SC 29201 P 803.771.4400 F 803.779.0016

MYRTLE BEACH P.O. Box 3646• Myrtle Beach, SC 29578
2103 Farlow St., Suite B, Myrtle Beach, SC 29577 P 843.448.1008 F 843.448.1533

www.RichardsonPlowden.com

REPLY TO: Columbia
E-Mail: spugh@richardsonplowden.com
Direct Dial: (803) 576-3721

December 17, 2010

VIA E-MAIL

John B. White, Jr., Esquire
Harrison, White, Smith & Coggins, P.A.
178 West Main Street
Spartanburg, South Carolina 29306

RE: *State of South Carolina v. Janssen Pharmaceutica, Inc., et al.*
Civil Action No. 2007-CP-1438
Our File No. 6419-001

Dear John:

Attached please find a copy of the following expert reports in the above-referenced matter:

1. Dr. Eric Johnson's 12/13/10 report;
2. Dr. Eric Johnson's 12/14/10 supplemental report;
3. Dr. Ellen L. Gandle's report;
4. Dr. John W. Newcomer's report; and
5. Dr. William E. Wecker's report.

Please note that the attached reports of Drs. Gandle, Johnson and Newcomer are in supplement to their prior reports produced to you in this case. Should you have any questions or comments, please do not hesitate to contact me.

Sincerely,

Steven J. Pugh

SJP:cam

Attachments

cc via email, w/ attach.:

Donald C. Coggins, Jr., Esq.
John S. Simmons, Esq.
Fletcher V. Trammell, Esq.
Elizabeth Dwyer, Esq.
Thomas Campion, Esq.
Kenneth A. Murphy, Esq.
Steven W. Hamm, Esq.

EXHIBIT J



COLUMBIA P.O. Drawer 7788 • Columbia, SC 29202
1900 Barnwell St., Columbia, SC 29201 P 803.771.4400 F 803.779.0016

MYRTLE BEACH P.O. Box 3646 • Myrtle Beach, SC 29578
2103 Farlow St., Suite B, Myrtle Beach, SC 29577 P 843.448.1008 F 843.448.1533

www.RichardsonPlowden.com

REPLY TO: Columbia
E-Mail: spugh@richardsonplowden.com
Direct Dial: (803) 576-3721

December 22, 2010

VIA HAND-DELIVERY

John S. Simmons, Esquire
Simmons Law Firm, LLC
1711 Pickens Street
Columbia, South Carolina 29202

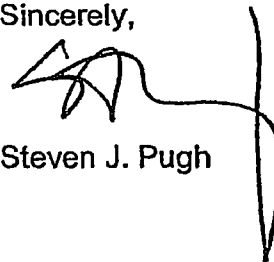
RE: *State of South Carolina v. Janssen Pharmaceutica, Inc., et al.*
Civil Action No. 2007-CP-1438
Our File No. 6419-001

Dear John:

Pursuant to my telephone conversation yesterday with John White, enclosed please find a hard drive containing electronic files that support the opinions in Dr. William Wecker's expert report. These materials will be relied upon by Dr. Wecker at trial.

Should you have any questions or comments, please do not hesitate to contact me.

Sincerely,



Steven J. Pugh

SJP:cam
Enclosure

cc (via e-mail) (w/o encl.): Donald C. Coggins, Jr., Esq.
John B. White, Jr., Esq.
Fletcher V. Trammell, Esq.
Elizabeth Dwyer, Esq.
Thomas Campion, Esq.
Kenneth A. Murphy, Esq.
Steven W. Hamm, Esq.

EXHIBIT K

HWS&C
HARRISON, WHITE, SMITH & COGGINS, P.C.
Attorneys at Law

Ben C. Harrison
John B. White, Jr.
Danny R. Smith
Donald C. Coggins, Jr.
Thomas A. Killoren, Jr.*
Wes A. Kissinger
Jeremy A. Dantin^o
Amanda H. Craven[^]
Allison P. Dunham
Griffin L. Lynch
Candice K. Lapham
Samuel R. Bass II

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SPARTANBURG, SC 29304
www.spartanlaw.com

TELEPHONE: 864-585-5100
TOLL FREE: 800-543-2990
FACSIMILE: 864-542-2993

FEIN 57-1088154

* also licensed in GA, NC, IL
^o also licensed in GA
[^] also licensed in FL

January 6, 2011

VIA U.S. MAIL AND EMAIL

Steve Pugh, Esquire
Richardson Plowden & Robinson, PA
P.O. Drawer 7788
Columbia, South Carolina 29202
SPugh@RichardsonPlowden.com

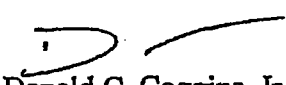
RE: State of South Carolina ex. rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina vs. Ortho-McNeil-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica, Inc. and/or Janssen, LP, and Johnson & Johnson, Inc.
Civil Action No.: 2007-CP-42-1438

Dear Steve:

Please find attached Plaintiff State of South Carolina's Notice to Take Videotaped Oral Deposition of William Wecker and Certificate of Service for same. If you have any questions, please do not hesitate to contact me.

With best regards, I remain,

Yours very truly,


Donald C. Coggins, Jr.

DCC, Jr./rmf

cc: Ken Murphy, Esquire (via email)
Sonny Jones, Esquire (via email)
Fletch Trammell, Esquire (via email)
John Simmons, Esquire (via email)
John B. White, Esquire (via email)
Griffin Lynch, Esquire (via email)
Elizabeth Dwyer, Esquire (via email)
Sam Bass, Esquire (via email)

STATE OF SOUTH CAROLINA

COUNTY OF SPARTANBURG

STATE OF SOUTH CAROLINA

ex. rel. Henry McMaster, in his capacity
as Attorney General of the State of
South Carolina,

PLAINTIFF,

v.

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA, INC.,
and/or JANSSEN, LP and
JOHNSON & JOHNSON, INC.,

DEFENDANTS.

) IN THE COURT OF COMMON PLEAS

) FOR THE SEVENTH JUDICIAL CIRCUIT

)
) PLAINTIFF STATE OF SOUTH
) CAROLINA'S NOTICE TO TAKE
) VIDEOTAPED ORAL DEPOSITION
) WILLIAM E. WECKER

) Civil Action No.: 2007-CP-42-1438

TO: Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or
Janssen, LP, and Johnson & Johnson, Inc. and its attorneys,

Ken Murphy, Esquire
Drinker Biddle & Reath LLP
One Logan Square
18th and Cherry Streets
Philadelphia, Pennsylvania 19103

Steven J. Pugh, Esquire
Richardson Plowden & Robinson, PA
P.O. Drawer 7788
Columbia, South Carolina 29202

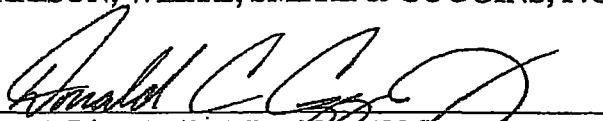
PLEASE TAKE NOTICE that pursuant to Rules 26 and 30 of the South Carolina Rules
of Civil Procedure, Plaintiff, by and through its undersigned attorneys, will take the oral and
videotaped deposition of William E. Wecker on January 27, 2011 at 9:00 AM at O'Melveny
& Myers, LLP, Two Embarcadero Center, 28th Floor, San Francisco, CA 94111, (415-984-
8700), and will continue day to day, Sundays and holidays excepted, until completed. The State

requests Janssen produce documents listed in Exhibit A at least one business day prior to the date of the deposition. The deposition will be taken before a person authorized by law to administer oaths, pursuant to South Carolina Rules of Civil Procedure and will be videotaped.

**STATE OF SOUTH CAROLINA
OFFICE OF THE ATTORNEY GENERAL**

Henry McMaster
Office of Attorney General
1000 Assembly Street, Room 519
Columbia, South Carolina 29201

HARRISON, WHITE, SMITH & COGGINS, P.C.

By: 

John B. White, Jr. (S.C. Bar No.: 5996)
Donald C. Coggins, Jr. (S.C. Bar No.: 1307)
178 West Main Street (29306)
Post Office Box 3547
Spartanburg, South Carolina 29304
(864) 585-5100 Telephone
(864) 591-0491 Fax

BAILEY PERRIN BAILEY

Fletcher V. Trammell (Texas Bar No.: 24042053)
Admitted *pro hac vice*
440 Louisiana, Suite 2100
Houston, Texas 77002
(713) 425-7100 Telephone
(713) 425-7249 Fax

SIMMONS LAW FIRM, L.L.C.

John S. Simmons (S.C. Bar No.: 10260)
1711 Pickens Street
Columbia, South Carolina 29202
(803) 779-4600 Telephone
(803) 254-8874 Fax

Attorneys for the State of South Carolina

January 6, 2011

Spartanburg, South Carolina

EXHIBIT A

Definitions

The following definitions apply to the foregoing Notice to Take Videotaped Oral Deposition, including those matters set forth in this Exhibit A, and are deemed to be incorporated into each subject and request for documents listed below:

1. "Identify" or "identity" with respect to persons, means to give, to the extent known, the person's full name, present or last known address, and when referring to a natural person, additionally, the present or last known place of employment.

2. "Janssen," "You," or "Your" refers to each of the defendants Janssen Pharmaceutica, Inc., Janssen LP, Johnson & Johnson, Inc., and all partners, directors, officers, employees, servants, agents, attorneys, joint ventures, or other representatives, including all corporations and entities affiliated with Janssen. The terms shall also include all predecessor business entities, as well as any predecessor's partners, directors, officers, employees, servants, agents, joint ventures or others acting on their behalf. The terms shall also include all foreign subsidiaries or foreign parent companies, as well as any foreign subsidiaries' or parent companies' partners, directors, officers, employees, servants, agents, joint ventures or others acting on their behalf.

3. "Person" means natural person, as well as corporate and/or governmental entity.

4. "Risperdal" means risperidone, also known by the brand name Risperdal, and any predecessor or non-final derivation of the drug that later became Risperdal. Also included in the definition of Risperdal are any chemical equivalents marketed in foreign countries.

5. "Relating to," "relate to," "referring to," "refer to," "reflecting," "reflect," "with regard to," "pertaining to," "concerning," or "concern" shall mean evidencing, regarding,

concerning, discussing, embodying, describing, summarizing, containing, constituting, showing, mentioning, reflecting, dealing with, relating to, referring to in any way or manner, or in any way logically or factually, connecting with the matter described in that paragraph of these demands, including documents attached to or used in the preparation of or concerning the preparation of the documents.

6. "Documents" as used in this Request is coextensive with the meaning of the terms "documents" and "tangible things" in South Carolina Rule of Civil Procedure 34, and shall have the broadest possible meaning and interpretation ascribed to the terms "documents" and "tangible things" under South Carolina Rule of Civil Procedure 34.

7. "Or" and "and" will be used interchangeably.

8. Unless otherwise indicated, the relevant time period for the information sought is 1980 to present.

9. A "custodial file" includes but is not limited to: all hard copy and electronic documents from all sources including all hard copy files; personnel files; desktop and laptop computers; and, personal computer devices such as Personal Digital Assistants (PDAs), BlackBerry's or other such devices. As more fully specified in the Definitions attendant to the State's Requests for Production of Documents, "documents" shall have the broadest possible meaning and interpretation ascribed to it, including but not limited to: writings, drawings, graphs, charts, photographs, phone records, and other data compilations from which information can be obtained. Additionally, any documents contained on any computers and all devices utilizing microchips to facilitate processing, analysis, or storage of data are included within a custodial file.

Request for Documents

All documents referred to by the Deponent or anyone assisting the Deponent in preparing for his testimony in addition to the following:

1. Curriculum vitae of Deponent: the present and all versions drafted or distributed for the past fifteen (15) years;
2. All communications to and from the Deponent related to Risperdal, including but not limited to emails;
3. Any and all documents prepared by, prepared for, or received by Deponent relating to Risperdal;
4. Any and all research materials relating to Risperdal prepared by, prepared for, or received by Deponent;
5. The custodial file for the Deponent;
6. Personnel files, including but not limited to,
 - a. Documents showing the compensation, including standard compensation and bonuses, that the Deponent received during the time he had Risperdal-related responsibilities.

STATE OF SOUTH CAROLINA

COUNTY OF SPARTANBURG

STATE OF SOUTH CAROLINA, ex rel.
Alan Wilson, in his capacity as
Attorney General of the State of South
Carolina,

PLAINTIFF,

v.

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC. f/k/a
JANSSEN PHARMACEUTICA, INC.
and/or JANSSEN, LP, and JOHNSON
& JOHNSON, INC.

DEFENDANTS.

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

Civil Action No.: 2007-CP-42-1438

PLAINTIFF THE STATE OF SOUTH
CAROLINA'S REPLY TO DEFENDANTS'
RESPONSE IN OPPOSITION TO
THE STATE'S MOTION
TO EXCLUDE THE EXPERT WITNESS
TESTIMONY OF DEFENDANTS'
EXPERT WITNESS,
DR. WILLIAM E. WECKER

TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR
DEFENDANTS

Plaintiff the State of South Carolina, *ex rel.* Alan Wilson,¹ in his capacity as the Attorney
General of the State of South Carolina (the "State"), hereby replies to the Memorandum of Law
in Opposition to the State's Motion to Exclude the Expert Testimony of Dr. William E. Wecker
filed by the above-captioned "Defendants," and shows the Court as follows:

I.
SUMMARY OF THE REPLY

Dr. Wecker's deposition testimony, elicited just last week, makes all the more glaring the
utter lack of scientific basis supporting his so-called "expert opinions." Dr. Wecker admitted on

¹ Pursuant to Rule 25(d)(1) of the South Carolina Rules of Civil Procedure, the Honorable Alan Wilson has
been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

the one hand that the sample size of 20 South Carolina prescribing doctors' depositions did not permit an accurate analysis of the type he purported to perform in Louisiana (involving 150 doctors' depositions, which was nevertheless excluded by the trial court there). But, Dr. Wecker claims that dozens of answers to questions asked of the 20 South Carolina doctors may (remarkably) be extrapolated to the entire population of South Carolina prescribers. Dr. Wecker did not calculate any confidence intervals supporting that broad assertion, and admitted that prior to this litigation, he has *never* based a survey exclusively on deposition testimony. Further, many of Dr. Wecker's contentions about the reliability of his "survey" run completely counter to the Federal Judicial Center's *Reference Guide on Survey Research*, which instructs this Court's admissibility review of Dr. Wecker's "survey."

Defendants also seek to lay the blame for any unreliability of Dr. Wecker's report and testimony squarely at the feet of **this Court** and the State. By complaining that the Court, at the State's urging, limited Defendants to only 20 prescriber depositions in South Carolina, Defendants hope to sidestep the fatal issue of the inherent unreliability of Dr. Wecker's "survey" opinions. But, Defendants ignore the opportunity this Court gave them to expand the number of prescriber depositions if the necessity of that expansion was shown. Defendants never demonstrated any such necessity.

Finally, Defendants should acknowledge—at a minimum—that there are areas of Dr. Wecker's testimony that are simply no longer relevant to the case. Indeed, Defendants admitted as much in the trial of the companion case in Louisiana.

For those reasons, which are further discussed in detail below, as well as for the reasons set forth in the State's Motion, the Court should exclude from trial Dr. Wecker's testimony and opinions.

II. ARGUMENT & AUTHORITIES

A. Dr. Wecker's Testimony Exposes the Unreliability of His Opinions in this Case.

On January 27, 2011, the State deposed Dr. Wecker concerning his proffered expert opinions in this case. His testimony simply confirmed what the State has argued all along with respect to Dr. Wecker's opinions here: that his testimony amounts to nothing more than unreliable *ipse dixit* and it would be unfairly prejudicial to the State for the jury to consider it.

With respect to the "survey" of 20 South Carolina prescribers, Dr. Wecker admitted that he "would have preferred 150" doctors' depositions be taken for his analysis, "but the Court determined that 20 was going to be allowed." (William Wecker, Ph.D. Dep. ("Wecker Dep.") at 68 (attached as Exhibit A).) He characterized the smaller sample size of 20 as "an important difference" in comparison to the sample of 150 doctors' depositions that were taken and analyzed in the parallel Louisiana litigation because "with only a sample of 20 to work with, it would have been difficult, perhaps impractical, to get the accuracy of results for the entire population of antipsychotic-prescribing doctors that [he, arguably,] was able to achieve when [he] had a larger sample size of 150" (though the Louisiana court ultimately excluded that same analysis and opinion). (*Id.* at 23-25 (Ex. A).)

Remarkably, however, Dr. Wecker repeatedly contended in his deposition that answers to certain broadly worded questions in the South Carolina prescribers' depositions—largely those questions beginning with the phrase "[i]n your experience" (*id.* at 27-39 (Ex. A))—*could be extrapolated to the entire population of South Carolina prescribers (and even prescribers in other states)* notwithstanding the admittedly small, unreliable sample size. (*Id.* at 27-28, 39-40, 60-61 (Ex. A).) When asked to explain his methodology for reaching that conclusion, Dr. Wecker offered merely that he reached it "[j]ust by reading the questions" from the depositions

(*id.* at 61 (Ex. A)); “[i]t’s just simple logic” (*id.* at 40 (Ex. A)); “[I]f a particular drug is judged as effective in treating psychotic disorders by doctors who are high-prescribing and in the best position to know the answer to that question, then I take that as a general proposition and of broad applicability” (*id.* at 60 (Ex. A)). His “scientific basis” for his bare opinion that a “general question applies generally” is simply that the proposition is “a tautology.” (*Id.* at 63 (Ex. A).) “[T]hat’s all I – all the answer that its need – that it needs. A general question applies to general things.” (*Id.* (Ex. A); *see id.* at 64 (“[T]he general questions that we have in this case, in my survey, they all – and which I enumerated for you about an hour ago, they apply – they apply generally.”) (Ex. A)).

With respect to the scientific reliability of that amazingly broad extrapolation to all South Carolina prescribers, Dr. Wecker admitted that he did not calculate any confidence intervals (i.e., margins of error) to test the accuracy of his opinion that the 20 prescribers’ answers to the so-called “general questions” also extended to the entire population of South Carolina prescribers and beyond. (*Id.* at 83 (Ex. A); Defs.’ Resp. to Pl.’s Mot. to Exclude Dr. Wecker at 5 (“At the survey’s conclusion, Dr. Wecker calculated population estimates with confidence intervals for the 101 most frequent prescribers – the group from which the sample size of 20 was drawn.”).) Moreover, Dr. Wecker admitted that prior to being retained by Defendants in this and the companion Louisiana case, *he has never based a probability survey opinion entirely on deposition testimony.* (*Id.* at 81-82 (Ex. A).)

The “survey’s” complete lack of reliability is further revealed by Dr. Wecker’s opinions and methods that run contrary to the Federal Judicial Center’s *Reference Guide on Survey Research*. In particular, as the State notes in its Motion to Exclude Dr. Wecker, the *Reference Guide* provides that, for surveys conducted as part of litigation, the attorneys “should have no

part in carrying out the survey.” Federal Judicial Center, *Reference Manual on Scientific Evidence* (Second) at 237 (2000) (*Reference Guide on Survey Research* chapter attached as Exhibit B to Pl.’s Mot. to Exclude). But, according to Dr. Wecker, it was “appropriate for attorneys to function as they did in this survey . . .,” assuming the dual (and conflicting) roles of supposedly unbiased interviewer and partisan advocate. (Wecker Dep. at 66 (Ex. A).) According to Dr. Wecker, it was not important who asked the questions in the “survey.” (*Id.* at 45 (Ex. A).) Additionally, Dr. Wecker deemed it “impossible” for the survey interviewers to be blind to the purpose and sponsorship of the survey, notwithstanding the *Reference Guide*’s admonition in favor of blind survey techniques in litigation. (Wecker Dep. at 67 (Ex. A); see Pl.’s Mot. to Exclude Dr. Wecker at 6 & n.4.) Dr. Wecker did not feel it was necessary that those conducting the “survey” have any training or background in psychology, sociology, marketing, communication sciences, or statistics, despite the *Reference Guide*’s strong urging that those conducting the survey have “graduate training” in one or more of those fields. (Wecker Dep. at 72-73 (Ex. A); see Pl.’s Mot. to Exclude Dr. Wecker Exhibit B at 238.) Finally, despite the *Reference Guide*’s call for independent validation of litigation survey results, only the staff at Dr. Wecker’s firm conducted any validation thereof. (Wecker Dep. at 77 (Ex. A); see Pl.’s Mot. to Exclude Dr. Wecker at 12.)

Lastly, Dr. Wecker expressed his intent to opine at trial that Defendants’ November 2003 “Dear Doctor” Letter (“November 2003 DDL”) “was an accurate reflection of the [medical] risks posed by Risperdal.” (Wecker Dep. Tr. at 19 (Ex. A).) When asked to describe his methodology used in forming that opinion—*absent any medical training or training with respect to antipsychotic drugs*—Dr. Wecker explained that he reached his opinion merely by “reading the articles” referenced in the November 2003 DDL. (*Id.* at 6-8, 19-20 (Ex. A).) He did nothing

more. (*Id.* at 20 (Ex. A).) Indeed, before being retained by Defendants, he had never read an article on antipsychotic drugs. (*Id.* at 17 (Ex. A).)

B. Defendants Themselves Are to Blame for the Statistically Invalid Sample Size Relied Upon by Dr. Wecker.

Defendants appear to blame the Court and the State for the unreliably small sample size employed by Dr. Wecker. (Defs.' Resp. in Opp'n to Pl.'s Mot. to Exclude Dr. Wecker at 4; Wecker Dep. at 68 (Ex. A).) But, Defendants ignore the fact that this Court—in granting leave for Defendants to depose 20 South Carolina prescribing physicians—expressly invited Defendants “to renew the motion [for leave to depose prescribing physicians] after th[o]se twenty (20) depositions [were completed] if the necessity of additional depositions is shown.” (Order (June 26, 2009) at 3 (attached as Exhibit B).) But, as the Court and Defendants well know, Defendants never took the Court up on that offer to expand the number of doctors Defendants intended to depose. They cannot now be heard to complain about the limited scope of depositions supporting their purported “survey” based upon any action by the Court or any limitations on the number of depositions previously sought by the State.

C. Defendants Themselves Have Admitted that, Given the Narrow Parameters of a Deceptive Trade Practices Claim, Certain of Dr. Wecker's Opinions Are No Longer Relevant.

The State points out in its Motion to Exclude Dr. Wecker that—notwithstanding the State's position that Dr. Wecker's entire opinion is irrelevant and that it be excluded on that and other grounds—there are plainly areas of Dr. Wecker's opinion that are simply no longer germane to the State's narrow SCUTPA claim. (Pl.'s Mot. to Exclude Dr. Wecker at 4.) In the Louisiana trial, the jury there faced the same narrow issue, and Defendants' counsel admitted that (at a minimum) there were areas of Dr. Wecker's testimony that were immaterial to that deceptive trade practices case:

[by Defendants' counsel, Mr. Brody:] Now, true, when we started this process it was a different case; there were additional claims, there were additional counts. And so some of what Dr. Wecker asked the physicians, some of the questions that were put to the doctors, you know, I don't think still have anything to do with what we're doing here today. Did any Janssen sales representative ever market Risperdal to you for an off-label use in children? And so Dr. Wecker is not going to be asked about that today and he's not going to talk about that.

THE COURT: You don't intend to put this into evidence?

MR. BRODY: Do not intend to put that into evidence. No, Your Honor.

(Trial Tr., *Caldwell ex rel. the State of Louisiana v. Janssen Pharmaceutica, Inc.*, Nos. 04-C-3967-D, 04-C-3977-D, Trial Day 9 at 11 (La. 27th D. Ct. Oct. 12, 2010) (attached as Exhibit C).)

The State contends—at a bare minimum—that similar areas of irrelevant testimony should be excluded from trial here, and it is hopeful that Defendants will agree to such exclusions—if Dr. Wecker is allowed to testify at all, which the Court should not permit for all the reasons already stated.

III. CONCLUSION

For all the above reasons, as well as for the reasons set forth in the State's Motion, the Court should exclude from trial Dr. Wecker's testimony and opinions.

Respectfully submitted,

STATE OF SOUTH CAROLINA
OFFICE OF THE ATTORNEY GENERAL

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FILED
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SOUTH CAROLINA
JAN 11 2011
COLUMBIA

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Date: January 31, 2011

Spartanburg, South Carolina

Attorneys for the State of South Carolina

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SPARTANBURG COUNTY
SOUTH CAROLINA
JAN 31 2011
H. JOSEPH BAILEY

EXHIBIT A

FILED
CLERK OF COURT
SOUTHERN DISTRICT
OF NEW YORK
JUL 21 1964
W. H. B. BLACKLEY

STATE OF SOUTH CAROLINA COURT OF COMMON PLEAS
COUNTY OF SPARTANBURG SEVENTH JUDICIAL CIRCUIT

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STATE OF SOUTH CAROLINA
ex rel. Henry McMaster, in
his Capacity as Attorney
General of the State of
South Carolina,
 Plaintiff,

vs.

Civil Action No.
2007-CP-42-1438

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA, INC.,
and/or JANSSEN, LP and
JOHNSON & JOHNSON, INC.,
 Defendants.

_____ /

Deposition of
WILLIAM E. WECKER, Ph.D.

Thursday, January 27, 2011

REPORTED BY: JOHN WISSENBACH, RDR, CRR, CBC, CCP,
CLR, CSR 6862

FILED
CLERK OF COURT
SPARTANBURG COUNTY
SOUTH CAROLINA
JAN 27 2011
M. ROBERTS

09:07:51 1 INDEX OF EXAMINATIONS
 09:08:06 2 Page
 09:08:09 3 EXAMINATION BY MR. TRAMMELL 5
 09:08:14 4 EXHIBITS MARKED FOR IDENTIFICATION
 09:08:18 5 No. Description Page
 09:08:22 6 (none)
 09:08:27 7 --o0o--
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1 THE VIDEOGRAPHER: Here begins volume I,
 2 videotape number 1 in the deposition of William
 3 Wecker in the matter of State of South Carolina vs.
 4 Janssen Pharmaceuticals, et al., in the State of
 5 South Carolina, County of Spartanburg, in the Court
 6 of Common Pleas for the Seventh Judicial Court,
 7 Civil Action Number 2007-CP-42-1438.
 8 Today's date is January 27th, 2011. Time
 9 on the video monitor is 9:08. The video operator
 10 today is Jefree Anderson, a notary public contracted
 11 by Merrill Court Reporting, San Francisco,
 12 California. This video deposition is taking place
 13 at O'Melveny & Myers LLP, in San Francisco,
 14 California.
 15 Counsel, please identify yourselves and
 16 state whom you represent.
 17 MR. TRAMMELL: Fletch Trammell, State of
 18 South Carolina.
 19 MR. COWAN: Robert Cowan, State of South
 20 Carolina.
 21 MR. BRODY: Steve Brody, for the
 22 defendants.
 23 MS. HOOGS: Jessica Hoogs, for the
 24 defendants.
 25 THE VIDEOGRAPHER: The court reporter today

09:09:13 1 BE IT REMEMBERED that, pursuant to the laws
 09:09:16 2 governing the taking and use of depositions, on
 09:09:28 3 Thursday, January 27, 2011, commencing at 9:08 a.m.
 09:09:29 4 thereof, at the law offices of O'Melveny & Myers
 09:09:29 5 LLP, Two Embarcadero Center, 28th Floor, San
 09:09:29 6 Francisco, California, before me, JOHN WISSENBACH, a
 7 Certified Shorthand Reporter, personally appeared
 8 WILLIAM E. WECKER, Ph.D., called as a witness by the
 9 plaintiff, who, being by me first duly sworn, was
 10 thereupon examined as a witness in said action.
 11 APPEARANCES OF COUNSEL
 12 For the Plaintiff
 13 BAILEY PERRIN BAILEY
 14 BY: FLETCH TRAMMELL, Attorney at Law
 15 ROBERT W. COWAN, Attorney at Law
 16 The Lyric Center, 440 Louisiana, Suite 2100
 17 Houston, Texas 77002
 18 (713) 425-7100
 19 ftrammell@bplaw.com
 20 For the Defendants:
 21 O'MELVENY & MYERS LLP
 22 BY: STEPHEN D. BRODY, Attorney at Law
 23 1625 Eye Street, NW
 24 Washington, D.C. 20006-4001
 25 (202) 383-5167
 sbrody@omm.com
 09:10:05 21 O'MELVENY & MYERS LLP
 09:10:09 22 BY: JESSICA A. HOOGS, Attorney at Law
 09:10:15 23 Two Embarcadero Center, 28th Floor
 09:10:18 24 San Francisco, California 94111-3823
 09:10:20 25 (415) 984-8885
 jhoogs@omm.com
 ALSO PRESENT: JEFREE ANDERSON, Videographer

1 is John Wissenbach, of Merrill Court Reporting.
 2 Would the reporter please swear in the witness.
 3 WILLIAM E. WECKER, Ph.D.,
 4 having been first duly sworn, testified as follows:
 5 THE VIDEOGRAPHER: Please begin.
 6 EXAMINATION BY MR. TRAMMELL
 7 Q. Please state your name for the record.
 8 A. William E. Wecker.
 9 Q. Dr. Wecker, where do you live?
 10 A. I live in Novato, California. It's about a
 11 half hour north of here.
 12 Q. And what do you do for a living?
 13 A. I'm a statistician and applied
 14 mathematician.
 15 Q. Do you work somewhere?
 16 A. William E. Wecker Associates, Incorporated.
 17 It's a small consulting firm of myself and other
 18 mathematicians.
 19 Q. Who do you consult for?
 20 A. A wide variety of businesses and
 21 governments. I can try to give you a list if you
 22 want.
 23 Q. What percentage of your work is devoted to
 24 consulting for litigation purposes?
 25 A. Since we're not very big, that varies a

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09:10:27 1 lot.
 09:10:29 2 Q. How about right now?
 09:10:29 3 A. I'm not sure how to interpret that.
 09:10:30 4 Logically right now is 100 percent, because what I'm
 09:10:30 5 doing right now is part of litigation. But over a
 09:10:34 6 longer span of time, I had this question put to me
 09:10:36 7 before and was asked to go look at actual time
 09:10:45 8 records, and which I did. I think it was over about
 09:10:50 9 a five-year period I looked. And it came out easy
 09:10:52 10 to remember. My time was spent one-third,
 09:10:58 11 one-third, one-third. I was putting one-third time
 09:11:02 12 in on matters relating to litigation; one-third time
 09:11:09 13 on more traditional consulting, where there was no
 09:11:15 14 apparent litigation in view; and then one-third time
 09:11:22 15 on professional activities, such as organizing
 09:11:28 16 conferences or writing papers or teaching, things
 09:11:36 17 like that.
 09:11:36 18 Q. You've been retained by Janssen in this
 09:11:39 19 case?
 09:11:43 20 A. I have.
 09:11:48 21 Q. And you've been asked to render certain
 09:11:53 22 opinions about the State's case?
 09:11:57 23 A. I've been asked to form expert opinions,
 09:12:00 24 yes.
 09:12:04 25 Q. You've been retained by -- who have you

Page 7

09:12:22 1 been retained by?
 09:12:26 2 A. I --
 09:12:28 3 Q. In this case.
 09:12:30 4 A. I'm pausing because I have to think. I
 09:12:31 5 just think of the word Janssen. But I seem to
 09:12:32 6 recall that there's more than one corporate entity
 09:12:38 7 with the name Janssen. And so I'd have to ask
 09:12:39 8 counsel exactly which corporate entity is the
 09:12:43 9 retention --
 09:12:46 10 Q. For --
 09:12:51 11 A. -- party.
 09:12:53 12 Q. For purposes of the deposition, can we call
 09:12:58 13 them Janssen today? Does that make sense to you?
 09:13:06 14 A. Yes.
 09:13:09 15 Q. Okay.
 09:13:20 16 A. Could you speak up just a little bit? I
 09:15:13 17 can --
 09:15:18 18 Q. Sure.
 09:15:23 19 A. -- barely hear you.
 09:15:25 20 Q. Have you been retained by Janssen in any
 09:15:29 21 other cases?
 09:15:37 22 A. Yes.
 09:15:39 23 Q. What other cases?
 09:15:42 24 A. One similar to this in Louisiana and one in
 09:15:46 25 Texas and one in Pennsylvania.

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1 Q. How about New Mexico?
 2 A. I think maybe New Mexico, although I
 3 haven't really done any work there yet.
 4 Q. What were you asked to do in this case?
 5 A. The most complete answer to that is to call
 6 your attention to my expert report in this case,
 7 which describes exactly what I've done. And I have
 8 a copy here. And maybe I can just mention the table
 9 of contents, because there are quite distinct
 10 topics. If you had my report and you went to the
 11 second page, you'd see a table of contents. And it
 12 describes certain statistical analyses of what's
 13 called observational data, which are claims data, in
 14 three different -- of three different types. And
 15 then there is a survey that I conducted of
 16 physicians in South Carolina. That's a separate
 17 activity.
 18 And then I've -- you'll see in Roman
 19 numeral III of the table of contents, I have some
 20 opinions about the CATI study and also about eight
 21 published peer-reviewed studies that were cited by
 22 Janssen in its November 10th, 2003 mailing. I think
 23 that covers it.
 24 Q. Okay. Before we talk about what your
 25 opinions are in this case, could you describe your

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1 medical training, please.
 2 A. You may be confused. I'm here as a
 3 statistician. I'm not a medical doctor.
 4 Q. Okay. Do you have any medical training at
 5 all?
 6 A. No.
 7 Q. Are you an expert in any field of medicine?
 8 A. To the extent that mathematics and
 9 statistics are involved in medicine, I am an expert.
 10 And there are such areas: x-ray interpretation and
 11 processing, genetics. There are certain areas where
 12 my expert subject come into play within the world of
 13 medicine. But most people, including myself, think
 14 of medicine as the sort of thing that an M.D. does
 15 on a day-to-day basis, and I don't do anything like
 16 that.
 17 Q. Okay. Are you an expert in psychiatry?
 18 A. I'd say "same answer," but it sounds like --
 19 I'm not being clear. So I'll say to the extent that
 20 there are areas in psychiatry, as there certainly
 21 are, where statistics or mathematics turns out to be
 22 a important -- play an important role, yes in there
 23 I would be an expert. But not as a general matter.
 24 I'm certainly not a psychiatrist.
 25 Q. Okay. That's not clear enough. Can you

Pages 6 to 9

09:18:19 1 tell me in what ways you're an expert in psychiatry?
 09:18:21 2 A. I'm not an expert in psychiatry. But --
 09:18:29 3 Q. Okay.
 09:18:35 4 A. -- from -- but I have to explain my answer.
 09:18:39 5 There are aspects of psychiatry where
 09:18:47 6 statistical analysis plays a role, and to the extent
 09:18:49 7 that we were referring to some subject in psychiatry
 09:18:52 8 or activity in psychiatry that happens to be of a
 09:18:58 9 particular character involving statistics, then, of
 09:18:58 10 course, I would be an expert in that. So I didn't
 09:18:58 11 want to leave that out. But fundamentally I'm
 09:18:58 12 simply not a psychiatrist, don't claim to be.
 09:18:58 13 Q. Can you describe your background with
 09:18:58 14 antipsychotic drugs?
 09:18:58 15 A. I'm trying to understand the question.
 09:18:58 16 MR. BRODY: Object to form.
 09:18:58 17 THE WITNESS: I've never taken an
 09:18:58 18 antipsychotic drug. We'll start with that. I'm
 09:18:58 19 not -- I've never designed one. I have worked in
 09:19:02 20 the litigations that we discussed earlier, and those
 09:19:02 21 involve that as a subject matter.
 09:19:02 22 BY MR. TRAMMELL:
 09:19:02 23 Q. Have you undertaken --
 09:19:02 24 A. That's as close -- I'm sorry.
 09:19:02 25 Q. Go ahead.

009:17:14 1 A. That's as close as I can understand your
 009:17:16 2 question. I'm not really sure exactly what I'm
 009:17:18 3 answering there.
 009:17:19 4 Q. What -- have you undertaken any study of
 009:17:22 5 antipsychotic drugs?
 009:17:23 6 A. Well, in this case I've undertaken the
 009:17:26 7 study that I've described to you a moment ago,
 009:17:28 8 resulting in my report. And in the State of
 009:17:30 9 Louisiana, I did something quite similar. That's
 009:17:32 10 the extent of my studies.
 009:17:34 11 Q. Okay. So prior to being retained by
 009:17:36 12 Janssen, you had undertaken no study of
 009:17:38 13 antipsychotic drugs, right?
 009:17:40 14 A. Correct.
 009:17:42 15 Q. Okay. Did you do any research about
 09:17:57 16 antipsychotic drugs after being retained?
 009:18:07 17 A. I did the research that was appropriate and
 009:18:09 18 necessary to arrive at the opinions and facts
 009:18:09 19 described in my report.
 009:18:09 20 Q. What did you do?
 009:18:09 21 A. Well, that's -- that's a two-hour answer.
 009:18:12 22 Do you really --
 09:20:45 23 Q. Well --
 009:18:13 24 A. -- want to do that?
 009:18:14 25 Q. No.

1 What types of research did you do?
 2 A. I suggested a moment ago to look into broad
 3 types. The best place that I could think to direct
 4 you is the table of contents of my report. And I've
 5 run that -- through that with you once. And so they
 6 are also the types of research that I undertook.
 7 Q. Okay. So your reference in your report
 8 certain studies, right?
 9 A. I do.
 10 Q. Okay. How did those studies come to your
 11 attention?
 12 A. Well, the studies that come to mind as I
 13 listen to your question are the studies listed on
 14 paragraph 43 of my report. And there are other
 15 studies that may be mentioned here and there, but
 16 that's prominent in my mind as I answer your
 17 question. There are eight of them listed there.
 18 And they came to my attention because they were
 19 listed in an attachment that was part of a mailing
 20 that I described to you a moment ago.
 21 Q. Okay. Are these the only studies you
 22 reviewed in conducting your research of
 23 antipsychotic drugs?
 24 MR. BRODY: Objection; form.
 25 THE WITNESS: I have Exhibit 3 to my

1 report, a list of materials considered, and there's
 2 a section in there, "Books, Articles, and Papers."
 3 BY MR. TRAMMELL:
 4 Q. Uh-huh.
 5 A. And you'll see that there are more listed
 6 there than -- than just those eight.
 7 Q. How did these studies come to your
 8 attention?
 9 A. Well, different ones in different ways.
 10 They -- the first one is a book by Johnson and
 11 Bhattacharyya.
 12 I can spell that for you later. Let me
 13 just write this down, so that we can remember this.
 14 Q. I just want to focus on the studies --
 15 A. I'm just trying --
 16 Q. -- of antipsychotic --
 17 A. -- to help him spell Bhattacharyya.
 18 Q. I understand.
 19 A. It will just take me a second.
 20 Okay. So you've instructed me that I can
 21 skip the books and go to -- to articles.
 22 Q. Right.
 23 A. And so I'm on page 2 now of this list. And
 24 you've asked me a new question, about how they came
 25 to my attention.

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09:20:52
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09:25:25

Q. Right.

A. Okay. I've indicated the answer to that for eight of them. And I can't answer for sure, due to lack of recollection for some of these, but it's either that they were mentioned in other materials that I'd been presented with, like in the reports of other experts or perhaps in other publications, and so they came to my attention that way, or I think in some cases they were simply called to my attention by counsel. But I'm not in every case able to tell you which of those two. But I think it would be one of those two in every case.

Q. Counsel for Janssen send you these articles?

A. No, not — sometimes yes; sometimes no. Because I have my own way to get articles. But I can't tell you which one exactly is which. But you've correctly hit on the two mechanisms. One is sometimes they've sent an article. Sometimes I've procured it on my own.

Q. Did you do any independent research of antipsychotic drugs for this case?

A. All of my research was independent.

Q. Did you do any independent literature review?

1 get my understanding. I think I have the complaint
2 somewhere, and I'd like to refer to it if you want a
3 really complete or accurate answer. But basically
4 the plaintiffs are alleging that -- I think that
5 their complaint has changed over time, but they are
6 complaining about the November 10, 2003 letter and
7 the content thereof and the truthfulness or lack of
8 truthfulness of assertions made in it, and they're
9 complaining about marketing practices in general and
10 the efficacy of the medication Risperdal in terms of
11 its effect on psychotic patients who benefit from
12 these kinds of medicines, including the side effect
13 aspects of these medications, which are important.

14 If you want to know more precisely than
15 that, because that's just a rough recall, then I'd
16 like to get my hands on the complaint, and I can
17 just read it back to you.

18 Q. I'm going to get back to that. But what is
19 epidemiology?

20 A. It is the statistical study of human
21 health. And that's -- that's all it is, although
22 sometimes people forget that injuries may also be a
23 part of epidemiology. In fact, there's a book
24 called "Injury Epidemiology." So when I say human
25 health, I don't mean just the flu. I could include

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1 A. Everything I looked at was independent,
2 independent in the sense that it was under my
3 direction and control. I'll -- and understand the
4 word "independent" to mean that.
5 Q. Sure. You testified that --
6 A. I couldn't hear this.
7 Q. You testified that certain of the articles
8 referenced were articles referenced in a letter from
9 Janssen; others were referenced by expert reports.
10 Aside from those two mechanisms of finding articles
11 related to antipsychotics, did you do an independent
12 search of the medical literature on antipsychotic
13 drugs?
14 A. Just a moment. Let me look at this, and
15 I'll think about that.
16 No, I think those were the two means, by
17 reference from other documents or materials that
18 were just sent to me.
19 Q. Are your opinions summarized in your expert
20 report?
21 A. Yes.
22 Q. What is your understanding of the
23 allegations the plaintiff makes in this case?
24 A. Just a moment.
25 I've read the complaint, and that's where I

1 traffic accidents. But as long as it's a
2 statistical study of those things, then it's called
3 epidemiology.

4 Q. Can somebody go to school to learn how to
5 be an epidemiologist?

6 A. Sure. They have to study statistics, and
7 then they get a job in which they apply their
8 statistical training to aspects of human health.

9 Q. Is there such a thing as a degree in
10 epidemiology?

11 A. Not in -- not usually, no. But some
12 schools have it, but not -- not many, in my
13 experience.

14 Q. Do you have a degree in epidemiology?

15 A. No. There was no department of
16 epidemiology where I went to school.

17 Q. Do you consider yourself an expert in
18 epidemiology?

19 A. Yes, because I'm an expert in statistics,
20 and I have for more than 20 years had a major
21 component of my work applying statistics to studies
22 of human health.

23 Q. You said you rendered an opinion about --
24 you haven't said this, actually. But you said the
25 plaintiff made an --

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1 A. I'm not able to hear you. Rendered a what?
2 Q. You said the plaintiff made allegations
3 about the November 10th, 2003 letter, right?
4 A. I believe that's correct.
5 Q. Okay. Do you have an opinion about the
6 plaintiff's aggregations in this case?
7 MR. BRODY: Objection to form. Which --
8 which allegation?
9 BY MR. TRAMMELL:
10 Q. With respect to the November 10th, 2003
11 letter.
12 A. Well, that's such a sharp question -- and
13 I'm not criticizing the question, but it's such a
14 sharp question, I think I'd better get the complaint
15 in front of me, so we can know exactly which aspect
16 of which allegation I'm going to be commenting on.
17 Q. Did you render an opinion about the
18 November 10th, 2003 letter in your report?
19 A. I did in the material in section Roman
20 numeral III, part (a), which refers to the eight
21 studies that are described, or at least listed, in
22 the -- yeah, they're listed, and they're
23 characterized in the November 10, 2003 mailing. And
24 there's no sharp line here between the issues that
25 might be discussed in the context of the November

1 A. Reading --
2 Q. Describe it.
3 A. -- the statement in the letter and then
4 reading the articles.
5 Q. Anything else?
6 A. No.
7 Q. Do you have any training in analyzing
8 medical literature?
9 A. I certainly do when that literature is
10 inherently statistical in its character. And that's
11 the case with these articles.
12 Q. Prior to reading these articles, had you
13 ever --
14 A. I missed it. I -- I just can't hear you
15 very well.
16 Q. Prior to reading these articles for
17 purposes of this --
18 A. Prior to reading, or part of reading?
19 Q. Prior to reading these articles for
20 purpose -- for the purpose of this litigation, had
21 you read medical literature on antipsychotic drugs?
22 A. Yes.
23 Q. When?
24 A. When I was working on the Louisiana
25 project.

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09:38:57 1 I'm using these notebooks because -- for lack of my
 09:38:58 2 own documents, which haven't arrived yet.
 09:38:59 3 MR. BRODY: Okay. But I just -- I just
 09:39:00 4 want to be sure at some point in time we put on the
 09:39:01 5 record everything that we've provided in response to
 09:39:02 6 the document requests that came with the deposition
 09:39:03 7 notice.
 09:39:04 8 MR. TRAMMELL: Sure. And you don't object
 09:39:05 9 to using these notebooks for purpose of this
 09:39:06 10 deposition, do you?
 09:39:07 11 MR. BRODY: Oh, no, not at all.
 09:39:08 12 MR. TRAMMELL: Okay.
 09:39:09 13 Q. And you don't have any trouble referencing
 09:39:10 14 these notebooks to answer these questions?
 09:39:11 15 A. You're talking to me now?
 09:39:12 16 Q. Yes.
 09:39:13 17 A. No. I think it's a good idea.
 09:39:14 18 Q. Okay.
 09:39:15 19 A. Because I made them precisely so you would
 09:39:16 20 have a nice, coherent set of my materials.
 09:39:17 21 Q. Okay.
 09:39:18 22 MR. BRODY: And just for the record, I
 09:39:19 23 believe all but one of the documents that's provided
 09:39:20 24 in the notebooks is something that you -- was
 09:39:21 25 previously identified or you previously had. But we

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09:39:22 1 can cover that later.
 09:39:23 2 MR. TRAMMELL: Sure.
 09:39:24 3 Q. Can you point to me in your report where
 09:39:25 4 your survey methodology is described?
 09:39:26 5 A. Well, let me -- I'm going to do that, yes.
 09:39:27 6 But let me tell you how I'm going to do it. There's
 09:39:28 7 a table of contents here on page 2. And it's in --
 09:39:29 8 it begins with Roman numeral II(a), which is on page
 09:39:30 9 4. So then you turn to page 4 and -- internally
 09:39:31 10 numbered page 4 and find Roman numeral II(a), and
 09:39:32 11 that's where it begins.
 09:39:33 12 Q. Is the basic methodology you describe here
 09:39:34 13 the same as the methodology you applied in
 09:39:35 14 Louisiana?
 09:39:36 15 A. There's similarities, and there's
 09:39:37 16 differences.
 09:39:38 17 Q. What are the differences?
 09:39:39 18 A. At a -- at a broad level, the main
 09:39:40 19 difference is that in Louisiana the Court permitted
 09:39:41 20 a much larger sample of doctors for me to get
 09:39:42 21 questions and answers from. There was 150. And in
 09:39:43 22 this particular case, it's a much smaller number of
 09:39:44 23 20.
 09:39:45 24 Q. Is that an important difference?
 09:39:46 25 A. It's an important difference. But are

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1 you -- I take it you want me to stop answering your
 2 first question?
 3 Q. We'll go back to it. Tell me whether --
 4 MR. BRODY: Well, I -- all right. Well, I
 5 just want to note for the record that Dr. Wecker has
 6 not completed answering the prior question. We
 7 object to --
 8 BY MR. TRAMMELL:
 9 Q. You can go ahead and finish the other
 10 question. I'll get back to it.
 11 A. It's -- well, we're distracted now, so why
 12 don't you start again. And it's clear that there
 13 are other differences, and differences that I might
 14 help you understand better if I explain them. But
 15 we'll get to that, I'm sure. And I'll just wait for
 16 your question.
 17 Q. We can do that now. I'll go through the
 18 differences after you've told me what they are.
 19 What are the other differences, aside from the
 20 sample size, or aside from the number of depositions
 21 conducted?
 22 A. Well, that -- that leads, as I was about to
 23 explain, to a difference of design. With a -- with
 24 only a sample of 20 to work with, it would have been
 25 difficult, perhaps impractical, to get the accuracy

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1 of results for the entire population of
 2 antipsychotic-prescribing doctors that I was able to
 3 achieve when I had a larger sample size of 150. So
 4 facing that practical problem, I changed the design
 5 to focus on a much smaller number of doctors rather
 6 than all antipsychotic-prescribing doctors. And
 7 with that smaller number of high-prescribing
 8 doctors, totaling 101, in my analysis, a sample of
 9 20 was sufficient to make good estimates for that
 10 particular population. That's the important
 11 difference.
 12 Q. Any other important differences?
 13 A. Not that are coming to mind. I think
 14 that's the key difference.
 15 Q. Okay. Aside from the number of depositions
 16 you had to review in the two cases, is the
 17 fundamental methodology the same in Louisiana and
 18 South Carolina?
 19 A. No.
 20 MR. BRODY: Object to form.
 21 THE WITNESS: No. And I just explained
 22 that it was not the same.
 23 BY MR. TRAMMELL:
 24 Q. Okay. So the distinction in the
 25 methodology, aside from the number of depositions,

Pages 22 to 25

09:42:48 1 is the sample you considered, right?
 09:42:52 2 A. No.
 09:42:54 3 Q. Okay. Tell me again what the distinction
 09:42:56 4 is in the fundamental methodology.
 09:42:58 5 A. The distinction is that the population
 09:42:59 6 about which my sample was able to make extrapolated
 09:43:01 7 statements is different in the two cases. In
 09:43:03 8 Louisiana it was all Louisiana prescribers of
 09:43:05 9 antipsychotic medicines. In South Carolina it's the
 09:43:07 10 high-volume prescribers, the ones that prescribe
 09:43:09 11 antipsychotic medicines the most, which is a much
 09:43:11 12 smaller group.
 09:43:13 13 I'd like to add something here. There are
 09:43:15 14 some things that one learns from the group of
 09:43:17 15 high-prescribing doctors that I think do generalize
 09:43:19 16 to situations beyond those doctors, those 101
 09:43:21 17 doctors, because they are inherently of a general
 09:43:23 18 nature, having to do with the efficacy of the drug
 09:43:25 19 or side effects, something like that. There are
 09:43:27 20 other questions that would be more problematic to
 09:43:29 21 try to extrapolate beyond the group of 101. And if
 09:43:31 22 we come to the details, I can give you my view as to
 09:43:33 23 which ones are which.
 09:43:35 24 I'm finished.
 09:43:37 25 Q. Is the difference in the number of

1 sufficiently general nature that they are
 2 generalizable beyond the doctors themselves.
 3 Q. Which questions?
 4 A. Well, we can pull that out and look at it.
 5 But I'll give you the idea.
 6 If -- if the conclusion reached by the
 7 majority of -- the great majority of the -- the
 8 sample from the 101 is that Risperdal is an
 9 effective way of treating antipsychotic symptoms --
 10 that's not exactly one of the questions, but it's --
 11 they're -- they're like that -- then these are the
 12 doctors that are in a position best to know the
 13 answer to those things.
 14 Q. Okay.
 15 A. And so -- okay. I'll stop if you want.
 16 Q. Oh, no. I think, unfortunately, we're
 17 going to have to have you identify which of the
 18 questions. So do you have a reference to the
 19 questions that were --
 20 A. Yes, I've got the questions.
 21 Q. -- analyzed?
 22 A. I've got the questions. Let me see if I
 23 can find them. Just give me a moment.
 24 Q. Sure.
 25 Maybe Exhibit 4.

09:43:23 1 depositions you had available to review an important
 09:43:25 2 difference?
 09:43:27 3 A. Yes, it's important, because it led to a --
 09:43:29 4 quite a different statistical approach and design.
 09:43:31 5 If I'd have had 150 available to me, I'd have done
 09:43:33 6 something different than I did. But I had 20, so I
 09:43:35 7 designed a statistical methodology that was going to
 09:43:37 8 be effective within that limitation.
 09:43:39 9 Q. Okay. And what is your opinion as to the
 09:43:41 10 population that those 20 doctors are representative
 09:43:43 11 of?
 09:43:45 12 MR. BRODY: Objection to form.
 09:43:47 13 THE WITNESS: Well, this is a factual
 09:43:49 14 matter. And it is 101 highest-prescribing doctors.
 09:43:51 15 I'll add a little bit to that. You might say, well,
 09:43:53 16 where would 101 come from? And it's because there
 09:43:55 17 happened to be a tie at the -- for prescriptions at
 09:43:57 18 the position of 100. So I went to 101.
 09:43:59 19 BY MR. TRAMMELL:
 09:44:01 20 Q. Okay. So the opinions you've rendered
 09:44:03 21 based on the 20 depositions are intended to
 09:44:05 22 extrapolate to the 101?
 09:44:07 23 A. That, for sure. And then in the case of
 09:44:09 24 some questions and answers put to the
 09:44:11 25 high-prescribing 101 doctors, I think they are of a

1 A. Exhibit 4 is going to probably serve us
 2 well. It is --
 3 MR. BRODY: They're also in Exhibit 5. The
 4 print's a little bigger in Exhibit 5. It's easier
 5 to read.
 6 THE WITNESS: Yeah, that's -- that's
 7 helpful. Thank you.
 8 Exhibit 5. And I'll mention, before I turn
 9 to you to listen to your next question, that, of
 10 course, these questions were put in a legal
 11 deposition to doctors, and those questions were
 12 recorded verbatim, so that the best source --
 13 although an awkward source for our purpose at the
 14 moment, the best source is really the deposition.
 15 Then you can read what a court reporter wrote down
 16 as to the actual question. But Exhibit 5 of the
 17 notebook that you and I both have is probably a good
 18 enough source for us now.
 19 BY MR. TRAMMELL:
 20 Q. Okay. I think you just said this, but is
 21 Exhibit 5 enough information about these questions
 22 for you to be able to answer my question about what
 23 information you were able to take from these
 24 depositions to extrapolate to the entire South
 25 Carolina prescribing population?

09:52:58 1 A. I think so.
 09:52:02 2 Q. Okay. Can you identify those questions for
 09:52:08 3 me, please.
 09:52:10 4 A. Let's go down one at a time. The questions
 09:52:12 5 in Exhibit 5 are numbered. And the first one is
 09:52:53 6 numbered 12, because the questions 1 through 11 are
 09:52:23 7 just preliminary questions about the name of the
 09:52:09 8 doctor, and so on.
 09:52:04 9 MR. BRODY: I think -- I think we only --
 09:52:04 10 well -- yeah. Go ahead. Sorry.
 09:52:08 11 THE WITNESS: Okay. So I'm going to start
 09:52:17 12 with 12.
 09:52:52 13 12 would not be generalizable. That would
 09:52:55 14 be -- that -- you could generalize from the sample
 09:52:59 15 of 20 to the population of 101, but I would not
 09:53:02 16 generalize that beyond that.
 09:53:05 17 BY MR. TRAMMELL:
 09:53:09 18 Q. Okay. And just for -- I mean, if you want
 09:53:23 19 to look at these and then answer my question, that's
 09:53:24 20 fine. I think --
 09:53:28 21 A. Okay. We can take a break. Because as I
 09:53:30 22 look through, there's 86 of these. And so we could
 09:53:33 23 spend quite a bit of time on this.
 09:53:36 24 Q. Okay. Let's go off the record and let you
 09:53:36 25 look through it.

09:53:56 1 A. Okay.
 09:53:58 2 THE VIDEOGRAPHER: Going off the record,
 09:53:59 3 the time is 9:45.
 09:54:01 4 (Recess taken.)
 09:54:03 5 THE VIDEOGRAPHER: We are back on the
 09:54:05 6 record. The time is 9:50.
 09:54:06 7 BY MR. TRAMMELL:
 09:54:08 8 Q. Dr. Wecker, have you had an opportunity to
 09:54:50 9 review the questions in Exhibit 5 to your report?
 09:54:53 10 A. Yes.
 09:54:58 11 Q. Okay. Which of the questions listed in
 09:54:03 12 Exhibit 5 are capable of providing information that
 09:54:17 13 could be extrapolated to the entire South Carolina
 09:54:22 14 prescribing population?
 09:54:24 15 A. Okay. Let me answer that by going through
 09:54:20 16 them one at a time.
 09:54:28 17 The first -- and let -- I'm going to
 09:51:31 18 preface here as to what I'm doing. Some of these
 09:51:35 19 questions -- and I'll give an example of one -- are
 09:51:41 20 particular to the doctor who was answering the
 09:51:46 21 question. That's not the kind that you've just
 09:54:38 22 asked me about. But to make it clear that there's
 09:54:31 23 two kinds, I think I'd better give an example of
 09:54:31 24 both.
 09:54:32 25 So question number 12, which happens to be

1 the first question on my list beginning in Exhibit
 2 5, asks the doctor if he's ever treated pediatric
 3 patients, meaning patients zero through 12 years
 4 old. That would be a particular question for that
 5 doctor. And the answers to those questions in the
 6 sample would be extrapolatable, generalizable, to
 7 the sample of the population of 101, but I would not
 8 use them to extrapolate to any doctors outside that.
 9 Okay. So that's one that's not on the list.
 10 Then go to -- all the way to number 30,
 11 because 12 through 29 are the first kind, the --
 12 I'll call them the particular kind. The general
 13 kind would start with 30, as to whether, in the
 14 experience of the high-prescribing doctors,
 15 Risperdal is generally effective for treating the
 16 positive symptoms of schizophrenia.
 17 This is a factual question about the
 18 effectiveness of medicine in patients with
 19 schizophrenia. And 100 percent of the doctors asked
 20 this question answered yes to this. So I think it
 21 is quite sensible to say that what these doctors who
 22 have the most experience with antipsychotic drugs
 23 and are in the best position to answer questions
 24 about efficacy of psychotic drugs has to say is of a
 25 general nature that goes beyond a particular doctor

1 or group of doctors.
 2 Q. Okay.
 3 A. So I'm going to call those the general
 4 ones. And then I'm going to read the other ones
 5 that I have here, that are of that general
 6 character. Is that okay?
 7 Q. Yeah. I guess all I really want you to do
 8 is identify them on here for me.
 9 A. But counsel for Janssen has asked me to
 10 read the question, so that the record is clear as to
 11 what the questions were.
 12 Q. That's fine.
 13 A. So I --
 14 Q. It's actually the first question I have in
 15 Exhibit 5. Is that the one you're talking about?
 16 "In your experience, is Risperdal generally
 17 effective for treating the positive symptoms?"
 18 MR. BRODY: That's
 19 BY MR. TRAMMELL:
 20 Q. -- "of schizophrenia?"
 21 THE WITNESS: That's not the first
 22 question. That --
 23 MR. BRODY: That's the first --
 24 THE WITNESS: That's the -- that's the
 25 first question on the second page. It's number 30.

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1 BY MR. TRAMMELL:
2 Q. Right. Okay. That's one, though?
3 A. That's one.
4 Q. Okay.
5 A. And then 31 is another of the general kind.
6 "In your experience, is Risperdal generally
7 effective for treating the negative symptoms of
8 schizophrenia?"
9 32 is of the general kind. "In your
10 experience, do patients who take Risperdal have
11 better overall outcomes more frequently than
12 patients who take a first-generation antipsychotic?"
13 That's of the general kind.
14 33 is of the special kind, because it
15 begins with "In your practice." So I'm not going to
16 put 33 on the general list.
17 34 is of the general kind. "In your
18 experience, are patients who take first-generation
19 antipsychotics, such as Haldol and Thorazine, more
20 likely to experience extrapyramidal and
21 anticholinergic" --
22 Q. "Cholinergic."
23 A. "Cholinergic." I'm going to spell that one
24 for you. A-N-T-I-C-H-O-L-I-N-E-R-G-I-C -- "side
25 effects than patients who take second-generation

1 40 is of the general kind. "In your
2 experience, are patients who consistently take their
3 antipsychotic medications less likely to require
4 costly follow-up treatment, such as in-patient
5 psychiatric care, than patients who do not
6 consistently take their medications?"
7 41 is of a general kind. "In your
8 experience, are patients who consistently take their
9 antipsychotic medications less likely to require
10 costly follow-up treatment, such as emergency room
11 care, than patients who do not consistently take
12 their medications?"
13 42. This is also of the general kind. "In
14 your experience, does increased patient compliance
15 with antipsychotic prescriptions result in overall
16 conservation, as opposed to consumption, of health
17 care resources?"
18 43 is of the general kind. "In your
19 experience, does the use of Risperdal typically
20 conserve health care resources as compared to
21 first-generation antipsychotics?"
22 New page, 3.
23 44 is of the general kind. "In your
24 experience, does increased patient compliance with
25 antipsychotic prescriptions typically decrease the

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1 antipsychotics?" That's on the general list.
2 35 is of the general kind. "In your
3 experience, are patients who take first-generation
4 antipsychotics, such as Haldol and Thorazine, more
5 likely to experience tardive dyskinesia than
6 patients who take second-generation antipsychotics?"
7 And for the court reporter, these hard
8 medical words, you can -- at a break I'll just show
9 you this list, and you can copy from there, to get
10 the spellings right.
11 Then 36 is also in the general category.
12 "In your experience, does Risperdal typically have a
13 more moderate side effect profile than
14 first-generation antipsychotics?"
15 37 is of the general kind. "In your
16 experience, is Risperdal typically better tolerated
17 than first-generation antipsychotics?"
18 38 is of the general kind. "In your
19 experience with antipsychotic medications, are both
20 efficacy and tolerability important considerations
21 in the choice of which antipsychotic to prescribe?"
22 I'm on 39 now. It's of the general kind.
23 "In your experience, do both efficacy and
24 tolerability increase the likelihood that a patient
25 will take an antipsychotic medication consistently?"

1 human consequences of psychiatric illness?"
2 45 is of the general kind. "In your
3 experience, does compliance taking antipsychotic
4 medications typically make patients less likely to
5 experience recurrence of psychosis?"
6 46. Referring back to the previous
7 question as a predicate, 46 says "Less likely to be
8 violent." That's of the general kind.
9 47. "Less likely to be an extreme burden
10 on family members." That's of the general kind.
11 "Less likely to experience worsening of
12 their condition." 48. That's of the general kind.
13 49, of the general kind. "Overall, in your
14 experience, is Risperdal a reasonably safe and
15 effective medication for treating schizophrenia and
16 other psychotic disorders?"
17 50 is of the general kind. "Overall, in
18 your experience, is Risperdal a safer and more
19 effective medication for treating schizophrenia and
20 other psychotic disorders than the first-generation
21 medications?"
22 51 is of the general kind. "In your
23 experience, are there circumstances when the
24 off-label use of medications is appropriate?"
25 52. "In your experience, is it fair to say

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1 that off-label use of medications is not an uncommon
2 practice?" I put that in the general category.

3 53. "In your experience, are there
4 circumstances when the off-label use of
5 antipsychotic medications is appropriate?" General
6 category.

7 54, in the general category. "In your
8 experience, is it fair to say that off-label use of
9 antipsychotic medications is not an uncommon
10 practice?"

11 Now, 55 through 60 I think are of the
12 particular kind, and so I'm moving to the next page.

13 And on the -- page 4, I move all the way
14 down to 66 before I hit another of the general kind.
15 "Based on your training and experience, is it common
16 for medications to have both benefits and risks?"

17 67. "Based on your training and
18 experience, is it your understanding that all
19 antipsychotic medications," dash, "both
20 first-generation and second generation," dash, "have
21 potential side effects?"

22 68. "Are you aware of an association
23 between antipsychotic medications and weight gain?"
24 That one is of a -- I think I put that in the
25 specific or particular category, not a general one.

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1 69, also that's going to be a particular
2 one.

3 So I'm now down on 74 to find the next
4 general one. "Would you agree that the 1993 package
5 insert for Risperdal advised of an association
6 between Risperdal and weight gain?"

7 75. "Would you agree that the 1993 package
8 insert for Risperdal advised of an association
9 between Risperdal and diabetes?"

10 76. 4 -- 74, 5, and 6 were all of the
11 general kind.

12 76. "Would you agree that the 2004 package
13 insert for Risperdal incorporated a class warning of
14 hypoglycemia and diabetes?"

15 77 and 78, they're of the particular kind.

16 And all the rest are of the particular
17 kind, up -- and 86 is the end. And so I'm finished
18 with the answer to your question.

19 Q. Could you describe your methodology that
20 you used to determine that those -- the answers to
21 those questions could be extrapolated to the entire
22 South Carolina population of prescriber?

23 A. Yes. It's easy. If they were -- if the
24 question was asking something that would be
25 particular to a doctor, such as whether he's

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1 received a document or whether he treats a pediatric
2 patient, then one could extrapolate from the sample
3 only to the population that was sampled.

4 When the question is of a factual nature
5 and that fact is a fact about the world in general,
6 then these high-prescribing doctors, who are in a
7 position to know the facts being inquired about, are
8 giving — giving us information that is of a very
9 general character, and — and so that information
10 applies broadly.

11 Q. What's your basis for that methodology?

12 MR. BRODY: Objection to form.

13 THE WITNESS: It's just simple logic.

14 BY MR. TRAMMELL:

15 Q. Do you make any distinction in your report
16 between the general-kind questions and the specific
17 kind?

18 A. The distinction is made by the questions
19 themselves. I haven't grouped them, the way I just
20 did now in answering your questions. But certainly
21 the distinction is made on a question-by-question
22 basis.

23 Q. Where did these questions come from?

24 A. I'm the author of these questions. But I
25 consulted with counsel and read the complaint and

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1 the other materials that I -- are on my list of
2 items considered. And through that complete
3 process, I eventually crafted these questions.
4 Q. Okay. Did counsel for Janssen play any
5 role in writing these questions?
6 A. They --
7 MR. BRODY: Objection to form.
8 THE WITNESS: They played a role in
9 listening to my proposed questions and commenting
10 occasionally, like "That's confusing" or "I don't
11 understand that one so well," and then we'd work on
12 better language. So, yes, they played a role. And
13 it was for me an important role. But I maintained
14 the overall direction of the project.
15 BY MR. TRAMMELL:
16 Q. Why was their role important?
17 A. Because they better understand the issues
18 in the case than I do, and they -- and this -- this
19 set of questions is designed to shed light on issues
20 that are in contention in this litigation.
21 Q. What is a survey?
22 MR. BRODY: Objection to form.
23 THE WITNESS: There are many different
24 kinds. But usually when people say "survey," or at
25 least in the context of a statistician being asked

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1 about a survey, they mean something called a sample
2 survey. So a sample survey is first one that looks
3 at a few things and then, by careful design of
4 the — which ones are looked at, is empowered, in a
5 scientifically defensible way, to extrapolate those
6 results to a larger number that they haven't
7 actually looked at. It sounds impossible to do.
8 How can you say something about something you've
9 never looked at? But by a probability sample, you
10 actually have that ability. So that's the sample
11 part of the sample survey.

12 Then the survey part of a sample survey
13 pair of words is that information is collected.
14 That can be either from human beings who answer
15 questions or it can be from observations of human
16 beings, or it can be from something that doesn't
17 involve human beings at all. All of that could be a
18 sample survey.

19 BY MR. TRAMMELL:

20 Q. Did you conduct a survey for purposes of
21 rendering your opinion in this case?

22 A. Yes.

23 Q. Describe your — the methodology underlying
24 your survey in this case.

25 MR. BRODY: Objection to form.

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1 THE WITNESS: Okay. Well, I'm going to not
2 simply read my report, which is one way to -- and a
3 good way, to answer this question, but I'll direct
4 you to the right spot that you can read it later,
5 and then I'll just summarize or characterize what's
6 there. Just a moment.

7 So that begins on page 4 of my report. But
8 rather than reading through those details, I'll just
9 give you the general idea.

10 The -- first, a population of the 101
11 highest-prescribing doctors was identified, by
12 looking at records of prescriptions. And the short
13 version of that is if a doctor prescribed a great
14 many antipsychotic prescriptions, he or she could
15 find themselves on this list of high-prescribing
16 doctors.

17 So having identified the 101
18 high-prescribing doctors in South Carolina, based on
19 prescription records, I then used a random number
20 generator, which is analogous to flipping coins, but
21 it's done with a computer, to identify an -- what's
22 called an equal-probability or simple random sample
23 of 20 from the 101.

24 I think I'll stop there, because I'm not
25 sure how much detail you want. And I'll answer any

1 follow-up if you like.
2 BY MR. TRAMMELL:
3 Q. Are there generally accepted principles
4 that have to be applied in conducting a survey?
5 A. I'm thinking about that.
6 There's so many different kinds of surveys,
7 that are done in so many different circumstances,
8 that it's difficult to say that there's one
9 principle that always needs to be applied. But if
10 a -- but here's one that I think qualifies for --
11 for consideration, even though I can think of some
12 situations where it is not necessary. But most of
13 the time it is necessary to have a sample which is
14 what's called a probability sample. And a
15 probability sample is a sample in which each and
16 every member of the population has a known and
17 non-zero probability of selection. That's just the
18 definition of it.
19 Now, the -- I immediately think of a case
20 where you don't have to do that. So even that is
21 not always the case. But that would be the most
22 broadly applicable requirement.
23 Q. Is --
24 A. Let me say a little bit more about that.
25 The reason that that's so important is because that

1 is the mechanism by which, in most cases, one gets a
2 scientific underpinning to the extrapolation from
3 the sample to the population.

4 Go ahead.

5 Q. Is it important -- is it important who asks
6 the questions in the survey?

7 A. No, that -- that can vary greatly from one
8 context to another.

9 Q. Okay. And I'm talking specifically about
10 the kind of survey you're relying on in this case.
11 In this kind of survey, is it important who does the
12 questioning?

13 MR. BRODY: Object to form.

14 THE WITNESS: I'm thinking of how to answer
15 that. Surely you don't mean who by name, but maybe
16 by profession or something like that? When you
17 say -- I think I'd have to say I don't understand
18 the question, because I don't know quite what you
19 mean by "who."

20 BY MR. TRAMMELL:

21 Q. I don't mean by name.

22 A. Okay. Well, in this -- in this particular
23 design, there -- which I think has very respectable
24 merit, and I'm pleased with this design, you really
25 don't have a choice, because the questions are put

10:16:30 1 to deponents in a legal deposition under oath, and
 10:16:33 2 therefore they could only be asked by lawyers,
 10:16:36 3 because they're the only ones empowered to do that.

10:16:39 4 If I'm misunderstanding your question --

10:16:42 5 Q. Yeah, I'm not sure that was an answer to my
 10:16:46 6 question.

10:16:49 7 A. Well, then I apologize. But I'm doing my
 10:17:00 8 best. If you could try it again.

10:17:03 9 Q. Sure. Does it matter or not who actually
 10:17:06 10 conducts the survey? If it does matter, then why?

10:17:10 11 MR. BRODY: Objection to form.

10:17:13 12 THE WITNESS: Well, that's still confusing
 10:17:16 13 for me, because although you've told me previously
 10:17:19 14 that when you say "who," you don't mean a person's
 10:17:22 15 name, I don't know if that predicate continues with
 10:17:25 16 this question or not; and whether it does or not,
 10:17:28 17 I'm not sure what "who" means if it doesn't mean a
 10:17:31 18 person.

10:17:34 19 BY MR. TRAMMELL:

10:17:38 20 Q. Can the identity of the person conducting
 10:17:41 21 the survey contribute bias to results?

10:17:44 22 MR. BRODY: Objection to form. Do you mean
 10:17:47 23 this survey or any survey?

10:17:50 24 BY MR. TRAMMELL:

10:17:53 25 Q. Surveys of this type.

10:18:50 1 A. Well, "surveys of this type" could be
 10:18:53 2 broad, and I'm not sure what it encompasses. But I
 10:18:56 3 can answer for this survey.

10:18:59 4 Q. Well, what I'm trying to understand is,
 10:19:02 5 you've described your -- you've described this as a
 10:19:05 6 survey, using a statistical sample. In surveys of
 10:19:08 7 this kind, can the identity of the questioner
 10:19:11 8 contribute bias to the results?

10:19:14 9 A. I don't think so. And I guarded against
 10:19:17 10 that very well, because I trained the persons asking
 10:19:20 11 the questions to ask them from a script, and wrote
 10:19:23 12 the script out from them -- for them from which they
 10:19:26 13 read. And to the extent that there's any doubt
 10:19:29 14 about that, we have a court reporter transcript of
 10:19:32 15 the entire process. So I think that we have
 10:19:35 16 adequate safeguards against any unwanted
 10:19:38 17 manipulation of the process.

10:19:41 18 Q. And the purpose of those adequate
 10:19:44 19 safeguards is to eliminate bias?

10:19:47 20 A. No, "bias" is a term of art for me, so I
 10:19:50 21 don't think I would use that word here. But the
 10:19:53 22 purpose is to ensure that the same questions are, in
 10:19:56 23 the same order, put to the different deponents.

10:19:59 24 Q. What safeguards were implemented to prevent
 10:19:59 25 bias?

1 MR. BRODY: Objection; form.

2 THE WITNESS: "Bias" is a statistical term
 3 of art, and so I -- it makes not good sense to me to
 4 use it in the way you've used it in that question.
 5 So perhaps I can interpret it as a layman's thought,
 6 to mean some kind of corruption of the process, or
 7 something like that. Is that fair?

8 BY MR. TRAMMELL:

9 Q. No.

10 Can the bias of a questioner in a survey
 11 affect the objectivity of the results of the survey?

12 A. Again, "bias" is a term of art for me, and
 13 I would never use it in the way you're using it in a
 14 sentence. So I have to interpret it in some
 15 nonexpert, layman's fashion.

16 So "bias," as I try to interpret your
 17 question, of the questioner must mean that he -- the
 18 questioner has a particular point of view that's
 19 different than somebody else's point of view about
 20 something. Okay. I can accept that as a thought.
 21 But I -- I've -- I've got safeguards built into
 22 that, because the bias -- the -- I'm sorry, not the
 23 bias, but the questioner is reading from a script.
 24 And to ensure that the question is reading from the
 25 script, I have a court reporter present, writing

1 down every word that's being asked and answered. So
 2 I give no license to the questioner.

3 Q. Okay. And the script you're referencing is
 4 the questions in Exhibit 5, right?

5 A. That's not exactly, but approximately.
 6 The -- Exhibit 5 is a summary. The script that I
 7 actually gave to the lawyers to read from is -- was
 8 not Exhibit 5, but -- but it has those questions on
 9 it. And then they read from there, and then I
 10 tabulated the answers in Exhibit 5.

11 Q. Okay. Is it important that surveys be
 12 conducted in an objective manner?

13 A. I'm not sure how to interpret that one.
 14 I'm not sure what an unobjective manner would mean.
 15 I think it's important that a survey be done in a
 16 thoughtful manner and by procedures that are well
 17 thought out. I'm not sure what objective, versus
 18 unobjective, would mean.

19 Q. Surveys conducted for purposes of
 20 litigation are -- well, I'll say this: Surveys
 21 conducted by a party to litigation are done to
 22 support that party's position. Wouldn't you agree
 23 with that?

24 A. Not necessarily. But they're done to shed
 25 some light on the subject matter; I'll give you

10:22:42 1 that.
 10:22:48 2 Q. Okay. If a party to a litigation conducts
 10:22:52 3 a survey, is it possible that that survey could be
 10:22:56 4 done in a way that's not objective?
 10:22:59 5 MR. BRODY: Objection to form.
 10:23:02 6 THE WITNESS: If, by "a party," you mean
 10:23:05 7 like a plaintiff or a defendant, and not a
 10:23:08 8 statistical expert, then there's every likelihood
 10:23:11 9 that the survey would be flawed in many, many ways,
 10:23:14 10 because it really requires an expert to do that kind
 10:23:17 11 of work.
 10:23:20 12 BY MR. TRAMMELL:
 10:23:23 13 Q. Okay.
 10:23:26 14 A. The work isn't all that difficult for an
 10:23:29 15 expert. But a layman hasn't got a chance to get it
 10:23:32 16 right.
 10:23:35 17 Q. What qualifies someone as an expert to
 10:23:38 18 conduct a survey?
 10:23:41 19 A. I think they need to be trained at an
 10:23:44 20 advanced level in statistical analysis.
 10:23:47 21 Q. You said before that you trained the people
 10:23:50 22 who conducted the survey in this case, right?
 10:23:53 23 A. Yes.
 10:23:56 24 Q. Okay. Who were they?
 10:23:59 25 A. There are two of them. And I think one of

10:24:09 1 them's name was Pugh. And -- I don't know if I have
 10:24:12 2 their names anywhere.
 10:24:15 3 I don't -- I think one of them -- I could
 10:24:18 4 try to think during a break. I forgot the other
 10:24:21 5 one's name. There were two of them. It was not
 10:24:24 6 Mr. Brody. They were South -- from South Carolina,
 10:24:27 7 I believe. And the actual training was done by one
 10:24:30 8 of my staff, who went and met with them. I didn't
 10:24:33 9 go myself. But I directed the effort.
 10:24:36 10 I'll -- I'll make a note here to try to
 10:24:39 11 come up with the names of the two lawyers.
 10:24:42 12 Q. Have you ever met either of the lawyers?
 10:24:45 13 A. No. I've met -- I've never met any lawyer
 10:24:48 14 in this case, that I can think of at the moment. I
 10:24:51 15 can think of some names over the phone, but only
 10:24:54 16 Mr. Brody that I've met in person.
 10:24:57 17 Q. And describe --
 10:25:00 18 A. I'm sorry. I may be wrong about that. I'm
 10:25:03 19 not sure who all the lawyers are that are involved
 10:25:06 20 in this case, so I -- if there's some that were in
 10:25:09 21 the Louisiana case that are also in your case, I may
 10:25:12 22 have met them in the Louisiana context.
 10:25:15 23 Q. No, that's okay. All I really wanted to
 10:25:18 24 know is whether you met the two lawyers that
 10:25:21 25 conducted the survey in this case.

1 A. The answer to that I'm sure of, and the
 2 answer to that is no.
 3 Q. Okay. And describe the training that those
 4 two lawyers received in conducting surveys.
 5 A. Well, in conducting this survey.
 6 Q. Right.
 7 A. I didn't give them a general training.
 8 The --
 9 Q. Well, just to be clear, you didn't give
 10 them any training, right? I'm talking about you,
 11 Bill Wecker.
 12 A. I did not -- well, I'm not ready to agree
 13 with that. I was not present, but I was involved in
 14 the determination of what -- that they would receive
 15 this training and what it would be, and then I sent
 16 one of my staff to meet with them. So I was
 17 involved.
 18 The -- the training basically was to
 19 impress upon them the need to use a script, because
 20 lawyers don't usually do that when they go to
 21 depositions. They may have notes. They may have
 22 thoughts in their head about what they want to do.
 23 But they simply are not, in my experience, reading
 24 from a script, and -- it's not natural for them to
 25 do that. And so I needed to impress upon them that

1 they really had to do that, and practice them at
 2 that so that they were faithful to that requirement,
 3 and indicate that in some cases a follow-up
 4 clarifying question was appropriate, but they
 5 couldn't just go wandering off the script.
 6 And you can see cases in the deposition
 7 where -- where there is a clarification in a
 8 follow-up, but that's simply clarifying an answer.
 9 That's not going on to some different topic that
 10 happened to occur to them at the moment.
 11 Q. Okay. That was the training?
 12 A. Yeah, that was the training.
 13 Q. And who did it?
 14 A. The person who actually met with them was
 15 Mr. Hoff of my staff. H-O-F-F.
 16 Q. And what are Mr. Hoff's qualifications?
 17 A. He has a master's degree in applied
 18 mathematics from the University of Chicago. He was
 19 actually my graduate student at the University of
 20 Chicago.
 21 Q. Is Mr. Hoff an expert in survey techniques?
 22 A. Yes, he is by now. He's done a lot of
 23 them.
 24 Q. What qualifies him as an expert in survey
 25 techniques?

10:29:26 1 MR. BRODY: Objection.
 10:29:26 2 THE WITNESS: Training and experience.
 10:29:28 3 BY MR. TRAMMELL:
 10:29:28 4 Q. And what is his training in survey
 10:29:29 5 techniques?
 10:29:30 6 A. The training in survey techniques is
 10:29:31 7 essentially training in statistics, because
 10:29:38 8 there's -- there's -- I can think of no concept in
 10:29:40 9 survey thinking that is not essentially statistical
 10:29:42 10 in nature. Well, maybe that's not completely true,
 10:29:50 11 but it's predominantly the case.
 10:29:52 12 Q. And you're an expert in survey techniques,
 10:29:54 13 right?
 10:29:56 14 A. Yes.
 10:29:58 15 Q. Okay. Is it important that an expert in
 10:30:00 16 survey techniques write the questions that are going
 10:30:02 17 to be used in the survey?
 10:30:04 18 A. I suppose not. But normally it's a good
 10:30:06 19 idea. But different situations call for different
 10:30:08 20 practical applications. So I -- I can conceive of
 10:30:10 21 hypothetical situations that could occur in practice
 10:30:12 22 where it would be exactly the opposite. It would be
 10:30:14 23 important that they don't.
 10:30:16 24 Q. Okay. With a survey of this kind, was it
 10:30:18 25 important that an expert in survey techniques wrote

10:30:16 1 the survey questions?
 10:30:18 2 A. I think yes, but not, meaning by that
 10:30:20 3 "yes," that they would exclusively be involved in
 10:30:22 4 the writing.
 10:30:24 5 Every time I've ever done a survey that's
 10:30:26 6 anything like the ones we are talking about here,
 10:30:28 7 where a human being is going to be asked a question,
 10:30:30 8 I've found that questions are refined and restated,
 10:30:32 9 and you try them out on test people, and -- and if
 10:30:34 10 the people seem confused, it helps you understand
 10:30:36 11 what's confusing about the way you've written the
 10:30:38 12 question.
 10:30:40 13 So although lawyers are very good at asking
 10:30:42 14 questions -- it's a part of their profession -- I
 10:30:44 15 find they're only about mediocre when it comes to
 10:30:46 16 asking survey questions. They don't seem to quite
 10:30:48 17 have that craft down.
 10:30:50 18 Q. Are there principles that have to be
 10:30:52 19 applied in determining the sample of a population
 10:30:54 20 that will be surveyed?
 10:30:56 21 A. Yes. It's the concept of a probability
 10:30:58 22 sample, that I described to you about 15 minutes
 10:31:00 23 ago.
 10:31:02 24 Q. Is it important that the sample consist of
 10:31:04 25 all elements of the population it's intended to

1 represent?
 2 A. It makes no sense. A sample can't consist
 3 of all elements.
 4 Q. Is it important that the sample --
 5 A. I'm sorry. I guess it can, because a
 6 census is the case where that happens. But that --
 7 I didn't think we were talking about that. So it's
 8 possible, but it's an extreme and unusual case.
 9 Q. Well, is it important that a sample account
 10 for the differing characteristics of the population
 11 it's intended to represent?
 12 MR. BRODY: Objection to form.
 13 THE WITNESS: It's important that a sample
 14 be a probability sample if it's -- if it's to enjoy
 15 the scientific underpinnings of an extrapolation,
 16 except in certain special cases that you can inquire
 17 about if you want. Now, once you've got that,
 18 you've got everything you need.
 19 BY MR. TRAMMELL:
 20 Q. Can a sample apply to an entire population
 21 if it overemphasizes certain groups to the exclusion
 22 of others?
 23 MR. BRODY: Objection to form.
 24 THE WITNESS: Yes.
 25 BY MR. TRAMMELL:

1 Q. Why?
 2 A. Because all that's required is that a
 3 sample be a probability sample, leaving aside the
 4 special cases, which rarely occur. And once you've
 5 got that, you've got what you need for a scientific
 6 basis for extrapolation. There's no rule that says
 7 one element of a population cannot be sampled more
 8 frequently than others or, as you say in your
 9 question, emphasized more than others. That's not a
 10 rule. That's not a requirement.
 11 MR. BRODY: Fletch, we've been going for
 12 about an hour and a half. Is this a good time for a
 13 break?
 14 MR. TRAMMELL: Let's take a break. Yep.
 15 THE VIDEOGRAPHER: Going off the record,
 16 the time is 10:31.
 17 (Recess taken.)
 18 THE VIDEOGRAPHER: We are back on the
 19 record. The time is 10:41.
 20 BY MR. TRAMMELL:
 21 Q. Dr. Wecker, we've taken a break. Are you
 22 ready to proceed?
 23 A. Yes.
 24 Q. Earlier in the deposition, you talked
 25 about -- you identified certain questions in Exhibit

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1 5 as the type of questions from which you could get
2 information that could be extrapolated to the entire
3 population of South Carolina prescribers. Do you --
4 A. Nope.
5 Q. -- recall that?
6 A. Actually, that's not the way I phrased it.
7 But I did indicate there were some questions that
8 were general in nature and did not have a limitation
9 to the particular doctors answering the question or
10 the 101.
11 Q. Okay. Do the answers to those questions
12 provide information that can be extrapolated to the
13 entire population of South Carolina prescribers?
14 A. I think the answer is yes. But I have to
15 explain it. The general questions are generally not
16 questions about South Carolina doctors per se.
17 They're questions about medications and patients.
18 Q. Let me ask you a better question.
19 MR. BRODY: Were you finished?
20 THE WITNESS: That's fine.
21 BY MR. TRAMMELL:
22 Q. Did you form any opinion about any
23 particular population based on the answers to those
24 general questions?
25 A. Yes.

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1 Q. What population?
2 A. It depends on the question. But if it's a
3 question about the efficacy of a particular drug in
4 the treatment of psychotic disorders, the population
5 would be the population of people with psychotic
6 disorders.
7 Q. What was the purpose of including the
8 general questions that you identified in the survey?
9 A. Well, there are a lot of them, and
10 different ones may have different points that
11 they're trying to illuminate. But basically they
12 are -- those are questions that were motivated by
13 the allegations and issues in contention in the
14 lawsuit.
15 Q. Did you form any opinion based on the
16 answers to those questions?
17 A. Yes.
18 Q. Okay. And did you form any opinion about
19 the opinions of South Carolina prescribers based on
20 the answers to those questions?
21 A. Yes.
22 MR. BRODY: Objection to form.
23 BY MR. TRAMMELL:
24 Q. Which South Carolina prescribers --
25 A. The --

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1 Q. -- did you form an opinion about?
2 I'm sorry.
3 A. The 101 high-prescribing South Carolina
4 doctors.
5 Q. Okay. Did you form an opinion about the
6 opinions of any South Carolina prescribers beyond
7 the 101 that you -- that were included in your
8 sample size?
9 MR. BRODY: Object to form.
10 THE WITNESS: I think the answer is yes,
11 because some of the questions were of such a general
12 nature that they referred to a phenomenon that is
13 not limited to the -- say the particular patients
14 that the high -- high-prescribing doctors were
15 serving. So if a particular drug is judged as
16 effective in treating psychotic disorders by doctors
17 who are high prescribing and in the best position to
18 know the answer to that question, then I take that
19 as a general proposition and of broad applicability.
20 BY MR. TRAMMELL:
21 Q. Applicability to at least all South
22 Carolina prescribers?
23 A. If it's a -- if it's a general proposition
24 with respect to a drug in certain kinds of patients,
25 then it would be with respect to all such patients

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1 and drugs used in conjunction with those patients
2 that are administered or served by medical doctors
3 in South Carolina, and even in other states.
4 Q. Okay. Please describe the methodology you
5 implemented to form that opinion.
6 MR. BRODY: Objection to form.
7 THE WITNESS: I don't implement a
8 methodology. I just observe that some propositions
9 are general in character and some are specific to
10 doctors.
11 BY MR. TRAMMELL:
12 Q. And what is your methodology in forming
13 that opinion?
14 A. Just reading the questions.
15 Q. It's your own personal analysis of the
16 questions, right?
17 MR. BRODY: Objection to form.
18 THE WITNESS: I wrote the questions. It's
19 my own personal analysis, but it's not an attempt to
20 read somebody else's mind. I'm the author of the
21 questions.
22 BY MR. TRAMMELL:
23 Q. What is your scientific basis for that
24 opinion?
25 MR. BRODY: Objection. What opinion?

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1 MR. TRAMMELL: The opinion he's just been
2 describing.
3 THE WITNESS: Well --
4 MR. BRODY: Object to form.
5 THE WITNESS: If you mean the opinion that
6 some of these questions are of a specific nature and
7 some are of a more general nature, it's just -- the
8 basis is just reading the questions. It's plain on
9 its face.
10 BY MR. TRAMMELL:
11 Q. What is your scientific basis for the
12 assumptions you make about the answers to the
13 general questions?
14 A. I'm --
15 MR. BRODY: Object to form.
16 THE WITNESS: I don't know what assumptions
17 you're referring to.
18 BY MR. TRAMMELL:
19 Q. The assumptions we've been discussing.
20 THE WITNESS: I haven't been --
21 MR. BRODY: Object to form.
22 THE WITNESS: -- discussing any
23 assumptions.
24 BY MR. TRAMMELL:
25 Q. Okay. The opinion that we've just been

1 generally because that's what "general" means.
2 BY MR. TRAMMELL:
3 Q. Does a general question apply generally in
4 all circumstances of probability sampling analysis?
5 A. I think I'd have to look at a specific
6 question to answer that, because there is always a
7 possibility of some very unusual question that one
8 could dream up hypothetically.
9 Q. What is --
10 A. But I think --
11 Q. Sorry.
12 A. But I think it applies -- the general
13 questions that we have in this case, in my survey,
14 they all -- and which I enumerated for you about an
15 hour ago, they apply -- they apply generally.
16 Q. And what is your scientific basis for that
17 statement?
18 MR. BRODY: Objection.
19 THE WITNESS: I've already explained it. A
20 general question applies generally because it's the
21 nature of the question.
22 BY MR. TRAMMELL:
23 Q. Are you familiar with the knowledge, skill,
24 training, and experience of the 20 doctors that were
25 deposited in South Carolina?

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1 referencing, that the answers to general questions
2 can be applied generally -- and, again, you can
3 rephrase that if I mischaracterize it. I'm just
4 trying to reference the opinion that we've just been
5 discussing.
6 A. That's fine.
7 Q. What is your scientific basis for that
8 opinion?
9 A. That a general question applies generally?
10 It's a tautology.
11 Q. That's it?
12 A. As far as your question goes, that's all
13 I -- all the answer that its need -- that it needs.
14 A general question applies to general things.
15 Q. Under all circumstances?
16 MR. BRODY: Objection; form.
17 THE WITNESS: I'm sure there are many, many
18 specifics that we could find that would be
19 interesting and unusual, but to all the
20 circumstances that I think apply here.
21 BY MR. TRAMMELL:
22 Q. Why does a general question apply generally
23 under these circumstances?
24 MR. BRODY: Object to form.
25 THE WITNESS: General questions apply

1 A. Only to a small degree, because they
2 answered some questions about that, and I know their
3 credentials and know something about their activity
4 and practice. But that's it.
5 Q. Were those doctors experts on Risperdal?
6 A. I would say so. They're high-prescribing
7 doctors, and they prescribe anti -- not just high
8 prescribing, but high prescribing of antipsychotic
9 drugs.
10 Q. Okay.
11 A. So they would be in the best position to
12 know about clinical practice and effects and side
13 effects of -- of all antipsychotic drugs.
14 Q. To the extent you consider those doctors
15 experts, what is the basis of their -- what are the
16 areas of their expertise, and what is the basis of
17 those areas of expertise?
18 MR. BRODY: Objection; form.
19 THE WITNESS: I'm thinking about how best
20 to answer this.
21 The -- as a back -- as a preliminary here,
22 I'm pointing out that my questions are of a factual
23 nature. I'm not soliciting expert opinions per se,
24 although I can go along with your question and say
25 that these are experts at their craft. But they're

10:54:29 1 mostly questions of a factual nature. That's why
 10:54:33 2 many of the questions begin with "In your
 10:54:36 3 experience" or "In your practice." So they're
 10:54:39 4 asking factual questions.
 10:54:42 5 And I think the reason I credit the
 10:54:45 6 statements of these doctors is that they are
 10:54:48 7 demonstrably the people who are doing the most with
 10:54:51 8 psychotic patients and antipsychotic drugs. Who
 10:54:54 9 else would be in a better position to know how
 10:54:57 10 antipsychotic drugs are working with psychotics than
 10:55:00 11 the people who are in their jobs? I can't think of
 10:55:03 12 anybody else.
 10:55:06 13 BY MR. TRAMMELL:
 10:55:09 14 Q. Is it appropriate for an attorney to carry
 10:55:12 15 out a survey of this kind?
 10:55:15 16 A. It's appropriate for attorneys to function
 10:55:18 17 as they did in this survey, at my direction;
 10:55:21 18 absolutely.
 10:55:24 19 Q. Do you agree or disagree with the statement
 10:55:27 20 that an attorney should have no part in carrying out
 10:55:30 21 a survey of this kind?
 10:55:33 22 A. When you added the "of this kind," then I
 10:55:36 23 have to disagree with that, although I can think of
 10:55:39 24 other circumstances not of this kind where I might
 10:55:42 25 agree with it.

10:56:04 1 Q. Is it important in a survey of this kind to
 10:56:07 2 have the interviewers blind to the purpose and
 10:56:10 3 sponsorship of the survey?
 10:56:13 4 A. It's impossible. So, therefore, it's --
 10:56:16 5 it's not important, because it's not -- not --
 10:56:19 6 simply not a part of the structure of this
 10:56:22 7 particular design.
 10:56:25 8 Now, in others -- in other surveys, it's a
 10:56:28 9 good idea in some cases. But as you say -- when you
 10:56:31 10 say "a survey of this kind," I'm really
 10:56:34 11 understanding that to mean in the survey that I
 10:56:37 12 conducted here. And so the -- I'm sorry. You
 10:56:40 13 started another question. Please go ahead.
 10:56:43 14 MR. BRODY: No, you --
 10:56:46 15 BY MR. TRAMMELL:
 10:56:49 16 Q. Please finish your answer.
 10:56:52 17 A. No, that -- no, that's fine. Let him go
 10:56:55 18 ahead.
 10:56:58 19 Q. Were you finished with your answer?
 10:57:01 20 A. No. But I -- when I get interrupted, I
 10:57:04 21 sort of lose the thread. So go ahead.
 10:57:07 22 Q. Okay. When you were initially contacted
 10:57:10 23 about rendering an opinion in this case, after you
 10:57:13 24 had an opportunity to determine the type of -- or
 10:57:16 25 the number of doctors for whom depositions you would

1 like to review, did you suggest a number to counsel
 2 for Janssen?
 3 A. Well, after I became aware of the number
 4 that were possible to review, we were past the point
 5 of my suggesting. That was a determination made by
 6 the Court.
 7 Q. Did you ever request 150 depositions be
 8 done?
 9 A. Yes. I would have preferred 150. And --
 10 but the Court determined that 20 was going to be
 11 allowed. And therefore, what I would have done with
 12 a sample of 150 is not quite the same thing as I did
 13 with a sample of 20. And I've discussed that with
 14 you earlier today.
 15 Q. Why 150?
 16 A. It's a matter of -- ultimately of the
 17 accuracy of the final result, which has to be an
 18 accuracy in part in anticipation, since you can't
 19 really know the accuracy until you've done the work.
 20 But there are ways to anticipate the accuracy, so
 21 that by studying the data and knowing the kind of
 22 data and certain statistical formulas relating to
 23 accuracy, one can simply anticipate that with a
 24 sample of 150, designed in a certain way, results
 25 can be achieved that would be perceived by people

1 looking at those results as reasonably accurate.
 2 Q. Is the size of the -- or is the number of
 3 depositions important to the accuracy of an opinion
 4 in a probability sampling model?
 5 MR. BRODY: Objection to form.
 6 THE WITNESS: Sample size is one of the
 7 factors that is influential in accuracy in
 8 statistical statements using a probability sample,
 9 but it's only one of several factors.
 10 BY MR. TRAMMELL:
 11 Q. It's an important factor, though, isn't it?
 12 A. It's one of the factors, and it's an
 13 important factor, but I don't know that I'd elevate
 14 it above the importance of other factors. It's
 15 just -- it's one of -- one of several.
 16 Q. Is it important that the sample size be
 17 determined by someone who is an expert in
 18 statistics?
 19 A. Yes and no. Sample size can be determined
 20 in an arbitrary fashion, and not by a statistician,
 21 and no validity to the statistical exercise is lost
 22 in that case. Larger sample sizes will generally
 23 promote greater accuracy than smaller. But in each
 24 case, large or small, a proper application of
 25 statistical methods does lead to a valid statistical

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1 result.
2 Q. But if it's a smaller sample size, it's a
3 less accurate result, right?
4 A. Not always.
5 MR. BRODY: Objection.
6 THE WITNESS: Other things equal, yes. But
7 other things don't have to be equal. And that's the
8 sum of it. With different sizes of sample, you do
9 different things.
10 BY MR. TRAMMELL:
11 Q. How was the sample size determined in this
12 case?
13 A. By the Court.
14 Q. Is the Court -- do you know the name of the
15 judge in this case, by the way?
16 A. No, I don't recall it. I've heard it, but
17 I don't recall it.
18 Q. Do you know whether Judge Couch is an
19 expert in statistical sampling methods?
20 A. I don't know, but I'd assume not.
21 Q. You said there were several factors,
22 several important factors, in conducting a
23 probability sampling analysis. And I think you said
24 sample size was one of them. What are the other
25 factors?

1 sample. That covers it.
2 Obviously you're not supposed to make
3 arithmetic errors in the process, and so on. But I
4 just leave all that aside.
5 Q. Can you describe --
6 A. I lost that. Did I describe, or --
7 Q. Can you describe --
8 A. Thank you.
9 Q. -- the level of training in psychology held
10 by the two lawyers who took the depositions that are
11 the basis of your opinion in this case?
12 A. No. I have no belief that they are trained
13 psychologists, in any event.
14 Q. How about sociology?
15 A. I have no knowledge other than that if
16 they're lawyers, they were trained in the law.
17 Other than that, I don't know anything about their
18 training.
19 Q. Okay. Is it important that the people who
20 conduct the depositions constituting this survey
21 have training in psychology?
22 A. No.
23 Q. How about sociology?
24 A. No.
25 Q. Marketing?

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1 A. No, I didn't say that. But I'm happy to
2 answer your question anyway.
3 Q. Sure. Please do.
4 A. I'm thinking about this.
5 It's too general. You -- I don't think --
6 it's as if -- and I hope I won't do this to your
7 questions very often, but it's -- it's as if you
8 were asking a medical doctor, "What's important to
9 curing patients?" And I think the answer has got to
10 be, "Well, you've got to tell me what kind of
11 patient, under what circumstance. What have they
12 got?"
13 And that's the same as a question put to a
14 statistician about what's important in a sampling
15 situation. There are so many different things that
16 can occur, that you can't just say very well.
17 Q. Let me try to do it better.
18 What are the -- what factors are important
19 to consider in determining whether a survey of this
20 type is reliable?
21 A. Really, there's -- there's only one, for
22 the word "reliable," and that is -- as I would use
23 the word "reliable," which means to me validity,
24 which means to me scientifically supported. And
25 that's just one thing: that you have a probability

1 A. No.
2 Q. Communications sciences?
3 A. No.
4 Q. Statistics?
5 A. No.
6 Q. Is it important that the people who
7 conduct -- conducted the depositions in this case
8 had training in survey research methods?
9 A. It was important they got the training that
10 I gave them, which was basically to learn how to
11 read from a script and not deviate. Other than
12 that, that's all I need.
13 Q. How about training in sampling?
14 A. No. There's no need for that. It makes no
15 sense.
16 Q. Training in measurement of a sample?
17 A. No.
18 Q. Training in interviewing?
19 A. Well, that's the training they got, because
20 the particular kind of interviewing we did here --
21 and there's many different kinds.
22 Thank you.
23 The particular kind did require training,
24 and -- I appreciate that -- and they got it.
25 Q. And, again, you weren't at the training,

11:05:06 1 right?
 11:03:00 2 A. I was not there.
 11:03:08 3 Q. Is the order of questions in a survey
 11:03:08 4 important?
 11:03:47 5 A. Sometimes, for some things, but other times
 11:03:52 6 not.
 11:03:58 7 Q. Is it important whether a question is
 11:03:58 8 open-ended or close-ended?
 11:03:59 9 A. It makes a difference. But both can be
 11:04:05 10 used.
 11:04:08 11 Q. Is the order of closed-ended questions
 11:04:04 12 important?
 11:04:09 13 A. I don't see a difference between that and
 11:04:52 14 the question a moment ago.
 11:04:58 15 Q. Just for the record, can you answer my
 11:04:53 16 question? Is the order of closed-ended questions --
 11:06:06 17 A. The order of questions, whether
 11:06:09 18 closed-ended or not, may be important in some
 11:06:09 19 situations and others not.
 11:06:30 20 Q. Can the order of closed-ended questions
 11:06:30 21 influence answers?
 11:06:30 22 A. Yes, I think it can, or it can even lead to
 11:06:48 23 hopeless confusion, which would influence the whole
 11:06:48 24 process. So there are some times that order makes a
 11:06:48 25 difference.

1 to much more scrutiny and -- than surveys generally
 2 are. I've done a lot of surveys both within
 3 litigation and not within litigation, and certainly
 4 there's a much more heightened attention to validity
 5 within the litigation context.
 6 Q. What validation checks did you implement
 7 for this survey?
 8 MR. BRODY: Objection; form.
 9 THE WITNESS: The validation consists of
 10 the process itself. I can validate the
 11 random-number generating procedure that I employed
 12 to its last detail, so that if there were concern or
 13 doubt about how the individuals were selected, I can
 14 show that -- I can relieve you of that concern.
 15 Because this is a very critical part of what makes
 16 for a valid survey. Record keeping and process are
 17 the means by which I achieved that.
 18 BY MR. TRAMMELL:
 19 Q. Were the results of the survey validated in
 20 any way?
 21 MR. BRODY: Objection to form.
 22 THE WITNESS: Well, in the best possible
 23 way, because it is rare that you have anything at
 24 all as close to a deposition transcript, that is
 25 word for word and undertaken as -- under oath.

11:08:29 1 Q. Is it important to validate the results of
 11:08:24 2 a survey of this kind?
 11:08:29 3 MR. BRODY: Objection to form.
 11:08:50 4 THE WITNESS: I'm thinking about the word
 11:08:52 5 "validate."
 11:08:59 6 It's important to be able to explain and
 11:08:58 7 show a basis for the validity of a survey of this
 11:09:03 8 kind. I'd say that. Maybe that's what the question
 11:09:08 9 meant.
 11:09:58 10 BY MR. TRAMMELL:
 11:09:50 11 Q. Well, is it important for surveys that are
 11:09:50 12 conducted at the request of a party for litigation
 11:06:03 13 be validated?
 11:06:03 14 A. Same answer. It's important, in surveys
 11:06:35 15 for litigation or any other survey, that the person
 11:06:48 16 in charge of the survey be able to explain and show
 11:06:48 17 why there is statistical underpinning to the work
 11:06:48 18 that was done and therefore why the whole
 11:06:48 19 undertaking is a valid undertaking. That I agree
 11:06:57 20 with.
 11:06:59 21 Q. Is there any heightened standard for
 11:06:54 22 validation for surveys conducted at the request of a
 11:06:52 23 party for litigation?
 11:06:58 24 A. Certainly. A survey conducted in
 11:06:48 25 litigation, such as the one we have here, is subject

1 If one sends interviewers out knocking on
 2 doors and asking people questions that they're
 3 supposed to ask, there's a -- there's a reasonable
 4 concern there that they didn't really ask the
 5 people, or they may not have even knocked on the
 6 door, and they falsified this, because they're lazy.
 7 So -- but we don't have any concern like that here,
 8 because we have actual deposition transcripts. We
 9 know what happened. So this is an unusual and very
 10 well-documented interview process.
 11 BY MR. TRAMMELL:
 12 Q. Who performed the validation of the results
 13 of this survey?
 14 MR. BRODY: Objection.
 15 THE WITNESS: I've explained what -- how I
 16 interpreted your several recent questions that asked
 17 about validations. And the answer is that I did
 18 that. I have help from staff as well. But I am
 19 very hands on in the work.
 20 BY MR. TRAMMELL:
 21 Q. The staff was the staff at Wecker and
 22 Associates?
 23 A. Yes.
 24 Q. Okay.
 25 A. Can I volunteer an elaboration? Or we can

11:30:28 1 skip it if you prefer.
 11:30:31 2 Q. That's an answer. I'm -- that's fine with
 11:30:34 3 me.
 11:30:36 4 A. Which?
 11:30:38 5 Q. Oh. I'm fine with the answer that's on the
 11:30:39 6 record.
 11:30:40 7 A. Okay.
 11:30:47 8 Q. Is it important whether or not the
 11:31:08 9 questions used in a survey are or are not suggestive
 11:31:09 10 of an answer?
 11:31:20 11 A. I'm not -- I'm thinking about that.
 11:31:22 12 I think it -- it depends. You certainly
 11:31:28 13 want questions to -- any question that's not
 11:31:29 14 open-ended is suggestive in one way or another. And
 11:31:30 15 so often that's a desirable thing, that is -- that
 11:31:31 16 is designed on purpose. So I'd have to say that
 11:31:32 17 that depends on the nature of the question and the
 11:31:33 18 nature of the undertaking.
 11:31:34 19 Q. Can it affect the integrity of the results
 11:31:35 20 of the questions or the results of the survey if the
 11:31:36 21 questions are suggestive of an answer?
 11:31:37 22 A. It depends. It certainly shapes the kinds
 11:31:38 23 of responses that are possible, and so in that sense
 11:31:39 24 it affects it, but it may not affect it in an
 11:31:40 25 undesirable way. It may be exactly what you want,

1 used deposition testimony as a basis for conducting
 2 a survey?
 3 A. If I can adjust the question to say as a
 4 part of the process of conducting a survey, because
 5 I wouldn't want to say it's the basis. There's
 6 other things. But the answer is yes, with that
 7 clarification.
 8 Q. Okay. Then let me ask another question.
 9 Have you ever conducted a survey, prior to
 10 this litigation, consisting entirely of deposition
 11 testimony?
 12 A. The answer is yes, but with the
 13 clarification that the survey doesn't consist
 14 entirely of deposition testimony. That's one of the
 15 elements, and a primary element. There's -- there's
 16 more to it than that.
 17 Q. What else is there to this survey other
 18 than deposition testimony?
 19 A. Well, the key thing is the method of design
 20 of the sample --
 21 Q. Okay.
 22 A. -- and the construction of a probability
 23 sample and the analysis of the data, a calculation
 24 of estimates. It's -- there's just more to it than
 25 that.

11:32:28 1 exactly what you want in order to shed light on the
 11:32:30 2 issue being investigated.
 11:32:31 3 Q. And just to be clear, you didn't attend any
 11:32:32 4 of the depositions of the 20 doctors, did you?
 11:32:33 5 A. That's correct.
 11:32:34 6 Q. And no member of your staff did, either?
 11:32:35 7 A. Correct.
 11:32:36 8 MR. TRAMMELL: Let's take a quick break.
 11:32:37 9 He's got to change tapes. And I'll talk to Rob real
 11:32:38 10 quick.
 11:32:39 11 THE VIDEOGRAPHER: This marks the end of
 11:32:40 12 tape number 1 in the deposition of William Wecker.
 11:32:41 13 Going off the record, the time is 11:13.
 11:32:42 14 (Recess taken.)
 11:32:43 15 THE VIDEOGRAPHER: This marks the beginning
 11:32:44 16 of tape number 2 in the deposition of William
 11:32:45 17 Wecker. Going back on the record, the time is
 11:32:46 18 11:30.
 11:32:47 19 MR. TRAMMELL: You ready?
 11:32:48 20 THE VIDEOGRAPHER: Ready.
 11:32:49 21 BY MR. TRAMMELL:
 11:32:50 22 Q. Dr. Wecker, we've taken another break. Are
 11:32:51 23 you ready to proceed?
 11:32:52 24 A. Yes.
 11:32:53 25 Q. Prior to this litigation, have you ever

1 Q. Okay. All those things aside, the -- the
 2 data that you analyzed was deposition testimony,
 3 right?
 4 A. Correct.
 5 Q. Okay. Have you ever conducted a survey
 6 prior to this litigation where the data that you
 7 analyzed consisted entirely of deposition testimony?
 8 A. Yes.
 9 Q. When?
 10 A. About two years ago.
 11 Q. In what case?
 12 A. The Louisiana case.
 13 Q. I understand. Prior to the Risperdal
 14 litigation.
 15 A. That wasn't your question.
 16 Q. Well, okay. When I say "this litigation,"
 17 I mean the Risperdal litigation.
 18 A. You mean not limited to the South Carolina
 19 case that we're involved in at the moment?
 20 Q. Right. Prior to being retained by Janssen
 21 for the Risperdal litigation, have you ever
 22 conducted a survey in which the data you analyzed
 23 consisted entirely of deposition testimony?
 24 MR. BRODY: Objection. Just so it's clear,
 25 you mean prior to being -- prior to being retained

11:33:49 1 by Janssen to offer opinions in a case related to
 11:33:50 2 Risperdal? Is -- I mean, it --
 11:33:52 3 MR. TRAMMELL: Yes.
 11:33:53 4 MR. BRODY: I'm just trying to draw a
 11:33:54 5 distinction here.
 11:33:56 6 MR. TRAMMELL: I'm trying to account for
 11:33:57 7 all the state cases or anything he's done with you
 11:33:58 8 all like this.
 11:33:59 9 THE WITNESS: Okay. I think I understand
 11:34:00 10 the question. And I think the answer's no. But if
 11:34:01 11 I -- since I've done a lot of things in my life, if
 11:34:02 12 I didn't remember that, I'll just have to notify
 11:34:03 13 counsel and explain that the answer is different
 11:34:04 14 than I just gave you.
 11:34:05 15 BY MR. TRAMMELL:
 11:34:06 16 Q. Okay. If you come up with another time
 11:34:07 17 that you did that or another example of doing that,
 11:34:08 18 please let Mr. Brody or whoever know, so we -- so
 11:34:09 19 they can tell us.
 11:34:10 20 A. Sure.
 11:34:11 21 Q. Is that okay?
 11:34:12 22 A. That's what I already said I'd do.
 11:34:13 23 Q. Okay. If you'd go back to Exhibit 5 for
 11:34:14 24 me. Oh.
 11:34:15 25 A. Just one second.

11:34:45 1 Okay.
 11:34:46 2 Q. If you'll look at the confidence interval.
 11:34:47 3 A. Uh-huh.
 11:34:48 4 Q. I just want to confirm. The confidence
 11:34:49 5 interval here in Exhibit 5 applies to the 101
 11:34:50 6 doctors, right?
 11:34:51 7 A. Yes.
 11:34:52 8 Q. Okay. Dr. Wecker, have you ever conducted
 11:34:53 9 a clinical trial?
 11:34:54 10 A. No.
 11:34:55 11 Q. Have you ever conducted a retrospective
 11:34:56 12 database analysis?
 11:34:57 13 A. I don't know what that is. I may well have
 11:34:58 14 done it, but I just don't know, from your question,
 11:34:59 15 what it is that you're talking about.
 11:35:00 16 Q. Aside from this litigation, meaning the
 11:35:01 17 Louisiana litigation and the South Carolina
 11:35:02 18 litigation, the Risperdal litigation, have you
 11:35:03 19 conducted a review of a Medicaid or any other
 11:35:04 20 medical database for purposes of doing an outcomes
 11:35:05 21 analysis?
 11:35:06 22 A. I don't know what an outcomes analysis is,
 11:35:07 23 either. But I have looked at medical data in
 11:35:08 24 databases many times.
 11:35:09 25 Q. For what purpose?

1 A. To understand what's in them.
 2 Q. Have you ever analyzed a Medicaid or other
 3 medical database for the purpose of conducting the
 4 analysis you've conducted in this case?
 5 MR. BRODY: Objection to form.
 6 Do you --
 7 THE WITNESS: I don't understand.
 8 MR. BRODY: Do --
 9 THE WITNESS: Could I ask that we read that
 10 back? Because I just am confused by the question.
 11 BY MR. TRAMMELL:
 12 Q. Have you ever analyzed a Medicaid or other
 13 medical database for the purpose of conducting the
 14 analysis you've conducted in this case?
 15 A. Yes.
 16 Q. When?
 17 A. When I did the work I did in this case.
 18 Q. Other than in this case.
 19 MR. BRODY: I'm going to object to form.
 20 And I think I know what you're getting at, and I'm
 21 happy to explain it to you. But I won't say
 22 anything else if you don't want me to.
 23 MR. TRAMMELL: Please don't.
 24 MR. BRODY: Okay.
 25 BY MR. TRAMMELL:

1 Q. Prior to conducting your analysis in this
 2 case, have you ever analyzed a Medicaid or other
 3 medical database?
 4 A. Sure, lots of times.
 5 Q. For the purpose of conducting the analysis
 6 you conducted in this case?
 7 A. No. Because --
 8 Q. Okay.
 9 A. -- the analysis I did in this case couldn't
 10 have been done outside of this case.
 11 Q. If you could refer to your report, please,
 12 page 9.
 13 A. Okay. Yes.
 14 Q. Do you see it says "Observational Data."
 15 Under that it says -- I'm talking about paragraph
 16 26.
 17 A. Yes.
 18 Q. "Claims data produced by the plaintiff from
 19 South Carolina state databases is also useful for
 20 analyzing plaintiff's allegations." Then it says,
 21 "I performed three different analyses." Do you see
 22 that?
 23 A. Yes.
 24 Q. Have you ever performed those three
 25 analyses in any other case?

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11:38:30 1 MR. BRODY: You mean outside of Risperdal
 11:38:33 2 litigation?
 11:38:38 3 MR. TRAMMELL: Yes.
 11:38:44 4 THE WITNESS: No.
 11:38:49 5 BY MR. TRAMMELL:
 11:38:56 6 Q. Okay.
 11:38:58 7 A. These are very specific analyses, that
 11:39:00 8 pertain to Risperdal litigation, so I couldn't
 11:39:05 9 possibly do these outside of it.
 11:39:15 10 Q. Have you ever performed those three types
 11:39:26 11 of analyses based on a Medicaid database or other
 11:39:32 12 health care database in any other case?
 11:39:35 13 A. Well, I have to bring some understanding to
 11:39:39 14 the word "types of analyses." I certainly have
 11:39:43 15 analyzed other medical databases, and many times, in
 11:39:46 16 both litigation and nonlitigation settings, and they
 11:39:50 17 bear certain resemblances to this, but they're
 11:39:55 18 obviously not the same, because this is very
 11:39:58 19 particularized to the situation we have in this
 11:40:01 20 case.
 11:40:03 21 Q. Have you ever analyzed these types of
 11:40:06 22 databases for the purpose of determining the
 11:40:10 23 incidence of side effects?
 11:40:13 24 A. Yes.
 11:40:16 25 Q. When?

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11:40:30 1 A. Many times.
 11:40:36 2 Q. In litigation, I'm asking.
 11:40:38 3 A. Well, let me try to think.
 11:40:44 4 I'm going back several years, so my recall
 11:40:45 5 is imperfect, but I've done -- looked at medical
 11:40:49 6 databases with respect to side effects, meaning
 11:40:53 7 undesirable outcomes, in the context of asbestos
 11:40:58 8 litigation, done it in the context of tobacco
 11:41:00 9 litigation. There have been other insurance
 11:41:03 10 situations, the details of which I can't recall very
 11:41:06 11 well, where I've looked at medical data. And a very
 11:41:09 12 close relative to all this is accidents, because
 11:41:12 13 accidents and disease are very similar from a
 11:41:15 14 statistician's point of view. I've done that, too.
 11:41:18 15 Q. If you go to page 12, (b)(2) is "time to
 11:41:21 16 discontinuation."
 11:41:24 17 A. Yes.
 11:41:27 18 Q. Aside from this case or Risperdal
 11:41:30 19 litigation in general, have you performed a
 11:41:33 20 time-to-discontinuation analysis of a health care
 11:41:36 21 database?
 11:41:39 22 A. No.
 11:41:42 23 MR. TRAMMELL: Okay.
 11:41:45 24 I pass the witness.
 11:41:48 25 MR. BRODY: I have no questions. I just

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1 want to note for the record that we provided
 2 documents in response to the document request that
 3 was served with the deposition notice, several
 4 binders, which we've given, including binder marked
 5 N1, which contains Dr. Wecker's report, with
 6 exhibits, as well as two affidavits that he has
 7 prepared in this case; N2, which contains excerpts
 8 from the electronic files, that were previously
 9 produced to the plaintiff on the 22nd of December;
 10 N4, which contains coded depositions from the 20
 11 doctors who were surveyed; and then N3.1 through
 12 3.5, that contain copies of the materials considered
 13 by Dr. Wecker in the process of forming the opinions
 14 that he is offering in this case.
 15 And all of those documents, except for one
 16 of the documents, had previously been disclosed,
 17 identified, or provided plaintiff.
 18 MR. TRAMMELL: Which is the one that hasn't
 19 been?
 20 MR. BRODY: It's in one of the notebooks.
 21 It's a chart that lists the eight studies. And it
 22 is titled "Statements in Janssen's November 10, 2003
 23 mailing are supported by peer-reviewed studies cited
 24 in the mailing."
 25 MR. TRAMMELL: Hang on so I can look at it

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1 real quick.
 2 MR. BRODY: See if I can figure out which
 3 notebook it's in for you.
 4 THE WITNESS: Notebook 1.
 5 MR. BRODY: Notebook 1.
 6 THE WITNESS: Flyleaf.
 7 MR. BRODY: You have it right there? No,
 8 Let's see.
 9 MR. TRAMMELL: This is it?
 10 THE WITNESS: Look in the flyleaf.
 11 MR. BRODY: No, it's going to be in a
 12 different part. It's --
 13 MR. TRAMMELL: I tell you what. Can you
 14 just let me see a copy of it? I probably don't have
 15 any questions on it.
 16 THE WITNESS: Here.
 17 MR. BRODY: Well, we'll get there.
 18 Why don't we go off the record.
 19 THE VIDEOGRAPHER: Going off the record,
 20 the time is 11:44.
 21 (Discussion off the record.)
 22 THE VIDEOGRAPHER: We're back on the
 23 record. The time is 11:44.
 24 MR. BRODY: Dr. Wecker will read and sign.
 25 THE VIDEOGRAPHER: This marks the end of

Pages 86 to 89

11:45:05
11:45:09
11:45:11

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1 tape number 2 in the deposition of William Wecker.
2 Going off the record, the time is 11:45.
3 (Whereupon, the deposition was adjourned at
4 11:45 a.m.)
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Page 92

1 SIGNATURE OF DEPONENT (CONTINUED)
2
3 DEPOSITION DATE: January 27, 2011
4 REPORTER: John Wissenbach, CSR 6862
5 CASE CAPTION: State of South Carolina vs.
6 Ortho-McNeil-Janssen Pharmaceuticals, et al., etc.
7

8 PAGE LINE CHANGE REASON
9
10
11
12

13 WILLIAM E. WECKER, Ph.D. Date
14 I, David C. Roberts, Notary Public for the
15 State of South Carolina at Large, do hereby certify
16 that the deponent was advised of his or her right to
17 read and sign said deposition both verbally and in
18 writing. If the deponent fails to execute and
19 return foregoing Signature of Deponent pages within
20 the thirty (30) days allowed pursuant to the Rules
21 of Civil Procedure, the original transcript may be
22 filed with the court.
23

24 David C. Roberts, RPR, CRR, CMRS
25 My Commission expires
April 7, 2013

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1 SIGNATURE OF DEPONENT
2
3 DEPONENT: WILLIAM E. WECKER, Ph.D.
4 DEPOSITION DATE: January 27, 2011
5 REPORTER: John Wissenbach, CSR 6862
6 CASE CAPTION: State of South Carolina vs.
7 Ortho-McNeil-Janssen Pharmaceuticals, et al., etc.
8
9 (Please return both Signature of Deponent pages)
10

11 I, the undersigned, WILLIAM E. WECKER, Ph.D.,
12 do hereby certify that I have read the foregoing
13 deposition and find it to be a true and accurate
14 transcription of my testimony, with the following
15 corrections, if any:

16 PAGE LINE CHANGE REASON
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CERTIFICATE OF REPORTER

1
2
3 I, JOHN WISSENBACH, hereby certify that the
4 witness in the foregoing deposition was by me duly
5 sworn to testify the truth, the whole truth, and
6 nothing but the truth in the within-entitled cause;
7 that said deposition was taken at the time and place
8 therein stated; that the testimony of said witness
9 was reported by me, a Certified Shorthand Reporter
10 and disinterested person, and was thereafter
11 transcribed into typewriting, and that the pertinent
12 provisions of the applicable code or rules of civil
13 procedure relating to the notification of the
14 witness and counsel for the parties hereto of the
15 availability of the original transcript of the
16 deposition for reading, correcting, and signing have
17 been met, and that the transcript is a true record
18 of the testimony given.

19 And I further certify that I am not of
20 counsel or attorney for either or any of the parties
21 to said deposition, nor in any way interested in the
22 outcome of the cause named in said caption.

23 DATED:
24
25

JOHN WISSENBACH, CSR No. 6862

Pages 90 to 93

EXHIBIT B

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M. ROSE BLANCHLEY

STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA
ex rel. Henry McMaster, in his capacity
as Attorney General of the State of
South Carolina,

Civil Action No. 07-CP-42-1438

Plaintiff,

ORDER

v.

JANSSEN PHARMACEUTICA INC.,
JANSSEN, L.P. and
JOHNSON & JOHNSON, INC.,

Defendants.

This matter comes before me on Defendants', Ortho-McNeil-Janssen, Inc. and Johnson & Johnson (collectively, "Janssen"), Motion to Compel Responses To Its First Set of Requests For Production And Interrogatories, Plaintiff The State of South Carolina's ex rel. Henry McMaster, in his capacity as Attorney General of The State of South Carolina, (the "State"), Motion to Compel Documents Responsive to the State's Seventh Set of Requests for Production Directed to Defendants, and Defendants' Motion For Leave to Depose 150 Prescribing Physicians and Institutions: hearing was held on June 15, 2009 in Spartanburg, South Carolina. Fletcher V. Trammell of Bailey Perrin and Bailey, and John B. White, Jr., of Harrison, White, Smith & Giggins, P.C. represented the State. Kenneth A. Murphy of Drinker Biddle & Reath, L.P., and Steven J. Pugh of Richardson Plowden & Robinson, P.A., represented Janssen. Upon consideration of the above-described Motions, the Memoranda and Responses of the parties filed therewith, and the oral arguments of counsel, I hereby order as follows:

I. The State's Motion To Compel Documents Responsive to the State's Seventh Set of Requests for Production is Denied Without Prejudice

By its Motion, the State has requested the entry of an Order to Compel Defendants' Responses To the State's Seventh Set of Requests for Production. Among other things, the State's Seventh Set of Requests sought all Field Conference Reports generated in the State of South Carolina, all Call Plans implemented by Defendants' sales representatives in the State of South Carolina, and all documents produced by Defendants in the New Jersey lawsuit styled Lynn Powell v. Janssen Pharmaceutica, Inc., et al. The Court is satisfied that Defendants have commenced the process required to locate, process and produce documents responsive to those requests. Defendants expect to produce responsive documents by July 15, 2009. To the extent the State deems the production incomplete, the State may renew its Motion at that time.

II. Defendants' Motion To Compel Responses To Its First Set of Requests For Production And Interrogatories Is Denied Without Prejudice

By Its Motion to Compel, Defendant Janssen has sought an Order compelling the State to produce and/or identify, among other things, 1.) documents and information reflecting articles, studies and other information the State contends Defendants misrepresented or concealed from South Carolina physicians – as alleged in the Complaint; 2.) the identity of South Carolina physicians who contend that Defendants sales representatives encouraged the prescription of Risperdal for off-label purposes; 3.) the amount of money the State contends it spent to purchase Risperdal and/or underwrite the cost of Risperdal prescriptions.

In response, the State argues that the documents requested are part and parcel of expert reports and analyses that are not yet due. The State argues that Defendants'

requests in this regard are premature and improper. The Court will not require the State to produce these documents and information at this time. However, the State shall produce all responsive documents and information well in advance of the relevant expert(s) deposition(s), to allow Defendants adequate time to prepare for the deposition and to conduct any follow-up discovery Defendants may deem necessary. Defendants may renew their Motion should the State fail to produce responsive documents in advance of any relevant expert deposition.

In addition, Defendants seek various documents and files related to Drug Utilization Review activities performed on behalf of the State by third-party contractors. As to these documents, the Court accepts the representations of the State's counsel, and is satisfied that the State has produced all Drug Utilization Review-related documents within its custody and control.

III. Defendants' Motion For Leave to Depose 150 Prescribing Physicians and Institutions Is Denied In Part.

By its Motion For Leave To Depose 150 Prescribing Physicians and Institutions, Defendant Janssen seeks leave to depose a statistically significant sample of universe of South Carolina physicians who prescribed Risperdal and other antipsychotic medicines to South Carolina residents. The Court will grant the Defendant leave to depose twenty (20) prescribing physician depositions to be conducted. The Court will allow the Defendant to renew the motion after these twenty (20) depositions if necessity of additional depositions is shown.

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IT IS FURTHER ORDERED, that by July 8, 2009, the State shall fully comply with this Court's Order dated March 19, 2009, with regard to the personnel files of Messrs. Martin Brecher and Wayne Macfadden.

IT IS SO ORDERED this 26th day of June, 2009.


Honorable Roger L. Couch

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A CERTIFIED COPY



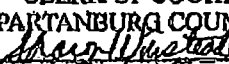
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SPARTANBURG COUNTY
BY:  D.C.
DATED 7-1-09

EXHIBIT C

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Transcript of the Testimony of **TRIAL DAY 9** **JANSSEN**

Date: October 12, 2010

Volume: 1

Case:

Printed On: 10/18/2010

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Page 6	Page 8
1 are cited here. If the Court wishes, 2 I can present them, but it addresses 3 facts or underlying opinions of expert 4 witnesses. And the highlighted 5 portion I'd like to just take a second 6 and review it. It says, expert 7 witnesses may not rely primarily upon 8 the opinions of experts who are not 9 called as witnesses at trial. 10 Permitting an expert to relay the 11 conclusions representing the 12 collective opinion of other experts 13 and not just the opinion of the expert 14 him or herself is improper as 15 constituting inadmissible hearsay. An 16 expert may testify so long as the 17 expert bases his or her opinion on his 18 or her own examination and 19 conclusions, not solely on the opinion 20 of another expert. An expert should 21 not be permitted simply to repeat 22 another's opinion without bringing to 23 bear on it his own expertise or 24 judgment. And an expert in one field 25 cannot be a conduit for the opinions	1 whether or not they relate to 2 causation issues that the Court has 3 already ruled are not part of this 4 case. And, um -- in addition, I was 5 handed a number of slides this 6 morning, Judge. Now, I can 7 interrupt -- or I can -- I don't want 8 the try your patience first thing 9 Tuesday morning, but I could take a 10 second to throw these up on the Elmo 11 and go through them, but I mean -- 12 THE COURT: 13 Why don't we do this: Let's deal 14 with the questions one at a time so 15 that we can have a response. Because 16 my memory is not as good as it used to 17 be, and I certainly wouldn't want to 18 be the sole, single court in the 19 United States of America to make a 20 mistake. 21 MR. RYAN: 22 Well, this is Louisiana. Other 23 Courts in other jurisdictions have 24 addressed it. 25 THE COURT:
Page 7	Page 9
1 of experts in another field. 2 And it cited a number of cases, 3 and we have them here, with extra 4 copies for the Court to look at, where 5 they've said that; you just can't be a 6 conduit for other expert opinions. 7 And that's what we submit is going on 8 here, is that they have -- I want to 9 object to this right now, is that 10 there's 150 depositions that are 11 sitting here on the floor that 12 apparently they plan to point to 13 during this, but we submit that this 14 is not the type of information 15 reasonably relied upon, um -- one 16 second, Your Honor -- reasonably 17 relied upon by experts. 18 Is that -- you know, Judge, I 19 want to -- so on a global level, we 20 object to any of this coming in, is 21 that these questions -- and then kind 22 of on an alternative basis, Your 23 Honor, we have -- we have a number of 24 objections relating to the relevancy 25 of a lot of these questions, um --	1 All right. Let's have your 2 response with regard to whether this 3 statistician should testify at all. 4 What's the relevance? 5 MR. BRODY: 6 He should absolutely testify, 7 Your Honor, because first of all, as 8 to the admissibility, the results of 9 his survey of Louisiana doctors, FILED CLERK OF COURT SPRINGFIELD, MISSOURI 10 Louisiana Courts have specifically 11 addressed that issue, and in fact our 12 own Third Circuit here has said that 13 an expert's survey results are 14 admissible before a jury, and that the 15 method of testing or information 16 collection should be considered by the 17 jury in assessing what weight to give 18 the expert's conclusions that were 19 drawn from the survey. And that's 20 McDaniel versus Carencro Lions Club. 21 It's 934 So. 2nd 945. And the case is 22 completely consistent with the 23 principle set out in the Code of 24 Evidence, and Mr. Ryan cited it, is 25 that an expert is allowed to rely on

3 (Pages 6 to 9)

Page 10	Page 12
1 information that might be 2 inadmissible, that might be hearsay, 3 in forming his or her conclusions in 4 testifying in court. 5 This idea that somehow the fact 6 that you're doing this survey of 7 doctors makes it different simply 8 isn't supported by the questions that 9 were put to the doctors and the 10 answers that we intend to elicit from 11 Dr. Wecker today regarding questions 12 like, Did you see the November 10, 13 2003 letter? In your experience, does 14 Risperdal have fewer side effects with 15 your patients? Within your 16 experience, not in your opinion. In 17 your practice of medicine in he state 18 of Louisiana. Um -- when you got the 19 letter, did it cause you to change 20 your choice of antipsychotic for your 21 patients? All of those things go 22 directly to the materiality -- they 23 go -- first of all they go directly to 24 what happened here in Louisiana. They 25 go directly to the materiality of the	1 Courts, and decisions admitting it 2 have been upheld by Courts -- 3 THE COURT: 4 Other Courts? 5 MR. BRODY: 6 -- around Louisiana, Your Honor. 7 THE COURT: 8 How refreshing that is. It takes 9 such a load off of my mind. 10 MR. BRODY: 11 Well, it really comes down to the 12 Code of Evidence. 13 THE COURT: 14 All right. Where don't you help 15 me with -- Mr. Ryan cites Corpus Juris 16 Secundum, and particularly the 17 sentence which says, permitting an 18 expert to relay the conclusions 19 representing the collective opinion of 20 other experts is improper as 21 constituting inadmissible hearsay. 22 MR. BRODY: 23 Well, first of all, the -- 24 THE COURT: 25 That's at the bottom of -- I can
Page 11	Page 13
1 alleged and challenged conduct that's 2 at issue here. 3 Now, true, when we started this 4 process it was a different case; there 5 were additional claims, there were 6 additional counts. And so some of 7 what Dr. Wecker asked the physicians, 8 some of the questions that were put to 9 the doctors, you know, I don't think 10 still have anything to do with what 11 we're doing here today. Did any 12 Janssen sales representative ever 13 market Risperdal to you for an 14 off-label use in children? And so 15 Dr. Wecker is not going to be asked 16 about that today and he's not going to 17 talk about that. 18 THE COURT: 19 You don't intend to put this into 20 evidence? 21 MR. BRODY: 22 Do not intend to put that into 23 evidence. No, Your Honor. So what we 24 come down to is survey evidence that 25 is admissible, has been admitted by	1 give you my sheet that he gave me. 2 MR. BRODY: 3 No, I have the same thing. I 4 have the citation there, and I'm 5 seeing it for the first time as you 6 are. The citation there is to -- 7 there's a Georgia appellate case, a 8 New York Second Department state case, 9 something in the Second District Court 10 of Green County, Ohio, and a looks 11 like Supreme Court of Mississippi 12 case. 13 He's not being called to simply 14 repeat another expert's opinion. He's 15 being called to do what statisticians 16 do, which is design surveys and 17 statistical experts do, and report on 18 survey results, which as the Third 19 Circuit said, are properly tested 20 through cross-examination as to the 21 methods, as to the reliability of the 22 information, and it's up to the jury 23 to decide what weight to give that 24 testimony and whether to find the 25 expert's testimony credible.

4 (Pages 10 to 13)

STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.
Alan Wilson, in his capacity as Attorney
General of the State of South Carolina,

Civil Action No. 2007-CP-42-1438

Plaintiff,

v.

DEFENDANTS' OBJECTIONS TO
PLAINTIFF'S OPENING STATEMENT

ORTHO-McNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA INC.,
and/or JANSSEN, L.P. and
JOHNSON & JOHNSON, INC.,

Defendants.

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M. HOPE BLACKLEY

Pursuant to an agreement by the parties, and with the Court's approval, objections to a party's opening statement were to be made at the close of the opening statements rather than contemporaneously. Defendants assert the following objections to the State's opening statement:

1. Misstatement of Law: The State's counsel made several statements to the jury as to what the South Carolina Unfair Trade Practices Act ("SCUTPA") purportedly requires or does not require to establish liability. For example, counsel made several statements as to what was necessary for the State to establish the SCUTPA element of "public impact" and that it did not matter whether physicians were deceived as a result of any of the conduct of Defendants. Apart from the misstatement of law as to the necessary elements of SCUTPA, as the Court has not instructed the jury as to the law, Defendants request a corrective instruction to the jury to disregard

any statements by counsel as to what the law does or does not require to establish liability. The Court will charge the jury on the law at the end of the case.

2. Misstatement of Law: In a similar vein, counsel asserted to the jury that a pharmaceutical manufacturer has a "duty to communicate with the public". There is no such duty under the law generally and certainly any alleged such duty is not part of the State's SCUTPA claim, which is based, by the State's own admission, on two documents specifically written for and directed to healthcare providers. On this issue, Defendants also request a corrective instruction.

3. Relevance/Prejudice/Discovery Violations: The State's counsel during the opening also discussed Defendants' alleged violations of FDA regulations, namely, Janssen should have sent the November 2003 mailing to the U.S. Food and Drug Administration ("FDA") before it was sent to healthcare professionals. Alleged violations of federal regulations are not part of this action by the State's own admission in this action. See State's Supplemental Answer to Interrogatory No. 25 of Defendants' Fifth Set of Interrogatories ("[T]he State does not contend that Janssen's breach of any FDA-promulgated rule, regulation, or statute provides for the basis for Janssen's violation of the South Carolina Unfair Trade Practices Act."). Having disclaimed reliance on violations of any federal law, the State was not permitted to reference alleged violations of federal law or regulations in its opening. Defendants request a corrective instruction that violations of federal law or regulations are not part of this action and the Court will instruct the jury as to the applicable law.

4. Preemption/No Basis for Statement: The State's counsel also made references to the Defendants' alleged "failure to disclose" information to the FDA. This

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issue was the subject of a pretrial motion by Defendants' that was reserved by the Court until the time of trial. Such "fraud on the FDA" claims are preempted as a matter of law. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001). The State may not rely on alleged non-disclosures to the FDA as a basis for imposing liability and, as such, was precluded from making references to alleged non-disclosures by Defendants to the FDA in its opening. Further, neither of the two experts of the State presented any expert opinion or report that there was information that should have been disclosed to the FDA by the Defendants but was not. Defendants request a corrective instruction that alleged non-disclosures to the FDA are not part of this action.

5. Misstatements of Law/Fact: During the opening, the State's counsel showed to the jury a document referencing Dr. Scott Reines as a Janssen executive and asserted that his statements are admissions of the Defendants. As the State knows, Dr. Reines is not a Janssen executive and did not work for either of the two named Defendants. Thus, counsel's statements are misstatements of fact and law. Defendants request a corrective instruction as to this issue as well.

6. Misstatement of Law/Misstatement of Fact: In the opening, counsel stated that, in a July 2004 letter from Janssen, there was an acknowledgement by Janssen that the November 2003 letter was false and misleading. The letter contains no such acknowledgement; it merely states the position of the Division of Drug Marketing, Advertising, and Communications ("DDMAC") in the April 2004 warning letter. Further, the State's characterization and apparent use of the letter as a basis of liability by arguing that the July 2004 letter should have been sent earlier (or been the text used as part of the November 2003 mailing) violates South Carolina Rule of Evidence 407,

which provides, in pertinent part: "When, after an event, measures are taken which, if taken previously, would have made the event less likely to occur, evidence of the subsequent measures is not admissible to prove negligence or culpable conduct in connection with the event." Rule 407, SCRE. Defendants request a corrective instruction that any subsequent conduct by Janssen to comply with a request of DDMAC may not be considered in deterring liability under SCUTPA.

7. Misstatement of Law/Misstatement of Fact: The State's counsel also improperly referred to alleged action Janssen could have taken when it received the 2004 warning letter. This again is a misstatement of law and fact. The 2004 warning letter is formal and advisory and not action which can be challenged in court. 2004 FDA *Regulatory Procedures Manual* § 4-1-1. (THE "FDA does not consider warning letters to be final agency action on which it can be sued.")

8. Prejudicial Statement: Defendants also object to the State's statement that Defendants are being "prosecuted" by the State of South Carolina. This is not a criminal proceeding and the inference that Defendants' conduct is criminal in nature is prejudicial to Defendants. See Rule 403, SCRE. Defendants request a corrective instruction to the jury that the present case is not a "prosecution"; the State merely alleges that certain acts violate SCUTPA.

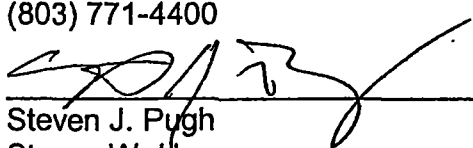
9. Prejudice/Relevance: The State made numerous references to marketing activities of the Defendants. Yesterday, Defendants again objected to the introduction of such evidence. The State represented to the Court that these materials were not a basis for the State's SCUTPA claim. In the opening, however, the State's counsel referred to these activities (specifically as to children, adolescents and the elderly) as

part of the deceptive trade practices of Defendants which took place in South Carolina. Defendants request a corrective instruction that any marketing activities of Janssen are not the basis of the State's claim; the State's claim is limited solely to the November 2003 mailing and the Risperdal package insert.

Respectfully submitted,

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ATTORNEYS FOR DEFENDANTS

Dated: March 8, 2011.

FILED
CLERK OF COURT
SPRINGFIELD COUNTY
MAR - 8 PM 4:51
M. HOPE BLACKLEY

STATE OF SOUTH CAROLINA

COUNTY OF SPARTANBURG

STATE OF SOUTH CAROLINA

ex. rel. Alan Wilson, in his capacity
as Attorney General of the State of
South Carolina,

PLAINTIFF,

v.

ORTHO-MCNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA, INC.,
and/or JANSSEN, L.P., AND
JOHNSON & JOHNSON, INC.

DEFENDANTS.

) IN THE COURT OF COMMON PLEAS

) FOR THE SEVENTH JUDICIAL CIRCUIT

) Civil Action No.: 2007-CP-42-1438

) PLAINTIFF THE STATE OF SOUTH
) CAROLINA'S RESPONSE IN
) OPPOSITION TO DEFENDANTS'
) OBJECTIONS TO PLAINTIFF'S
) OPENING STATEMENT

TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR
DEFENDANTS

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson,¹ in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Response in Opposition to the Objections to Plaintiff's Opening Statement ("Objections") filed by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc. (collectively, "Janssen" or "Defendants"), and would respectfully show the Court as follows:

¹ Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

1. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State's Counsel Regarding the Elements of the State's SCUTPA Claim.

Defendants object to statements by the State's counsel regarding the elements of the State's SCUTPA claim including "what was necessary for the State to establish the SCUTPA element of 'public impact' and that it did not matter whether physicians were deceived as a result of any of the conduct of Defendants" on the grounds that they were misstatements of law. (Def.'s Objections at 1.) However, the State recited verbatim S.C. Code Ann. § 39-5-20 as follows: "[u]nfair methods of competition and unfair or deceptive acts or practices of the conduct of any trade or commerce are hereby declared unlawful." (Trial Tr., 3/8/11, at 192:2-7, attached hereto as Exhibit A.) Wholly consistent with S.C. Code Ann. § 39-5-110(a), the State further explained that "if the Attorney General finds that any businessperson is violating that law within the State of South Carolina, the Attorney General has the right and the duty to bring an action against them to enjoin them from continuing to do that and to also collect civil [penalties]." (Trial Tr., 3/8/11, at 192:8-14 (Ex. A.)) Compare with S.C. Code Ann. § 39-5-110(a) ("If a court finds that any person is willfully using or has willfully used a method, act or practice declared unlawful by § 39-5-20, the Attorney General, upon petition to the court, may recover on behalf of the State a civil penalty of not exceeding five thousand dollars per violation."). Also consistent with South Carolina case law interpreting SCUTPA, the State explained that SCUTPA "is only for cases that have significant public impact." (Trial Tr. 3/8/11, at 204:8-12 (Ex. A.)) See *Wright v. Craft*, 640 S.E.2d 486, 501 (S.C. Ct. App. 2006); *Dowd v. Imperial Chrysler-Plymouth, Inc.*, 381 S.E.2d 212, 214 (S.C. Ct. App. 1989); *Noack Enters., Inc. v. Country Corner Interiors of Hilton Head Island, Inc.*, 351 S.E.2d 347, 349-50 (S.C. Ct. App. 1986).

Moreover, as the statutes' plain language evidences and South Carolina courts (including this Court) have made clear, SCUTPA does not require proof of fraud or irreparable harm to any consumer or physician, but only that misrepresentations have occurred in order to prove violations thereof. *See, e.g., State ex rel. McLeod v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984); *Inman v. Hyatt Chrysler Plymouth, Inc.*, 363 S.E.2d 691, 692 (S.C. 1988). Specifically, South Carolina courts "have refused to link proof of unfair or deceptive trade practices to proof of common law fraud." *McLeod*, 313 S.E.2d at 338; *see, e.g., Inman*, 363 S.E.2d at 692; *see also State ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 348 S.E.2d 381, 383-84 (S.C. Ct. App. 1986) (refusing to apply heightened common law standard of actual knowledge relative to "willfulness" under SCUTPA); *accord*, Ralph King Anderson, Jr., *South Carolina Requests to Charge – Civil*, 2009, § 34-3 ("Proof of common law fraud is not required to establish a violation under the Unfair Trade Practices Act.") (citing cases). Likewise, "there is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive" under South Carolina law. *McLeod*, 313 S.E.2d at 338; *accord* Ralph King Anderson, Jr., *South Carolina Requests to Charge – Civil*, 2009, § 34-3. Further, the State is not required to establish deceptiveness at all if it demonstrates that the conduct at issue is simply unfair under SCUTPA. *See Wright*, 640 S.E.2d at 498 (citing S.C. Code Ann. § 39-5-20(a) ("The UTPA declares "unfair *or* deceptive acts or practices in the conduct of any trade or commerce . . . unlawful.") (emphasis added)). Entirely consistent therewith, the State explained that "[t]here is no requirement in the Act that we prove that any doctor relied on [the November 2003 "Dear Doctor" letter] or relied on what they said in writing a prescription," and, more generally, "we don't have to prove reliance." (Trial Tr., 3/8/11, at 204:13-21 (Ex. A.).)

Lastly, notwithstanding the foregoing, the standard *South Carolina Requests for Charge – Civil* already includes basic charges addressing Defendants’ objection. Ralph King Anderson, Jr., *South Carolina Requests for Charge – Civil*, 2009, § 1-2 (“I am, as the trial judge, made the sole and only instructor in the law. You must accept as correct the law as I charge it to you to be the correct law.”). *Cf. id.* § 1-8 (“You must not consider as evidence any statement of counsel made during the trial. Statements of counsel do not constitute evidence, rather counsel is articulating the position and contention of his client. This rule applies to the opening statement of counsel and the closing argument.”)

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants’ objections regarding the State’s purported misstatements of law as to what SCUTPA requires or does not require to establish liability.

2. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State’s Counsel Regarding Defendants’ Duty to Communicate Accurate Information Regarding Risperdal’s Safety Profile.

Contrary to Defendants’ contentions, the State’s claim under SCUTPA is not that a drug manufacturer has a general duty to communicate to the public but, rather, that Defendants have a duty to not to disseminate false and misleading information regarding Risperdal consistent with S.C. Code Ann. § 39-5-20, which declares unfair or deceptive acts or practices, here including Defendants’ labeling and promotion of the drug, unlawful. Indeed, a drug manufacturer must adhere to specific requirements as to the content and format of its labeling of prescription drugs to provide for the “safe and effective use” of the drug and is ultimately responsible for ensuring that its labeling is revised to include a warning of serious adverse reactions and potential safety hazards “as soon as there is reasonable evidence of an association of a serious hazard with a

drug.” 21 C.F.R. § 201.57(e) (2006); *see also* 21 C.F.R. 314.70(c)(6)(iii)(A), (C) (2006); *accord Wyeth v. Levine*, 129 S. Ct. 1187, 1197 (2009). In other words, as “[t]his Court has previously noted[,] . . . drug manufacturers have a continuing duty to update [their] labels so as to include new more stringent warnings concerning the use and efficacy of [their] drugs and the warning associated therewith.” (Order, Feb. 25, 2011, at 7 (citing 21 C.F.R. 314.70(c)(6)(iii)(A), (C)).) Counsel’s statements regarding the requirements of prescription drug labeling are entirety consistent with South Carolina and federal law addressing the issue.

Furthermore, again, the standard *South Carolina Requests for Charge – Civil* already includes basic charges addressing Defendants’ objection. Ralph King Anderson, Jr., *South Carolina Requests for Charge – Civil*, 2009, § 1-2. *Cf. id.* § 1-8.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants’ objections regarding the State’s purported misstatements of law as to how and under what circumstances Defendants must communicate serious adverse reactions and potential safety hazards in its labeling.

3. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State’s Counsel Regarding Defendants’ Violations of Federal Law and Regulations.

The Court has already ruled that violations of federal regulations are probative of the willfulness, unfairness, and deception the State alleges relative to Defendants’ conduct in their product labeling under SCUTPA and are, likewise, admissible. (*See, e.g.*, Trial Tr., 3/11/11, at 1093:23-1095:6 (overruling Defendants’ objections on relevance, hearsay, and S.C.R. Evid. 403 grounds and admitting January 1999 DDMAC Notice of Violation to Janssen), attached hereto as Exhibit B; Order, Feb. 25, 2011, denying State’s Motion to Exclude the Expert Testimony of Sheldon Bradshaw and considering Bradshaw’s testimony regarding FDA regulations, violations

thereof, and “the significance of FDA and DDMAC actions” relevant under S.C.R. Evid. 401; Order, Feb. 11, 2011, denying Defendants’ Motion *in Limine* to Preclude the Introduction of Evidence of the April 19, 2004 DDMAC Letter and Any Evidence of or Reference to the Letter at Trial.)

Moreover and contrary to Defendants’ contentions, the State has not “disclaimed reliance on violations of any federal law” to show the willful nature of Defendants’ unfair and deceptive conduct in its Risperdal labeling. (Def.’ Objections at 2.) Rather, the State has alleged that Defendants’ failure to adhere to certain FDA regulations requiring that Defendants warn of serious adverse reactions and potential safety hazards in their product labeling as soon as there is reasonable evidence of an association of a serious hazard with their drug, including warnings through the dissemination of promotional materials related to Risperdal as well as their November 2003 “Dear Doctor” letter, are probative of Defendants’ unfair and deceptive conduct under South Carolina law and the willful nature thereof. However, the State seeks penalties based on violations of State, rather than federal, law—i.e., the jury will not be asked to decide any ultimate question regarding whether any FDA rule, regulation, or related law was violated, and neither will any such violation of FDA rules, regulations, or related law serve as the *per se* basis for the State’s allegations of SCUTPA violations.

Furthermore, as noted, the standard *South Carolina Requests for Charge – Civil* already includes basic charges addressing Defendants’ objection. Ralph King Anderson, Jr., *South Carolina Requests for Charge – Civil*, 2009, § 1-2. *Cf. id.* § 1-8.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants’ objections regarding the relevance,

prejudice, and discovery-related prejudice associated with counsel's statements regarding violations of federal law or regulations.

4. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State's Counsel Regarding Non-Disclosures to the FDA.

Despite Defendants' contention that evidence of their "non-disclosures" to the FDA is inadmissible because "[s]uch 'fraud on the FDA' claims are preempted as a matter of law," the State does not assert a "fraud-on-the-FDA" claim preempted under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001). (Defs.' Objections at 3.) *Buckman* does not preempt the State's SCUTPA claims or evidence offered in support thereof, including Defendants' non-disclosures to the FDA, because those claims are not "fraud-on-the-FDA" claims. *Id.* at 347-53 (holding that because the plaintiffs' state law "fraud-on-the-FDA" claims were based solely on the defendant's alleged violations of the FDCA's disclosure requirements, and not on a separate duty under state tort law, the presumption against preemption that normally applies in state law tort actions did not apply to the plaintiffs' state law "fraud-on-the-FDA" claims, and that those claims were preempted due to their conflict with the FDA's responsibility to police fraud committed against it). Unlike a "fraud-on-the-FDA" claim, the State's SCUTPA claims primarily involve Defendants' misrepresentations and omissions to doctors and patients and the willfulness of Defendants' conduct in that regard, about which Defendants' non-disclosures to the FDA are probative. The State's SCUTPA claims are based on Defendants' preexisting duties under that State law, not on Defendants' duty of disclosure to the FDA. (See, e.g., Pl.'s Second Am. Compl. ¶¶ 13, 24, 26, 37-38, 40, 45-46, 56-58.) In other words, the State does not seek to impose liability based solely on Defendants' non-disclosures to the FDA or other violations of FDCA requirements. See, e.g., *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 95 (2d Cir.

2006) (distinguishing *Buckman* because the plaintiffs asserted traditional state tort law claims that were “not premised principally (let alone exclusively) on a drug maker’s failure to comply with federal disclosure requirements” and noting that “in FDA-fraud cases, proof of fraud against the FDA is alone sufficient to impose liability”); *see also In re Pharm. Indus. Average Wholesale Price Litig.*, 582 F.3d 156, 176 (1st Cir. 1999) (“It is certainly true that the deception touched on a federal agency, but policing deceptive conduct is nonetheless a traditional area of state concern giving rise to a remedial scheme that is separate and distinct from, and predates, the federal law in question.”). Any evidence containing information that Defendants did not disclose to the FDA would be offered for the purpose of proving Defendants’ actual or constructive knowledge of Risperdal’s safety and efficacy, and the willfulness of their deceptive and unfair conduct, not simply to show Defendants’ concealment from the FDA.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants’ objections on federal preemption and other grounds relative to counsel’s statements regarding Defendants’ alleged “failure to disclose” information to the FDA.

5. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State’s Counsel Regarding Dr. Scott Reines.

Defendants contend that the State referred to Dr. Scott Reines “as a Janssen executive” although (allegedly) “Dr. Reines is not a Janssen executive and did not work for either of the two named Defendants.” (Defs.’ Objections at 3.) By his and Defendants’ own admissions as well as reflected in his curriculum vitae, Dr. Scott Reines served as Senior Vice President and Member of the Board of Directors for CNS, Pain and Translational Medicine for Defendants from December 2004 until September 2008. (See Curriculum Vitae, Scott Alan Reines, M.D.,

Ph.D., July 2009, attached hereto as Exhibit C.) Prior to that, Dr. Reines served as Vice President in the CNS and Pain Therapeutic Areas. (*See id.*)

In any event, counsel did not refer to Dr. Scott Reines as a "Janssen executive," but, rather, correctly identified him as "the president of Johnson & Johnson Pharmaceutical Research and Development" during the relevant time period. (Trial Tr. 3/8/11 at 222:7-14 (Ex. A).) Although Dr. Reines has since retired, his employment and/or job title during the relevant time period is material to this action.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants' objections regarding the State's purported misstatements of law and fact regarding Dr. Scott Reines.

6. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State's Counsel Regarding Defendants' Conduct in Response to DDMAC Communications.

Defendants argue that the State characterized the July 2004 corrected "Dear Doctor" letter as an acknowledgment by Defendants that the November 10, 2003 "Dear Doctor" letter was false and misleading. (Defs.' Mot. at 3-4.) The State is unable to locate such a characterization in the record, and Defendants provide no citation to one.

Further, Defendants argue that the State's characterization and use of the July 2004 "Dear Doctor" letter as an apparent basis for liability under SCUTPA is barred by S.C.R. Evid. 407. (*See* Defs.' Objections at 3-4.) However, the State has not offered the July 2004 "Dear Doctor" letter as evidence of subsequent conduct by Defendants to prove negligence or culpable conduct in connection with its dissemination of the November 2003 "Dear Doctor" letter. *See* S.C.R. Evid. 407. Rather, the State may use the July 2004 "Dear Doctor" letter to identify the information Defendants disseminated to South Carolina healthcare providers at that time

regarding Risperdal's safety profile and in contrast to Defendants' prior communications regarding the same through its November 2003 "Dear Doctor" letter, for example. Further, it unquestionably likely that Defendants would insist on the admission of the July 2004 "Dear Doctor" letter as a time-fixed limitation on culpability, especially where the State has indicated its intention to limit the penalties it seeks to roughly that timeframe, or at least during 2004.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants' objections regarding the State's alleged misstatements of law and/or fact relative to its characterization and use of Defendant's July 2004 "Dear Doctor" letter.

7. The Court Should Overrule Defendants' Objection Regarding the State's Characterization of the April 2004 DDMAC Warning Letter.

Defendants argue that the State stated actions that Janssen could have taken when it received the April 2004 DDMAC Warning Letter. (Defs.' Mot. at 4.) The State is unable to locate such a characterization in the record, and Defendants provide no citation to one.

In any event, Defendants object to the State's characterization of the April 2004 DDMAC Warning Letter and claim that the letter is merely "advisory and not an action that can be challenged in court." (Defs.' Objections at 4.) The State, however, contends that the April 2004 Warning Letter constitutes valid, enforcement action by the FDA against Defendants' "false" and "misleading" representations about Risperdal. The State's interpretation is consistent with all applicable federal regulations, expert testimony regarding the same, as well as Defendants' own prior acknowledgement that the April 2004 Warning Letter constitutes the "agency's position" on the issue. (Defs.' Mem. in Support of its Mot. *in Limine* to Preclude the Introduction Into Evidence of the April 19, 2004 DDMAC Letter and Any Evidence of or

Reference to the Letter at Trial at 7 (citing Regulatory Procedures Manual: Advisory Actions at 2 (Ex. C to Defs.' Mem.)).) Indeed, the Regulatory Procedures Manual on which Defendants have consistently relied in support of their argument, clarifies that the "Warning Letter was developed *to correct violations of the statutes or regulations*" and is "based on the expectation that most individuals and firms will voluntarily *comply with the law*" as set forth in the Warning Letter. (Regulatory Procedures Manual at 4-1 to 4-2 (emphases added), attached hereto as Exhibit D.) Furthermore, the *conclusions* the FDA reached in the April 2004 Warning Letter itself wholly support the State's position—e.g., "[f]ailure to correct the violations . . . may result in FDA regulatory action, including seizure of injunction, *without further notice*"; "DDMAC has concluded that the [November 10, 2003 Letter] is false or misleading in violation of Sections 502(a) and 201(n) of the [FFDCA] (21 U.S.C. 352(a) and 321 (n)); and "DDMAC has concluded, that these materials are false, misleading, and/or lacking in fair balance, and in violation of the [FFDCA]" (April 2004 Warning Letter, attached hereto as Exhibit E.) There is simply no basis for Defendants to argue that the April 2004 Warning Letter is not valid, effective FDA enforcement action of regulatory violations as determined by that agency or that the State's characterization of the April 2004 Warning Letter is otherwise inaccurate.

Although Defendants have not requested a corrective instruction as to this point, the State nevertheless opposes Defendants' characterization of the April 2004 Warning Letter as advisory and otherwise opposes Defendants' objection to the State's opening statements as alleged misstatements of law and/or fact.

8. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard the State's Characterization of the Nature of its Case Against Defendants.

Defendants contend that the State has inferred that its case against Defendants is a "criminal proceeding" and that "Defendants' conduct is criminal in nature." (Defs.' Objections at 4.) However, the State did not imply that this case is a criminal prosecution in its opening statements to the jury. Rather, the State used the term "prosecution" in accordance with its ordinary meaning as defined in Black's Law Dictionary and consistent with courts' use of the term in the context of litigation. Black's Law Dictionary (9th ed. 2009) (defining "prosecution" as "[t]he commencement and carrying out of any action or scheme"); see, e.g., *Atlantic Purchasers, Inc. v. Aircraft Sales, Inc.*, 705 F.2d 712, 717 (4th Cir.), cert. denied, 464 U.S. 848 (1983) (examining complaint in the context of UTPA litigation, and noting that it "gave no warning to Aircraft Sales that successful prosecution of the action could result in an award to Stella Maris of three times Stella Maris' actual damages").

Furthermore, as noted, the standard *South Carolina Requests for Charge – Civil* already includes basic charges addressing Defendants' objection. Ralph King Anderson, Jr., *South Carolina Requests for Charge – Civil*, 2009, § 1-2. Cf. *id.* § 1-8.

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants' objections regarding the State's allegedly prejudicial statement describing the nature of this action.

9. The Court Should Not Issue a Corrective Instruction to the Jury to Disregard Statements by the State's Counsel Regarding Defendant's Marketing Activities and the Scope of the State's Claims.

Contrary to Defendants' assertions that "the State's claim is limited solely to the November 2003 mailing and the Risperdal package insert," (Defs.' Objections at 5), this Court

has made clear that “the State initiated this action against Defendants . . . to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for their willful, deceptive and unfair course of conduct in Risperdal’s product *labeling*.” (Order, Feb. 25, 2011, at 1 (emphasis added); *see, e.g., id.* at 12 (excluding expert testimony of Dr. Jebaily and identifying “the real issue in this case” as “whether or not *the labeling methods* of the Defendant violated [SCUTPA]”) (emphasis added).) Further, in rejecting Defendants’ statute of limitations arguments and denying Defendants’ motions for summary judgment, the Court plainly articulated “the essential question before [the] Court”: “when the State Attorney General’s Office would have become aware of ‘unfair or deceptive acts or practices’ *in the Defendant’s marketing and labeling actions relative to the sale of Risperdal*.” (*Id.* at 6 (emphasis added); *see also id.* at 7 (considering “that the FDA does not allow or permit deceptive activities in the *marketing and labeling* of drugs”) (emphasis added); *id.* at 13-14 (denying Defendants’ Motion *in Limine* to Preclude the Expert Testimony of Dr. William Wirshing, M.D. and explaining that “[i]t appears . . . that he is in a position to testify concerning *the relationship between the actual effects of taking atypical antipsychotics and the marketing claims made by manufacturers*” and that he “will be allowed to testify *concerning the science behind the marketing*[,]” as “his testimony on the science behind the drugs and the effects that they may have on the human body *and how that compares to the marketing of the drug* . . . could be of assistance to a jury”) (emphases added); denying State’s Motion to Exclude the Expert Testimony of Sheldon Bradshaw and permitting Defendants’ use of his testimony “to rebut the Plaintiff’s contention that the DDMAC correspondence reflects an FDA ‘determination’ that *Janssen’s promotional materials and a November 2003 mailing to physicians* were ‘false and misleading’” (emphasis added).)

The Court further articulated the relevance and role of Defendants' marketing and promotional activities in the context of the litigation, more generally, as follows: "This trial is also becoming a trial, I think, concerning corporate reputation, corporate intentions, things of that nature, which has been . . . the argument that the defense has made." (Trial Tr., 3/11/11 at 1093:23-1094:2 (Ex. B); *see also id.* at 1087:7-1093:18.) In that regard, the Court admitted testimony and evidence, including Defendants' business plans and sales aids discussing off-label promotion, in support of the State's allegations of Defendants' corporate motive of off-label marketing as well as Defendants' false and misleading promotional campaigns relative to Risperdal and in violation of FDA regulations, *inter alia*. (*See id.*)

Based on all of the above, the Court should refuse to issue a corrective instruction to the jury as Defendants have requested and overrule Defendants' objections regarding the State's allegedly prejudicial and irrelevant references to marketing activities of Defendants.

Respectfully submitted,

**STATE OF SOUTH CAROLINA
OFFICE OF THE ATTORNEY GENERAL**

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SOUTH CAROLINA
SPARTANBURG COUNTY
MARCH 15 2011
JESSICA S. BAILEY

March 14, 2011

Spartanburg, South Carolina

Attorneys for the State of South Carolina

EXHIBIT A

FILED
SEP 16 1991
FBI - MEMPHIS
JAN 10 1992
FBI - MEMPHIS

STATE OF SOUTH CAROLINA

COURT OF COMMON PLEAS

COUNTY OF SPARTANBURG

SEVENTH CIRCUIT

STATE OF SOUTH CAROLINA

Ex rel. Henry McMaster, in his
Capacity as Attorney General of the
State of South Carolina,

Plaintiffs,

vs.

CASE NO. 2007-CP-42-1438

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS,
INC., f/k/a JANSSEN PHARMACEUTICA, INC.,
JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.,

Defendants.

VOLUME II

TRIAL BEFORE: THE HONORABLE
ROGER L. COUCH

DATE: March 8, 2011

TIME: 9:04 a.m.

LOCATION: Spartanburg County Courthouse
180 Magnolia Street
Spartanburg, SC

REPORTED BY: Susan M. Valsecchi, RPR, CRR
Certified Realtime Reporter

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FILED
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SPARTANBURG COUNTY
2011 MAR 13 PM 2:03
M. HOPE BLANCHLEY

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1 you the charge concerning the law. The foreperson
2 of the jury is the person who will preside over
3 your deliberations. And since you will not be
4 deliberating until the close of the trial, that's
5 not necessary.

6 That person also would communicate with
7 the Court during your deliberations and also the
8 person would write the verdict. All of those
9 functions take place once the case has been turned
10 over to you for your deliberations.

11 I will stress to you and I will tell
12 you that it's important that the verdict of the
13 jury at the close of the trial must be unanimous.

14 That means each and every one of you
15 would have to agree upon the verdict before it
16 becomes the verdict of the jury. Therefore, no
17 single juror is more important than any other
18 juror. Each of you will have a say in the ultimate
19 verdict of the case, since the verdict must be
20 unanimous. So I will appoint that person at the
21 close of the trial.

22 If you have any problems or issues
23 during the trial that you think should be brought
24 to the Court's attention, inform the bailiffs of
25 that fact, they'll inform me, and I will deal with

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1 those issues or problems should they arise. But
2 again, I will appoint the foreperson at the close
3 of the trial of this case.

4 Now, I want to be sure that I have not
5 violated anyone's rights in my opening comments to
6 you.

7 Is there an objection from the
8 Plaintiff?

9 MR. TRAMMELL: None from the Plaintiff,
10 Your Honor.

11 THE COURT: Is there any objection from
12 the Defense?

13 MR. PUGH: No, Your Honor.

14 THE COURT: Ladies and gentlemen, the
15 burden of proof on this case rests upon the
16 Plaintiff, and at the close of the trial, I will
17 explain to you what is meant by burden of proof and
18 the standard by which we judge that.

19 I'm telling you that because the
20 Plaintiff, therefore, will be allowed to go first
21 with its opening arguments or statements to you,
22 followed by the Defense. And then in the
23 presentation of evidence, the Plaintiff will be
24 allowed to go first, followed by the Defense.

25 At the close of the trial, we'll allow

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1 the attorneys to make closing arguments to you.
2 After that occurs, I will charge you concerning the
3 law to be applied to the facts as you find them to
4 be, and I will at that time turn the case over to
5 you for your deliberations and ultimate verdict in
6 the case. That's the procedure that we will follow
7 in the matter.

8 So at this time, I will allow the
9 Plaintiff to go forward with its opening statements
10 or argument.

11 Mr. Coggins, is that you?

12 MR. COGGINS: Yes, sir, Your Honor.

13 THE COURT: You may proceed.

14 MR. COGGINS: Good morning, ladies and
15 gentlemen.

16 As Judge Couch told you just a few
17 moments ago, your job in this case is to search for
18 the truth. A search for the truth can be sometimes
19 a long and winding road.

20 We want to thank you for your
21 willingness to be here. I know you weren't exactly
22 here voluntarily, but as Judge Couch said
23 yesterday, this is a very important civic duty.

24 As he indicated, a wise man once
25 said -- and I think it was Winston Churchill that

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1 said that, in peacetime, this is the greatest duty
2 a citizen can give to its government.

3 And a jury, like you are made up of
4 today in a civil case like this, as opposed to a
5 criminal case, is something that is uniquely
6 American. It is unique to our Constitution, that
7 any time our citizens, whether it be a single
8 person, a corporation, one person, many people, we
9 have a dispute with one another, a dispute over a
10 contract or somebody injured somebody else or
11 somebody did anything that wasn't right under the
12 law, we have the right to come in and not have a
13 political appointee or a government official make
14 the decision. We have the right to have a jury of
15 our peers, people from our same community to sit in
16 judgment. That's what you've been asked to do.
17 It's a sacred duty, I know you will take it
18 seriously, and we appreciate from the bottom of our
19 heart your willingness to be here and assist us in
20 this case.

21 The search for the truth, as I said,
22 can be a long and winding road. Over four years
23 ago, then Attorney General Henry McMaster
24 commissioned a team of lawyers to investigate a
25 case against Ortho-McNeil-Janssen formerly known as

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1 Janssen Pharmaceutica and its parent corporation, 2 Johnson & Johnson. The investigation was done, 3 recommendation was made, and the attorney general 4 secured the services of these lawyers to bring this 5 case. 6 Ladies and gentlemen, there's nothing 7 underhanded about that. The South Carolina law 8 provides that the attorney general can associate 9 lawyers and experts in the field to assist him in 10 the bringing of these types of cases. It's 11 something that he is allowed to do, and indeed, as 12 we show you as we go through in a case like this, 13 has the duty to do. 14 This case was filed in April of 2007, 15 almost four years ago. Over the last four years, 16 hundreds of thousands of documents have been 17 reviewed. Depositions have been taken of witnesses 18 all over the country. Some of those witnesses 19 don't even reside in this country, they live in 20 Europe. And from time to time, you will see us 21 refer to this cast of characters, because Johnson & 22 Johnson is one of the biggest corporations in the 23 world and Janssen Pharmaceutica is a huge medical 24 science division, pharmaceutical division. 25 And what we've done here is we've tried	1 Carolina is going to be made out of the mouths of 2 the executives and researchers and doctors at 3 Janssen Pharmaceutica. You will see them in living 4 color on that screen right there under oath, and 5 largely our case will be made based upon the 6 admissions and the acknowledgments that they make 7 on the record. 8 In addition, ladies and gentlemen, 9 we'll have expert witnesses who will come in. 10 Experts in the science with medicine, who will 11 explain to you what this case is about from a 12 scientific standpoint, because I don't think any of 13 us are experts in chemical compounds or 14 pharmaceuticals. 15 We'll have an expert that will come in 16 and explain to you about the regulatory system and 17 how that works, and what Janssen's duties were and 18 are with respect to their medicines, and one 19 medicine in particular. 20 And, folks, this case is largely about 21 what Janssen knew and when they knew it, and we'll 22 present the evidence to you by video deposition, by 23 live witnesses and by documents that will allow you 24 to follow that trail, that will allow you to 25 complete that search for the truth and find the
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1 to give you a list of folks who were in marketing, 2 who were in medical affairs, who were in corporate 3 governance, who are in regulatory affairs because, 4 as you know, prescription medicines are regulated 5 by the government. And then some miscellaneous 6 folks who are involved with their global 7 production, their global situation, because they 8 are a multinational or global corporation. 9 And, ladies and gentlemen, what you're 10 going to see in terms of evidence in a lot of cases 11 is deposition testimony, like Judge Couch said. 12 Many of these folks are spread out from 13 California to Boston, from Florida to New Jersey to 14 Belgium, all over the globe. And it would be 15 prohibitively expensive to bring each and every one 16 of those people here to testify to you from this 17 witness stand. 18 And so the lawyers have gone out and we 19 have taken these depositions, and, as Judge Couch 20 told you, those depositions are testimony, just as 21 if the witness was in that chair. They're taken in 22 front of an official court reporter, lawyers from 23 both sides are present and the lawyers get to ask 24 questions of the witness. 25 Much of the case for The State of South	1 truth at the end of the case. 2 Now, before I go further into the story 3 of the case, let me introduce you to a few people 4 that are going to be involved in the case, first of 5 all with respect to the trial team that was secured 6 by Attorney General McMaster and now that General 7 Wilson has asked to continue the prosecution of 8 that case. 9 My name is Don Coggins, I've practiced 10 law here in Spartanburg for over 26 years. I 11 practice with the firm of Harrison, White, Smith & 12 Coggins. My partner John White and I are part of 13 the team and are two of the folks you'll be hearing 14 from during this case. 15 Another part of our team, Mr. John 16 Simmons, a lawyer from Columbia, he's a former 17 United States attorney serving under the first Bush 18 administration. 19 Mr. Fletcher Trammell is an attorney 20 from the Houston firm of Bailey, Perrin and Bailey, 21 who has some special expertise in these types of 22 cases, that's the reason he was hired. The four of 23 us will be primarily speaking to you on behalf of 24 the attorney general's office. 25 Now, the attorney general has also

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1 appointed Assistant Attorney General Havird 2 Jones -- Sonny Jones, as we know him -- senior 3 analyst Jay Smith; they're seated there in the 4 first row. They have been working with us in this 5 case and supervising our work in this case and 6 they'll be here during the trial. 7 You will also see other clerks and 8 lawyers from our firms who will be in and out of 9 the case and assisting us with documents and making 10 sure that the exhibits are ready, that the 11 deposition videos are ready so that we hopefully 12 will not take more of your time than we absolutely 13 have to. 14 Now, I know that you were told when you 15 were given those questionnaires to fill out and 16 send back in to the clerk's office that this case 17 might last three weeks, and it might. 18 But I'm going to pledge to you right 19 now that the State is going to do everything we can 20 to put our evidence in in about a week. By the 21 first of next week, we hope to be through. So 22 hopefully if the Defense might can do likewise, we 23 might cut this thing down closer to two weeks 24 instead of three weeks. And I know every day we 25 can shave off of it will be a blessing to you, and	1 business with the public in The State of South 2 Carolina? 3 If you believe it was, the second 4 question you have to answer is, was it willful. In 5 other words, was it an accident, or did they know 6 they were doing wrong. Did they know they were 7 doing something wrong at the time. 8 If you answer yes to those questions, 9 then there will be a separate proceeding that 10 involves Judge Couch to determine whether or not 11 any civil penalties or fines are imposed. 12 This is not a civil case like a car 13 wreck or a product liability case where somebody is 14 coming in and saying, hey, I got hurt, give me a 15 lot of money from the defendant. This case is 16 simply about right and wrong, doing the right 17 thing. This case is about obeying the law, 18 following the rules and regulations instead of 19 twisting them around so that you can try to make 20 some kind of obscene profit. 21 This case is about corporate 22 responsibility, being a good corporate citizen, not 23 going out and trying to break the rules and lie to 24 people and deceive people all in pursuit of the 25 almighty dollar. At the end of the day, this case
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1 we'll try to do that. 2 South Carolina has a statute called the 3 South Carolina Unfair Trade Practices Act. It is 4 Section 39-5-20 of our code. And this is what it 5 says: Unfair methods of competition and unfair or 6 deceptive acts or practices of the conduct of any 7 trade or commerce are hereby declared unlawful. 8 There's another section of that law 9 that says if the attorney general finds that any 10 businessperson is violating that law within The 11 State of South Carolina, the attorney general has 12 the right and the duty to bring an action against 13 them to enjoin them from continuing to do that and 14 to also collect civil penalty. 15 Civil penalties are not the same thing 16 as damages. In this case, when we get to the end 17 of the trial and Judge Couch instructs you on the 18 law, as he indicated he would do at the same time 19 he appoints a foreperson, he will tell you that 20 you're going to decide two questions and two 21 questions only. 22 The first question is: Did the 23 Defendant's conduct that we show you evidence of 24 violate this statute? In other words, was it 25 unfair, was it deceptive in the way they did	1 is real simple, ladies and gentlemen. Every 2 witness that gets on that stand is going to take an 3 oath to tell the truth, the whole truth and nothing 4 but the truth. 5 If the Defendants had done that, that 6 simple thing, tell the whole truth and nothing but 7 the truth, we wouldn't be here. This case is about 8 a very large company that developed a little pill 9 that brought them huge, huge profits. 10 And, folks, the case is not about those 11 huge profits. The case is about how they went 12 about making those profits. Was it fair. Was it 13 deceptive? We submit to you that it was. 14 And in the story I'm going to tell you 15 here in the next few minutes, the big company is 16 Johnson & Johnson, little pill is Risperdal. 17 Risperdal, or as its chemical compound 18 is called risperidone, is what is called an 19 atypical antipsychotic medicine that was approved 20 by the FDA in 1993. It's used by doctors to treat 21 serious psychiatric illnesses such as 22 schizophrenia, bipolar disease. Ladies and 23 gentlemen, these are serious illnesses. 24 And if you don't mind, I want to step 25 down here because I don't want to be blocking these

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1 folks' view here on the other side. 2 These are serious mental illnesses. 3 When Risperdal was first approved, it was approved 4 for the treatment of manifestations of psychotic 5 disorders, psychoses. Later on in the early 2000s, 6 the label was changed and the approval was changed 7 to treat schizophrenia specifically. 8 Later, they got an addition to the 9 label that said they could treat the acute mania 0 phase of bipolar disorder, the so-called manic 1 depression, and only the extreme mania phase, 2 what's called Bipolar I by a lot of doctors and 3 scientists. 4 These are among the most serious mental 5 illnesses you can suffer. These are the people 6 that in an earlier time and place were locked away 7 from society because they were a danger to 8 themselves and they were a danger to others. 9 About 30 -- excuse me. About 50 years 0 ago, there was a first generation of antipsychotic 1 medications that came along and you'll hear those 2 referred to as typical antipsychotics or 3 first-generation antipsychotics. Those medicines 4 were a great revolution. They allowed a lot of 5 those people who have been institutionalized to	1 severely mentally ill need these drugs, and there's 2 no problem with that. 3 But, ladies and gentlemen, with respect 4 to those side effects that these drugs have, the 5 evidence is going to show Johnson & Johnson -- that 6 Janssen Pharmaceutica -- was not honest and did not 7 give full and fair information. 8 This case boils down to two things, and 9 you can remember them pretty easily because they 0 both start with L. This case boils down to the 1 letter and the label. Let's talk about the letter 2 first. 3 This is a letter that Janssen decided 4 to send out in November of 2003, November 10, 2003, 5 and it's a Dear Healthcare Provider letter. What 6 that is -- and you'll hear this referred to as a 7 Dear healthcare provider letter and a Dear Doctor 8 letter. Sometimes you will see the abbreviation 9 DHCP or DDL. 0 What these are designed to do are for 1 drug companies to convey important information to 2 prescribers, to doctors, if there's some new 3 development with respect to their drug. 4 And in this case, what precipitated 5 this letter was the FDA -- which I will tell you a
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1 live out in the community or to function. But they 2 had serious side effects. 3 That's why when the new generation or 4 the atypicals came along, it was a revolution. The 5 first one of those was Clozaril, it came along in 6 the late 1980s. Risperdal was approved in the 7 early 1990s, December of '93; the year of launch 8 was 1994. 9 Shortly after that, you had additional 0 drugs in the same class come along. Eli Lilly had 1 a drug called Zyprexa, which you will hear more 2 about in this case. Then you had AstraZeneca with 3 Seroquel, you had drugs like Geodon, Abilify. I 4 think there are a few new ones that have come out 5 even in the last few years. And these atypicals 6 were better on some of the side effects that had 7 plagued the first generation. 8 But they had side effect profiles of 9 their own. 0 Now, ladies and gentlemen, the evidence 1 is going to show that when these drugs are 2 prescribed directly, when doctors have full and 3 fair information and they can weigh the risks and 4 benefits of these drugs against the side effects, 5 these drugs are good drugs. The people who are	1 little bit more about who and what they are in a 2 minute -- but I think all of us realize that 3 generally the FDA approves prescription drug 4 medicines that we take. 5 The FDA came out and said, all of you 6 atypicals, all of you second generation, all of 7 these drugs that I just told you about, 8 AstraZeneca's Seroquel, Bristol-Myers' Abilify, 9 Lilly's Zyprexa, Novartis' Clozaril, and Pfizer's 0 Geodon, in addition to Janssen's Risperdal, all of 1 you have to put a warning, a class warning on your 2 label about the dangers of high blood sugar and the 3 development of diabetes as a result of taking these 4 medications. 5 So Janssen decides on their own to send 6 out this letter, and what they say is in this last 7 paragraph right here -- this is the important part, 8 ladies and gentlemen. They say that 9 hyperglycemia-related adverse events have 0 infrequently been reported in patients receiving 1 Risperdal. 2 I will submit to you that that was a 3 misleading statement. It omitted critical material 4 information, and we're going to show you evidence 5 that will prove that.

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1 Although confirmatory research is still 2 needed, a body of evidence from published 3 peer-reviewed epidemiology research -- and they 4 have up here, you can hardly see it here, but it's 5 a footnote that says 1 through 8 and they've got 6 some references attached that we'll look 7 at -- suggest that Risperdal is not associated with 8 an increased risk of diabetes when compared 9 to -- I'm sorry -- untreated patients or patients 10 treated with conventional antipsychotics. Evidence 11 also suggests that Risperdal is associated with a 12 lower risk of diabetes than some other studied 13 atypical antipsychotics. 14 I will submit to you that the evidence 15 is going to show that that was an untrue statement, 16 that that was a statement that omitted material 17 information that Janssen knew at the time they 18 published this letter. 19 They published this letter in November 20 of 2003 to over 700,000 doctors nationwide and 21 almost 7,200 doctors in South Carolina. Precise 22 number, I think the evidence will show is 7,194 23 South Carolina physicians. 24 Let's go to the next one. This is 25 their list of references that they have there	1 help me with this, they said that the Division of 2 Drug, Marketing, Advertising and Communications, 3 DDMAC -- which is a division of the FDA that has to 4 approve these type of communications -- has 5 reviewed a Dear Healthcare Provider letter for 6 Risperdal disseminated by Janssen Pharmaceutica on 7 November 10, 2003, the letter we just looked at. 8 DDMAC has concluded the DHCP letter is 9 false or misleading in violation of the Federal 10 Food, Drug, and Cosmetic Act. 11 That is the act that gives the FDA the 12 authorization to control and to monitor what drugs 13 and foods and cosmetics and things we put into our 14 body and put on our body are allowed. 15 DDMAC says that it's false and 16 misleading because it fails to disclose the 17 addition of information relating to hyperglycemia 18 and diabetes mellitus to the approved product 19 labeling. 20 And you see that initial there, PI, the 21 label is sometimes referred to as the label; it's 22 sometimes referred to as the package insert because 23 it's that several-page thing that is given to the 24 doctor with all of the prescribing information, 25 what it's approved to treat, what type of dose
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1 backing up those claims. Among the things that 2 they don't tell the South Carolina doctors are that 3 Dr. Amy Grogg, who is an author on two of those 4 studies, is an employee of Janssen, a very 5 high-level employee of Janssen. Dr. Ramy Mahmoud, 6 who is also a co-author on two of the studies, is 7 an employee of Janssen. Dr. Gianfrancesco, who is 8 on three of the studies, is a researcher who is 9 funded by Janssen. 10 Ladies and gentlemen, the evidence will 11 show that on these, you get what you pay for, and 12 they knew at the time they sent this out that they 13 had in their possession clinical evidence, just as 14 strong -- or stronger, actually -- that showed none 15 of this was true. It showed they were as bad as 16 the other atypicals, they caused Diabetes II, they 17 had no reasonable basis to say that they were 18 better than the other atypicals. 19 Now, ladies and gentlemen, the State of 20 South Carolina doesn't expect you to just take our 21 word for it. When the FDA got a load of this 22 letter they sent out in November of 2003, the FDA 23 sent them a warning letter and here is what they 24 said. 25 So I don't have to have Mr. Trammell	1 you're to use with a particular patient, what 2 population it's approved to treat. 3 And significantly, this was only 4 approved to treat adults 18 to 65. Not children, 5 not adolescents, not geriatrics. 6 But it gives the doctor all of that 7 information and then it gives the chemical compound 8 breakdown and it has warnings for things you need 9 to watch out for. 10 It has precautions for things that 11 aren't quite as bad, it has adverse reactions for 12 things that are not quite as bad. And then toward 13 the back, it has some things that are kind of 14 buried in the fine print that are other adverse 15 events, other reported adverse events. 16 Well, what this is talking about is a 17 warning, the most serious risk language that can be 18 found in a package insert. 19 And the FDA says that it minimizes the 20 risk of hyperglycemia-related adverse events, which 21 in extreme cases, is associated with serious 22 adverse events, including ketoacidosis, 23 hyperosmolar coma and death. Ketoacidosis, coma 24 and death. And that language is right out of the 25 warning. Nothing about infrequently and nothing in

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1 their letter about coma or death.
2 The FDA also says that it fails to
3 recommend regular glucose control monitoring to
4 identify diabetes mellitus as soon as possible.

5 In other words, if you're going to put
6 people on these medications, Doctor, you need to
7 start monitoring their blood sugar to see if it
8 goes up, to see if they're going to develop
9 diabetes. Nothing in that letter to the doctor
10 about developing diabetes -- about needing to
11 monitor your patients when you put them on our
12 medicine. And misleadingly claims that Risperdal
13 is safer than other atypical antipsychotics.

14 Again, there was nothing in that
15 warning mandated by the FDA that said they could
16 claim that they were better than the others. It
17 was a class warning for all of them, and as I told
18 you, the evidence will show they had information at
19 the time that showed they were as bad as the
20 others.

21 But here is the key part because this
22 is why the attorney general brings this case. The
23 healthcare community relies on Dear Healthcare
24 Provider letters for accurate and timely
25 information regarding serious risks and associated

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1 changes in labeling and the dissemination of this
2 letter at a time critical to educating healthcare
3 providers is a serious public health issue.

4 Every time somebody sells a car and
5 doesn't tell the other person that the brakes are
6 bad, every time somebody sells a house and tells
7 the other person that the roof doesn't -- doesn't
8 tell them that the roof leaks, the attorney general
9 doesn't come running into court and file an unfair
10 trade practice claim. It is only for cases that
11 have significant public impact. And, folks, there
12 is the public impact.

13 Now, having said that, I would caution
14 you about one thing. There is no requirement in
15 the act that we prove that any doctor relied on
16 that letter or relied on what they said in writing
17 a prescription.

18 This is not a fraud case. We don't
19 have to prove reliance. This is an enforcement
20 case. The law says you can't do this, if you do
21 it, you broke the law. It doesn't matter
22 what -- it's kind of like you go in to rob the
23 7-Eleven and it turns out there's no money in there
24 or the clerk pulls out a gun and you have to run
25 away. If the police catch you, the fact that you

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1 didn't get any money or the fact that the clerk ran
2 you away and was able to fend off the attack isn't
3 going to save you from prosecution. If you break
4 the law, you have to pay the consequences.

5 Now, here is what the letter says from
6 the FDA in more detail: The FDA is not aware of
7 substantial evidence or substantial clinical
8 experience to support Janssen's claim, that
9 evidence also suggests that Risperdal is associated
10 with a lower risk of diabetes than some other
11 studied atypical antipsychotics.

12 In other words, the FDA says the
13 science we have access to doesn't support this.

14 If you have data to suggest this claim,
15 please send it to us.

16 The FDA also says, the FDA's conclusion
17 regarding the lack of evidence to support a ranking
18 of risk among the atypical antipsychotics is
19 reflected in the following statement from the
20 warning section of the package insert for
21 Risperdal.

22 This is right out of the label that is
23 going with their medication into South Carolina at
24 this time.

25 And it says: Precise risk estimates

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1 for hyperglycemia-related adverse events in
2 patients treated with atypical antipsychotics are
3 not available.

4 They didn't contest that. They
5 accepted that label. That's in their label, not
6 the Zyprexa label, not the Seroquel label, it's in
7 theirs too because it's class warning, but it's in
8 their label, Risperdal's label.

9 And yet, in the letter to the doctor,
10 they say something completely different based on
11 science generated by their employees.

12 The Dear healthcare letter was not
13 submitted to the FDA at the time of initial
14 dissemination as required by postmarketing
15 reporting requirements.

16 Ladies and gentlemen, the evidence will
17 show that once you are marketing a drug after
18 you've been given approval by the FDA, the FDA
19 wants to keep up with what you're saying about that
20 drug to try to make sure that what you're saying is
21 fair and accurate. And so you're supposed to
22 submit a copy to them at the time you send it out.
23 Janssen didn't do that. We're going to talk a
24 little bit about that in a minute, and I think the
25 evidence will show exactly why they didn't do it.

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1 But, again, that's a violation. 2 And finally, down here, the letter 3 misleadingly omits material information about 4 Risperdal, minimizes potentially fatal risks 5 associated with the drug and claims superior safety 6 to other drugs in its class without adequate 7 substantiation. 8 DDMAC requests that Janssen immediately 9 cease the dissemination, quit sending this thing 10 out, promotional materials for Risperdal that 11 contain claims the same or similar to those 12 described above and provide a plan of action to 13 disseminate accurate and complete information to 14 the audience that received the violative 15 promotional materials. The violative promotional 16 materials being the November 10th letter. 17 Now, ladies and gentlemen, I am sure 18 that you, like me, would have the question why 19 would a responsible company like Johnson & Johnson, 20 why would an old and long established 21 pharmaceutical company like Janssen send out such a 22 flagrantly misleading and deceptive and unfair 23 letter. I submit to you the evidence will show 24 they did it for the reasons that corporations 25 always get in trouble for. They did it for the	1 1993 when they began marketing it in early 1994 and 2 then various things that happened along the way 3 until we get down here to the letter in November 4 and the warning letter in April that we just saw up 5 on the screen. 6 The process for having a drug approved 7 is something that I had never known anything about 8 and I don't know if you do or not. 9 But, basically, what happens is if a 10 pharmaceutical company is bringing a new compound 11 to market, if they think they have discovered a new 12 drug that will be helpful and also profitable to 13 them, they go through a process of testing. There 14 are a series of short-term clinical trials, phased 15 trials that they go through to test the drug and 16 they report those findings to the FDA. 17 Based upon what they report to the FDA, 18 the Food and Drug Administration makes its decision 19 about labeling the drug. 20 The FDA, what do they do, they're 21 charged with protecting the public health and 22 assuring that all drugs are safe and effective, 23 they enforce regulations, approve advertising, 24 labeling and promotions of drugs in the United 25 States. The label, as we said, is that seal of
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1 money. Let's go ahead and skip these two. 2 Risperdal sales, 1994, the year of 3 launch, \$172 million. 2004, ten years later, over 4 \$3 billion per year. If you take the actual sales 5 of Risperdal over that ten-year period, they add up 6 to approximately \$12 billion. 7 And at the time they were writing this 8 letter, they were around \$3 billion a year. But it 9 wasn't just what they had made, it was what they 10 were planning to make. This is from their 11 documents, this is evidence that you will see, why 12 invest in Risperdal. Projected sales, 2001 to 13 2010, first decade of this century, 33 billion 14 cumulative sales, 97 percent gross profit margin. 15 I don't know if any of you have ever operated your 16 own business, but a 97 percent gross profit margin 17 is something that is just incredible. 18 That's motive. That's a reason to send 19 out a letter that plays fast and loose with the 20 facts. 21 Now, let me tell you the rest of the 22 story. How did we get to this the point? I told 23 you earlier that Risperdal was approved in 1993 and 24 you're going to see various timelines in this case. 25 This is just one that shows the initial approval in	1 approval, it's what allows them to sell the drug. 2 And the FDA makes the final determination in 3 conjunction with the drug company based on 4 information provided by the drug company on the 5 content and language on the label. The label is 6 reviewed by the FDA periodically based on new 7 information obtained by the FDA. 8 And again, that new information can be 9 a couple of different things. It can be safety 10 information that is generated by later studies or 11 case reports where doctors are treating a patient, 12 they have something bad happen and they report it 13 to the FDA. They have a service called MedWatch 14 that you will hear about that they can report these 15 adverse events to. Or it can be information 16 provided by the drug company itself. 17 It can also be on the occasion of the 18 drug company asking for a new use for the product, 19 a new indication, a new disease treatment for it to 20 be approved for. So it's reviewed from time to 21 time. 22 DDMAC, we talked about before is just 23 the arm that handles all advertising and 24 promotional labeling. 25 The key factor on the labeling, ladies

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1 and gentlemen, is that the evidence will show, the
2 FDA has no testing lab. The FDA doesn't run drug
3 trials, FDA doesn't do testing for itself. FDA has
4 scientists and clinicians who are on staff to
5 review the submissions of the drug company. FDA
6 makes their labeling decisions based upon their
7 review of those submissions.

8 Just like a lot of things in society
9 today, garbage in, garbage out. The FDA's ability
10 to make a good decision about the labeling is
11 directly dependent upon the company giving them all
12 of the information.

13 And in this case, the evidence is going
14 to show that as to these side effects, and we're
15 not just talking about diabetes, there are a couple
16 of others, they didn't provide the information to
17 the FDA that they had.

18 The evidence is going to show that
19 they're required to provide that information not
20 only to the FDA, but to all of us, because the FDA
21 is just the vehicle through which it gets in the
22 label so that it goes to the doctors and they can
23 talk about it with their patients. We can look it
24 up in the Physicians' Desk Reference or go online
25 to any one of a number of websites where you can

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1 get the prescribing information for a drug you're
2 taking. That's how we get the information. And if
3 they don't disclose it, we don't have it, our
4 doctors don't have it.

5 And in this case, there was a really
6 good reason why they didn't want to talk about
7 these side effects. In other words, as we've just
8 seen, there were about 3 billion a year, and
9 possibly 33 billion reasons they didn't want that
10 information to get out.

11 The case is about the letter and the
12 label. The letter, we've shown you. We don't just
13 say that it was false and misleading and deceptive,
14 the FDA called them on it, they said it was, too.

15 The label, the evidence is going to
16 show they had information showing that this drug
17 posed a specific danger to the elderly, to
18 geriatrics, and yet they sold it to doctors to be
19 used in nursing homes with the geriatric
20 population.

21 There's going to be evidence to show
22 that with respect to children and adolescents,
23 there was a serious side effect, a hormonal side
24 effect called hyperprolactinemia. Prolactin is
25 simply an enzyme in the bloodstream in the body

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1 that generates what a human needs to generate milk,
2 that's where you get the lactin part. And what it
3 can cause is, in little boys and little girls, it
4 can cause them to grow enlarged breasts, it can
5 even cause them, even boys, to actually lactate, to
6 actually leak milk. It can also mess up their
7 hormonal system.

8 You will hear in a deposition excerpt
9 from one of their own scientists, that they know it
10 has some effect on the development of boys and
11 girls, that with little girls, it impacts their
12 menstrual cycle. With little boys, it impacts the
13 testosterone and the development of them.

14 You will hear from their scientists
15 that even though they know it impacts that, they
16 don't know how, they don't know exactly what it
17 does. And yet, you will see evidence that they
18 were calling on doctors, that they were promoting
19 this with their package insert to say that they
20 should treat these types of patients, that they
21 should give this powerful antipsychotic drug to
22 children, adolescents, the old folks in nursing
23 homes, despite the fact that it had not been
24 approved for that purpose, it had not been approved
25 for those populations and despite the fact that

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1 they knew there were dangerous side effects that
2 they weren't telling anybody about.

3 Now, I fully expect the defense to say,
4 but we did; it was in the label, it was in the
5 adverse events. Well, ladies and gentlemen, that's
6 what makes the label deceptive. That's why this
7 case is about the letter and the label.

8 Because you're going to hear testimony
9 from the regulatory expert that if you know you're
10 a drug company and you know there's a reasonable
11 association between your drug and a bad event, you
12 have a duty to publicize that and you have a duty
13 to let people know.

14 You don't allow it to be buried on Page
15 7 or 8 of a multipage, fine-print document where
16 you hope nobody will ever pay attention to it.

17 You have a duty to advise and
18 communicate that risk to doctors, patients and the
19 public. And in this case, specifically the public
20 in the State of South Carolina.

21 Now, folks, when the FDA approved the
22 label, this goes to show you that they knew the
23 rules from the beginning. The FDA put in the
24 approval paperwork that at the present time, in
25 1993, we would consider any advertisement or

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1 promotional labeling for Risperdal false, 2 misleading or lacking in fair balance. 3 If there's presentation of data that 4 conveys the impression that Risperidone is superior 5 to haloperidol -- that's Haldol -- that's one of 6 the first-generation antipsychotics -- or any other 7 marketed antipsychotic drug product with regard to 8 safety or effectiveness, why was it important to 9 tell them right from the beginning, you can't make 10 comparative claims? Because the FDA knows that's 11 how this works, that's how they sell this stuff, by 12 comparing it to the other drugs in the class and 13 saying theirs is better. 14 And as long as you do that factually 15 and accurately, there's nothing wrong with that. 16 In this case, they came right out of 17 the box right after Clozaril, they were the second 18 one out, 1993, '94. Clozaril had problems with 19 side effects that were very similar to some of the 20 first-generation antipsychotics. With respect to 21 Risperdal, they came out of the box and had a big 22 launch, they were a big hit. They were marketing 23 to doctors and saying, we're the big gun against 24 severe mental illness. But then Zyprexa launched 25 and Zyprexa is Lilly's drug and Zyprexa was eating	1 class, class label, class warning. And I'm going 2 to take you through just a little preview of what 3 the evidence is going to show about this, because I 4 think it's instructive in terms of showing what the 5 corporate strategy was and how these folks were 6 behaving and what they were doing with this drug. 7 It says: We have concluded that the 8 product labeling for all atypicals should be 9 updated to include information about these events. 10 Within a week, September 16, 2003, the 11 e-mails start. The notice comes on the 11th. This 12 is the 16th. 13 And Judge Couch was talking about that 14 search for the truth, you go down that road trying 15 to find the truth. You know, years ago before we 16 had computers, if you had conversations that took 17 place between corporate executives, unless somebody 18 had jotted something down on a pad or somebody got 19 an attack of conscience and admitted what they had 20 done in testimony, it was very hard to prove 21 anything. E-mail has changed all of that. E-mail 22 creates a digital footprint that allows you to 23 track this thing, just like a bloodhound right to 24 the end until you find the truth. 25 September 16, 2003, several of these
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1 into their market. 2 And, ladies and gentlemen, it's a small 3 market. The testimony, the evidence will show in 4 this case, that the incidence of schizophrenia in 5 the population is about one percent. The incidence 6 of Bipolar I or that acute mania type of bipolar is 7 about the same. 8 So you're talking about a market 9 population of about 2 percent and you're talking 10 about only being approved between the ages of 18 11 and 65, they had to broaden the market. And that's 12 why they moved off into geriatrics, that's why they 13 moved off into children and adolescents. They 14 needed to broaden the market. That's why they gave 15 out contrary information to the label. That's why 16 they didn't give the information that should have 17 been in the label. 18 They didn't communicate the information 19 that was in the label. All of those deceptive and 20 unfair trade practices in South Carolina, and they 21 did it to try to build a market. 22 Now, let's come back up to the FDA 23 warning. September 11, 2003 -- and, again, I'm 24 going to get out of the way so you folks can 25 see -- the FDA notified them about the diabetes	1 executives get together to talk about this warning. 2 And let's look at what they say. 3 From our perspective, we looked at some 4 rough financial scenarios to put this into 5 perspective. And if you will pardon me, I will try 6 to put it into perspective. 7 First scenario: Accept the current 8 label and launch bipolar. 9 If you look at the timeline, this is 10 around the time in 2003 they're getting their new 11 indication to treat bipolar disease. So that's 12 what they're talking about. And it says, if we do 13 that, a 55 to \$100 million dollar downside. So if 14 they take the FDA's required label, just as it is, 15 it can cost them as much as \$100 million. 16 Scenario two, submit further data to 17 the agency, strive for revised wording. But the 18 agency fails to accept, it delays bipolar approval. 19 That's another 5 to 7 million dollars it will cost 20 them. 21 Next scenario, submit further data to 22 the agency, meet in December for review. FDA 23 accepts revisions, low risk for Risperdal. We get 24 precaution versus a warning for others, other 25 competitors get class label. Upside, \$100 million

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1 in incremental sales. 2 What that shows you, ladies and 3 gentlemen, is how valuable it was to put that 4 deceptive information in that letter. If they 5 could get a precaution as opposed to a warning, if 6 they could get a lesser advisory, if they could go 7 out and market themselves as being a lesser risk 8 than all of the others, it was worth \$100 million 9 to them, by their estimates. 10 In fact, if you put this together, 11 between following the rules and accepting the FDA 12 label, or doing an end run and saying that you're 13 not as bad as the others, whether the label says 14 that or not, it's a \$200 million swing. That's a 15 pretty good financial reason for what comes next. 16 First thing they do is they start 17 negotiating with the FDA to see if they can get the 18 FDA to change the label. They want them to take 19 out this language about ketoacidosis, coma and 20 death. The evidence is going to show the FDA 21 didn't go along with it. The FDA said, the 22 language stays in, that's what's in the label. So 23 they just took it out of their letter; they didn't 24 mention it. 25 They tried to get the FDA to take out	1 They also decided that they would 2 leverage personal relationships to try to do a 3 little back channel negotiating with the FDA. The 4 evidence is going to show Dr. Rusty Katz is the FDA 5 enforcement person, the doctor who sent out the 6 letter in September advising of the class label and 7 saying that you've got to put this warning on your 8 drug. 9 Trish DeSantis is their global 10 regulatory leader. Now, the reason they want 11 Ms. DeSantis to leverage her personal relationship 12 is because the evidence is going to show that 13 Ms. DeSantis worked at the FDA from 1987 to 2000 14 before she went to work for Janssen. 15 This is the kind of revolving door that 16 we hear about in government too often where people 17 serve in congress and then they become lobbyists. 18 Well, here, the regulator becomes the regulated and 19 she becomes the back door. 20 Next. Same time this is going on, 21 after they've gotten notice of this warning and 22 this change in the class labeling, they have a 23 field training manual for their sales force. And 24 in it, they tell them to highlight low rate of 25 diabetes and low weight gain.
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1 this sentence: However, epidemiological studies 2 suggest an increased risk of treatment-emergent 3 hyperglycemia-related adverse events in patients 4 treated with atypicals studied. Precise risk 5 estimates for hyperglycemia-related adverse events 6 in patients with atypical antipsychotics are not 7 available. They tried to get that sentence taken 8 out. Didn't get taken out. 9 But they indicated that in the letter. 10 Now, the last sentence down here about the 11 available data are insufficient to provide reliable 12 estimates of differences in hyperglycemia-related 13 adverse event risk among the marketed atypical 14 antipsychotics. 15 That one, eventually they did get the 16 FDA to take out. And they thought, because of 17 that, they had a loophole, they could drive the 18 truck through. 19 Down at the bottom, they tried to get 20 the FDA to take out the language about needing to 21 start blood glucose monitoring at the same time you 22 start treatment with their drug. 23 Again, the FDA didn't agree to take 24 that out and, again, they conveniently failed to 25 mention that in the letter to doctors.	1 The evidence is going to show that they 2 were instructing their salespeople to go out and 3 tout their lower side effects than the others, even 4 though the FDA had told them in the warning in the 5 approved label language, you can't say you're 6 better than the others. 7 The next thing they did was Dr. Scott 8 Reines -- and you will see several e-mails from 9 Dr. Reines -- Dr. Reines, if I recall 10 correctly -- and, again, he's on our chart over 11 here -- Dr. Reines is the president of Johnson & 12 Johnson Pharmaceutical Research and Development. 13 He's on the corporate governance side on that 14 particular chart. 15 Dr. Reines says: Lilly's DDL is pretty 16 clever. 17 This same time this warning is coming 18 out, Eli Lilly was looking at maybe sending one of 19 these letters out about Zyprexa. They had gotten a 20 copy of it or gotten wind of it, they thought it 21 was pretty clever. 22 So Dr. Reines asked: How much 23 commercial liability would we incur if we sent a 24 similar letter about Risperdal, assuming the FDA is 25 unwilling to communicate the issue.

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1 In other words, if we can't get the FDA 2 to agree with us that we're better than the others, 3 how much commercial liability would we incur if we 4 went ahead and sent a letter anyway? 5 Then, the decision is made to send the 6 letter. And, ladies and gentlemen, I've been up 7 here long enough, and I'm not going to show you all 8 of the iterations of this; but suffice it to say, 9 the evidence is going to show that before that 10 letter went out dated November 10, 2003 with 11 Dr. Mahmoud's name on it, they went through several 12 iterations of that letter parsing the language and 13 pushing the envelope to decide exactly how far they 14 could go and how far they would take it in being 15 deceptive and omitting information. 16 Here is what they did: They find out 17 that the FDA wants them to put a warning on their 18 label and wants them to acknowledge that they have 19 a serious public health concern related to this 20 drug and its impact on causing or worsening 21 diabetes, and their reactions are to attempt to 22 alter the label, craft various Dear Doctor letters 23 with false and misleading claims, speculate about 24 how much commercial liability they would incur, and 25 instruct their sales reps to go ahead and advise	1 up with, they have made up. 2 Again, ladies and gentlemen, that's the 3 evidence of willfulness, that's the evidence of 4 deception, that's the evidence of omission of 5 material information. 6 This next e-mail here shows how they 7 got caught. Sent these letters out to the doctor, 8 didn't give the letter to the FDA. So how did the 9 FDA catch them? 10 About two weeks after they sent the 11 letter out to the doctors, the evidence is going to 12 show that the FDA came back around and said, you 13 know what, we think this is such important 14 information, we think you ought to do a Dear Doctor 15 letter, we think you ought to send one out to all 16 of the doctors to let them know about what 17 happened. 18 And now Janssen, redfaced, has to 19 acknowledge to the FDA, we've already sent one out. 20 And we meant to send it to you, but we'll send it 21 to you now. 22 And, in fact, I fully expect the 23 Defense to get up and make some -- some defense 24 about that they sent it to the scientific 25 department but not to the DDMAC Department, or
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1 doctors of their low risk of diabetes anyway. 2 You'll get to see -- and, in fact, 3 because I know sometimes it's hard to see that 4 screen, you will actually have a board here that 5 will show you the actual warning in the label that 6 was approved by the FDA and a comparison with what 7 they put in their letter. 8 And you will see that the FDA talked 9 about coma and death in patients, including those 10 treated with Risperdal. They don't say anything 11 about that in their letter. They talk about 12 hyperglycemia-related adverse events -- well, that 13 could be just an increase in blood sugar -- have 14 infrequently been reported. That's not what the 15 FDA says. 16 And then up here, it says that 17 epidemiological studies suggest an increased risk 18 of treatment-emergent hyperglycemia-related adverse 19 events in patients treated with the atypical 20 antipsychotics. 21 Down here, they talk about: A body of 22 evidence suggests that Risperdal was not associated 23 with an increase in the risk of diabetes. 24 Of course, they don't tell the doctor 25 that the evidence is evidence that they have come	1 whatever. I would submit to you, this e-mail right 2 here pretty much answers that question. 3 He says: Surprise request from the FDA 4 for DDL on diabetes labeling. We have corresponded 5 back to the FDA informing them of what 6 communications we have already had with physicians 7 regarding this label change. 8 If they sent it in about the same time 9 they sent it out, I would submit to you, he 10 wouldn't be saying that after they got this 11 surprise request, they corresponded back to them 12 about what they sent out. I would submit to you 13 that he would be telling them, well, just look at 14 that letter we sent you. That's what we sent out. 15 But this is how they got caught. 16 Now, after they got caught, we have 17 some more of these digital footprints. And I'm 18 going to run through these just really quickly for 19 you to kind of give you a flavor, a preview of what 20 you're going to hear about in the evidence. This 21 is also what happens at corporations once they have 22 taken liberties like this. 23 Down at the bottom, Dr. Reines, now he 24 wants to know, well, who cleared this letter, did 25 PRD have any sign-off.

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1 Mr. Grebb, the author of the one we 2 just saw about the surprise DDL notice from the 3 FDA, he answers back, well, it would have been 4 approved by this leader or that leader. 5 Mr. Reines: Do you think that's 6 sufficient? I'm troubled by the liberties they've 7 taken. 8 I fully expect the defense in this case 9 to be, we were right, the FDA was wrong, what we 0 put in that letter was true. 1 Ladies and gentlemen, that's what they 2 say now after the attorney general of The State of 3 South Carolina has called them to account. 4 I submit that when you look at the 5 evidence, look at it in context. Don't look at 6 what they say now that they know that their company 7 is being prosecuted by the State of South Carolina. 8 Look at what they said back at the time it happened 9 in the safety of their own little internet world 0 where they didn't think anybody was watching. 1 And he says: I'm troubled by the 2 liberties they have taken. 3 You use your good common sense and 4 judgment as to what you think that means. You're 5 going to hear from Dr. Reines in his video	1 warning letter comes out in April. 2 Dr. Reines talks about -- or excuse 3 me -- Mr. Grossman writes Dr. Reines and says: I 4 believe the FDA will not reverse their class 5 labeling without very compelling data, which we do 6 not have. 7 I expect that one of the defenses 8 you'll hear in this case is that the data bears us 9 out, we were right all along. I would submit 0 again, at the time it happened, their people said 1 they didn't have the data. 2 Up here at the top, Dr. Reines writes 3 back: Thanks for the update, Fred. Risk diabetes 4 is another example of agreeing with the FDA and 5 then trying to back out, which is going to hurt us, 6 agreeing to accept the label but then sending these 7 communications out all over the United 8 States -- and, in our case, specifically to South 9 Carolina -- that are contrary to the label, backing 0 out, going around the back door. 1 This next one, this one, like I said, 2 is exactly what happens with corporations, because 3 now the blame game sets in. 4 Down here at the bottom, we will look 5 at this one first. Dr. Reines is talking about
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1 deposition. But I think it's pretty clear that he 2 thinks they put some things in that letter they 3 shouldn't have: To me, it seems like off-label 4 promotion of differences among the atypical agents. 5 You're going to hear this term off 6 label come up. All that means is, that the FDA 7 approves this label and that's all you're approved 8 to promote from. 9 Doctors are perfectly free to prescribe 0 medications for people in disease states that are 1 beyond the approval. Doctors can prescribe off 2 label, because doctors have the clinical knowledge, 3 the education, the experience, to make a decision 4 about whether or not they want to try a particular 5 drug, understanding all of the risks and benefits 6 that it might have for their patient. 7 What is not allowed, what is against 8 the rules, what is against the law, is for a drug 9 company to have its sales force promoting things 0 for uses that are off the label. They can't go out 1 and sell that way. 2 That's exactly what they were doing 3 here. The next one, in January, after the FDA has 4 the November letter, and the FDA is considering 5 what they're going to do about it before the	1 that after JPI wrote such a flagrant letter about 2 Risperdal, the whole management team got 3 canned [sic] -- almost got canned. 4 He's talking about -- the evidence will 5 show he's talking about this November, 2003 letter. 6 Up here at the top: The warning letter 7 is ugly. As soon as I saw the JPI letter last 8 November, I called Gary and asked how it could have 9 gone out, but it was too late. No competent person 0 would have let it go out. It's really a black mark 1 for Johnson & Johnson. 2 The Defense may come in and try to tell 3 you in this trial, we didn't make a mistake, we 4 were right, the FDA was wrong, we didn't do 5 anything wrong. 6 Ladies and gentlemen, I would submit to 7 you, you know an admission when you see it, and you 8 will see the evidence as it's presented. 9 Now, as much as these e-mails show what 0 they were doing, when DDMAC came along and issued 1 that warning letter in April, and ordered 2 corrective action, I think it's instructive what 3 Janssen did. 4 They could have appealed it. They 5 could have contested it. They could have gone to

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1 court about it. They could have asked for some 2 other type of sanction. But what did they do? 3 They sent it out, just like the FDA 4 told them. They sent out over 9,000 of these 5 letters in South Carolina, I believe, based on the 6 figures they gave us in discovery, to South 7 Carolina doctors on July 21st, 2004, after fooling 8 around for a couple of months and whining with the 9 FDA, they finally accept the language that the FDA 10 says they have to say. And the FDA tells them and 11 they say to the doctors, that they conclude that 12 they disseminated a letter that omitted material 13 information, minimized risk, and made misleading 14 claims. 15 Those letters that they're 16 acknowledging omitted things, misled, contained 17 false information, those letters are the same 18 letters that went to South Carolina doctors. And 19 that's why we're here. 20 Let's go ahead. You'll see the letters 21 themselves when they come into evidence. You can 22 read them for yourselves. And the letters clearly 23 show an acknowledgment that they did wrongdoing. 24 And in fact, it's interesting, Dr. Mahmoud, the 25 same person that wrote the November letter, signed	1 about what they did. Those e-mails, those digital 2 footprints will show you that. 3 There was a significant public impact, 4 I showed you the language that the FDA cited in the 5 warning letter. Let me tell you what the real 6 public impact is in this case. 7 The real public impact is that they 8 were selling this stuff to be given to the most 9 vulnerable people in the State of South Carolina. 10 Children. Adolescents. Geriatrics. Elderly 11 people with dementia. People who have severe 12 mental illness who weren't competent to make 13 decisions for themselves. They were doing it 14 because they had to have an expanded marketplace 15 and reach their 33 billion dollar goal. 16 And they were doing it because if the 17 label stood, if the warning stood on diabetes, or 18 if they got a warning on prolactinemia, or they got 19 a warning on vascular issues in the elderly -- 20 which, by the way they did, and you will see 21 evidence that shows how they balked at that 22 warning. And you will also see evidence where they 23 say in an internal memo about how bad the warning 24 hurt them. 25 And they're talking about doing a Dear
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1 this one as well. 2 Now, ladies and gentlemen, once they 3 sent out this correction letter, they were called 4 and they finally submitted on the diabetes label. 5 Prolactinemia, some of this other stuff, went on in 6 2007. 7 The label and the letter. The label 8 was misleading because they didn't put all of the 9 information in it that they had a duty to report to 10 the FDA and see that it is put in there. They 11 didn't convey the information to the doctors when 12 their sales reps are delivering the labels. The 13 letter pretty much speaks for itself and I think 14 we've done enough about that. 15 Now, with respect to this case, that 16 brings us back to why we're here now. The Attorney 17 General brought this case because we believe the 18 evidence will show to you clearly that this 19 company, through its communications with doctors 20 and patients, with the public of South Carolina, 21 that it's put out deceptive and unfair promotional 22 materials. This letter, these labels. 23 That's the case before you. That's all 24 this case is about. 25 Janssen was willful and intentional	1 Doctor letter. They say never underestimate the 2 impact of a Dear Doctor letter, because they know 3 how the system works. 4 Now, very briefly, let me address a 5 couple of things about this and then I'm going to 6 sit down. 7 I told you what I thought they would 8 say about we were right, the FDA was wrong, and 9 that no doctors got deceived, so no harm, no foul. 10 And I told you about how none of that matters, 11 because this isn't about the FDA. This is about 12 the people of South Carolina. Doesn't matter if 13 any doctors were deceived, because it doesn't 14 matter what a doctor believed or didn't believe, 15 doesn't matter what a doctor read or didn't read. 16 What matters is what they did, what they published 17 in South Carolina. 18 You're also going to hear from them and 19 you're going to hear testimony about this and see 20 evidence about this, that South Carolina should 21 have been taking care of their own situation. 22 South Carolina should have been monitoring this 23 stuff if South Carolina is bothered so much by 24 Risperdal. 25 In the first place, Risperdal is a good

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1 drug for what it's meant to be used for and nobody 2 disputes that. And in the second place, that 3 revolving door works on this end, too. 4 In South Carolina, you're going to hear 5 about something called the budget proviso. And all 6 that is, is that is a thing that is put in the 7 South Carolina budget every year for the last 8 several years as a result of lobbying efforts by 9 these Defendants and other companies like them that 10 says South Carolina cannot regulate mental health 11 drugs. 12 Antipsychotic medication like this is 13 off the table when it comes to any of the type of 14 pharmacy review things that -- processes that the 15 State has. 16 You'll see evidence about something 17 called the DUR, the Drug Utilization Review for 18 Medicaid. They can't make anybody not prescribe 19 these drugs. They can't make anybody substitute 20 something else for one of these drugs. They can't 21 stop anybody from using Risperdal. 22 And you will hear that testimony from 23 the people who worked in that area. You're going 24 to see that -- and I'm sure they will point 25 out -- that in 1999, I believe it was, that the	1 were actually deceived. 2 What it is about is about the bad 3 behavior of Janssen. It is about Janssen's 4 misrepresentations and false claims. It is about 5 Janssen breaking the law and not playing by the 6 rules. And it is about Janssen's putting profits 7 over safety. 8 At the beginning of the case, I told 9 you that this case would be more bound to the 10 witnesses telling the truth, the whole truth, and 11 nothing but the truth. You know, I think for most 12 of us, when we're only exposed to that in a crime 13 drama or a TV series, it kind of goes in one ear 14 and out the other. 15 The truth, the whole truth and nothing 16 but the truth. It's not redundant or repeating the 17 same thing three times. It's important to tell the 18 truth. It's important to be accurate, but it's 19 also important to tell the whole truth because 20 every one of us here today knows that a half truth 21 is just another name for a lie. 22 The whole truth, nothing but the truth. 23 Nothing but the truth is what the physicians, the 24 patients, the public in South Carolina deserve to 25 know about this drug or any other drug that is sold
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1 Department of Mental Health in South Carolina sent 2 out a clinical advisory about the diabetes issue, 3 because that's how it all came about. Since they 4 didn't turn over what they knew, independent 5 research and these adverse events being reported by 6 doctors, all of this kind of came to a critical 7 mass around 2000, 2001, 2002, 2003. And that's why 8 the FDA had had enough and they issued the warning. 9 DMH sent out a clinical guidance, no 10 question, no question about that. But this isn't a 11 case about what DMH knew. This isn't a case about 12 what Medicaid knew. This is a case about what they 13 knew and what they did. 14 And they're going to try to distract 15 you, to divert your attention, to do everything 16 they can to avoid talking about what the case is 17 about, because when it comes down to it, it's real 18 simple. Did they do wrong. 19 Ladies and gentlemen, when it comes 20 down to it, this case is not about whether or not 21 Risperdal is a good or bad drug. It's not about 22 how many people Risperdal has helped, it's not 23 about how many people have been harmed by Risperdal 24 or have gotten diabetes while they were on the 25 drug, and it's not about whether or not any doctors	1 within our borders. 2 Folks, today the Attorney General 3 brings this case because those children, those 4 mentally ill adults, those elderly people with 5 dementia, they don't have anybody to speak for 6 them. That's why the Attorney General is charged 7 with the following the law and enforcing the law of 8 South Carolina. That's why we're here. Nobody 9 speaks for them if he doesn't. 10 At the end of this case, we're going to 11 ask you to return a verdict, not any money, not 12 going to ask you to tell us one dime that they 13 ought to have to pay. That's something that will 14 be up to His Honor, Judge Couch, to determine. 15 All we're going to ask you to do is to 16 bring back a verdict that says, if you're going to 17 do business in South Carolina, if you're going to 18 get some of that 3 billion dollars in sales of 19 Risperdal in South Carolina, you're going to play 20 by the rules. You're going to do it fairly, and 21 honestly, you're not going to omit anything, you're 22 going to tell the doctors everything they need to 23 know, the good, the bad and the ugly. 24 And at the end of the day, when we get 25 through with this case, we're going to ask you to

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1 render a verdict that speaks the truth and speaks 2 the truth to the people of South Carolina. Thank 3 you. 4 THE COURT: Ladies and gentlemen, we've 5 been going for a little over an hour, hour and a 6 half, but I told you we would take breaks from time 7 to time. This is one of our first breaks. And I 8 will instruct you, as I always will when you leave 9 the courtroom, not to begin any discussions 10 concerning this case, not even among yourselves, 11 until such time as I advise you to begin your 12 deliberations. 13 We'll take a short break, you can 14 retire to the jury room. The bailiffs will take 15 care of any needs you have. Thank you very much. 16 Remain seated while the jury retires, 17 please. 18 (The jury exits the courtroom.) 19 THE COURT: Court is in recess for 20 about 10 to 15 minutes. Thank you very much. 21 (A brief recess was held.) 22 THE COURT: Is the State ready to 23 proceed? 24 MR. COGGINS: Yes, sir, Your Honor. 25 THE COURT: Defense ready to proceed?	1 Now, I briefly introduced myself 2 yesterday. My name is Steve Pugh. I'm a lawyer 3 from Columbia. And along with Tom Campion and Ken 4 Murphy and Ed Posner, we represent the Defendants 5 in this case, Johnson & Johnson, the pharmaceutical 6 company that the Plaintiff's counsel talked to you 7 about called Janssen. And we have here in the 8 courtroom with us a Janssen scientist, Dr. Ivo 9 Caers. 10 Dr. Caers was the Risperdal group 11 product leader. Dr. Caers and his team of 12 scientists were responsible for the scientific 13 aspects in the development of Risperdal. 14 You heard briefly about mental illness 15 and particularly schizophrenia. Make no mistake, 16 schizophrenia is a horrible, incurable disease. 17 To the person afflicted with that 18 disease, it's devastating. To the families, to the 19 communities, and for -- it's as old as time -- for 20 thousands of years there was nothing we could offer 21 these folks. No remedy, no treatment. In fact, 22 for years and years, even in this country, they 23 were locked away, shuttered from society. 24 As the State's counsel talked to you 25 about, in fact, we have all heard probably
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1 MR. PUGH: Yes, sir. 2 THE COURT: Call the jury in. 3 (The jury enters the courtroom.) 4 THE COURT: All right. The record will 5 reflect the jury has returned to the courtroom. 6 As I watched you come back in, I 7 noticed you were searching for particular seats. 8 Don't be concerned about that. We have unlimited 9 seating or unassigned seating in the jury box, 10 except for the alternates. They always will sit on 11 this side. So perhaps they should come in last. 12 But other than that, you can sit anywhere in the 13 jury box, no preference, until I appoint a 14 foreperson. And then there will be that seat for 15 the foreperson. 16 Now, we have completed the opening 17 statement or argument by the Plaintiff. And at 18 this time, the defense is allowed to make its 19 opening statement or argument. You may proceed. 20 Mr. Pugh. 21 MR. PUGH: May it please the Court. 22 THE COURT: Yes, sir. 23 MR. PUGH: Counsel, ladies and 24 gentlemen. One thing I want you to take away is 25 this: The truth is the truth. Period.	1 off-color, jokingly in our lives, you're acting 2 crazy, they're going to send you down to Bull 3 Street if you don't straighten out, we've all heard 4 that here in South Carolina. 5 In the 1960s, some drugs came along 6 known as first-generation antipsychotics, had such 7 names as Thorazine or Haldol, as you heard 8 mentioned. Those medicines are also known as 9 typical antipsychotics. 10 And while they provided some benefit to 11 folks, they had some severe side effects. For 12 example, sedation; folks would just sit in the 13 corner sedated. Something called extrapyramidal 14 symptoms, which is a twitching, shaking, or 15 something even worse called tardive dyskinesia, 16 which are involuntary movements of the limbs of 17 your body in a repetitive manner. 18 You see, ladies and gentlemen, the 19 government doesn't invent medicine. It's left to 20 companies to do that and bring that medicine to 21 market and hopefully help people. 22 Now, after years and years of research, 23 Risperdal was brought to the market in 1994. As 24 the State's attorney told you, it's a member of a 25 group of drugs or a class of drugs known as

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EXHIBIT B

FILED
JUN 10 1964
ST. LOUIS COUNTY
JUN 10 1964
H. ROSE BLANCHET

STATE OF SOUTH CAROLINA

COURT OF COMMON PLEAS

COUNTY OF SPARTANBURG

SEVENTH CIRCUIT

STATE OF SOUTH CAROLINA

Ex rel. Henry McMaster, in his
Capacity as Attorney General of the
State of South Carolina,

Plaintiffs,

vs.

CASE NO. 2007-CP-42-1438

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS,
INC., f/k/a JANSSEN PHARMACEUTICA, INC.,
JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.,

Defendants.

VOLUME V (Pages 972 - 1188)

TRIAL BEFORE: THE HONORABLE
ROGER L. COUCH

DATE: March 11, 2011

TIME: 8:39 a.m.

LOCATION: Spartanburg County Courthouse
180 Magnolia Street
Spartanburg, SC

REPORTED BY: Susan M. Valsecchi, RPR, CRR
Certified Realtime Reporter

A. WILLIAM ROBERTS, JR., & ASSOCIATES

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1 aid and how you don't know whether those initial 2 sales aids were actually used or not. 3 Do you recall looking at a document 4 yesterday, the first ever sales training manual, 5 discussing those exact claims that the FDA said 6 were misleading? 7 A. Yes, there is certainly documents that 8 I have seen and reviewed that the messages of those 9 original aids -- those original sales aids 10 are -- were used in the training aids and the 11 different things that were given to sales reps and 12 told them about the drugs, yes. 13 Q. Now, he also asked you several 14 questions about 113, about patients may be 15 switching drugs in the extension phase of the 16 trial, maybe not. 17 Do you remember that? 18 A. Yes. 19 Q. Are you aware or in your research did 20 you -- or in your review of the company documents, 21 did you discover that Janssen did the analysis with 22 the patients who may have switched and without? 23 A. Yes, they did. And it didn't make a 24 difference whether or not it was analyzed with or 25 without.	1 related to promotional material for Risperdal? 2 A. Certainly the original -- the 3 original -- well, it wasn't a warning letter. 4 There was an original letter from DDMAC back when 5 the launch materials were sent out, if that's what 6 you're asking me. 7 Q. Mr. Murphy also asked you about 8 business plans and sales aids discussing off-label 9 promotion, right? 10 A. Yes. 11 Q. Okay. Specifically in the elderly, 12 right? 13 A. Yes. 14 Q. And questions were: Are you aware of 15 whether any of this off-label promotional material 16 actually went out to people, right? 17 A. Yes, I think -- I don't know if that 18 was his exact question, but we talked about that, 19 yes. 20 Q. And you said you weren't, right? 21 A. Yes, that's correct. 22 MR. TRAMMELL: Permission to approach, 23 Your Honor? 24 THE COURT: You may. 25 MR. MURPHY: Your Honor, can we
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1 Q. And when Janssen told the FDA that 2 Study 113 didn't exist, they didn't say, we've got 3 a study that you're looking for, but we're kind of 4 concerned about switching patients, so we will send 5 you the data with and without. Right? 6 A. No, they did not do that. 7 Q. Just told them it didn't exist, right? 8 A. Yes. 9 Q. Doctor, do you recall being asked a 10 question about this document? 11 A. Yeah. 12 Q. FYI, Ortho had no warning letters in 13 the past and Janssen had several, including these? 14 A. Yes. 15 Q. And Mr. Murphy asked you questions 16 about whether you were aware of any other warning 17 letters related to Risperdal, right? 18 A. Yes. 19 Q. And you said you weren't, right? 20 A. Well, I thought we were talking about 21 warning letters related to promotional materials 22 specifically, but, yes. 23 Q. Well, okay. 24 A. I thought that was his question, but... 25 Q. Were you aware of any DDMAC letters	1 approach? 2 THE COURT: You certainly may. 3 Mr. Trammell. 4 (Off-the-record discussion.) 5 THE COURT: Ladies and gentlemen of the 6 jury, again, I'm going to ask you to step to the 7 jury room. 8 Don't begin discussions until I tell 9 you to do so. Thank you very much. 10 (The jury exits the courtroom.) 11 THE COURT: All right, Mr. Trammell, if 12 you wish to put on the record your position with 13 regard to this information. 14 MR. TRAMMELL: Yes, Your Honor, in at 15 least a couple of times during this trial, once 16 during opening statement, and then extensively 17 yesterday, the defense counsel has opened the door 18 to the admissibility of the January the 5th, 1999 19 DDMAC letter from the FDA regarding Janssen's 20 off-label promotion of Risperdal in the geriatric 21 marketplace. 22 Yesterday during cross-examination 23 Mr. Murphy asked the witness whether she was aware 24 of off-label promotion of the geriatric variety, 25 specifically, being disseminated anywhere outside

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1 of the business plans. It created the implication 2 that these were internal discussion documents and 3 nothing that was discussed in those documents 4 actually made it out into the marketplace. 5 He also specifically asked her in the 6 same context as off-label promotion for the elderly 7 whether she was aware of Janssen ever receiving 8 another warning letter on Risperdal. I understand 9 the technical distinction he's making, but it 0 creates the implication that they have never been 1 admonished by the FDA for other marketing 2 activities or promotional activities, and that is 3 entirely untrue. 4 In order to correct the misimpression 5 that the jury has that they have never off-label 6 marketed, or that they've never been admonished by 7 DDMAC, the January 25th, 1991 letter has to come 8 in. 9 THE COURT: Tell me about that letter. 0 MR. TRAMMELL: I have a copy for the 1 court, Your Honor. May I approach? 2 THE COURT: You may, yes, sir. 3 Give me a moment to take a look. 4 It's referred to as Plaintiff's Exhibit 5 200; is that correct?	1 marketing. 2 This misimpression has to be corrected 3 for the jury, Your Honor; this is absolutely 4 admissible. They have opened the door. 5 THE COURT: Yes, sir. 6 MR. POSNER: Your Honor, there's been a 7 bit of briefing about this letter and you have seen 8 it before. 9 The letter is a letter which addresses 0 a supposed campaign that marketed Risperdal to 1 geriatric patients. It has nothing to do with the 2 claims involving the package insert or the November 3 2003 mailing. It doesn't mention diabetes. It 4 doesn't mention weight gain. It doesn't mention 5 prolactin. 6 The letter doesn't tend to show that 7 Janssen knew that it's November 2003 mailing about 8 diabetes risk was untruthful. It doesn't tend to 9 prove that Janssen knew that the package insert was 0 deceptive. It doesn't put Janssen on notice of any 1 risks. 2 What it actually says is that the risks 3 are disclosed in the package insert. That's what 4 the letter says. Okay. 5 Mr. Murphy -- on the
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1 MR. TRAMMELL: Yes, Your Honor. 2 THE COURT: All right. I have had a 3 chance to review it. 4 MR. TRAMMELL: Your Honor, to further 5 establish the record, Your Honor, on Page 893 of 6 yesterday's transcript, Mr. Murphy asked of the 7 witness: 8 Did you see any document indicating 9 that the Janssen sales representatives were going 0 and promoting off-label? 1 Answer to that question specifically, 2 she said: I haven't seen any documents, creating 3 the implication that there is no document. 4 That's exactly what the FDA said they 5 were doing. They identified sales aids, journal 6 ads, brochures, a letter, a calendar, a computer 7 program, saying that all of those things are in 8 violation of the federal regulations, they're false 9 and misleading, and they're off-label marketing 0 specifically in the context he was asking the 1 witness about. 2 The jury now has the implication that 3 they've never done it, never been in trouble with 4 the FDA except for this one time, and never acted 5 pursuant to this corporate motive of off-label	1 opening-of-the-door issue, Mr. Murphy did two 2 things. He asked Dr. Plunkett about internal 3 Janssen documents, as you will remember yesterday. 4 She acknowledged that various kinds of marketing 5 plans and sales training materials were internal 6 documents within the company. 7 And he asked her whether any of 8 those documents -- whether she had any reason to 9 believe that any of those documents, those internal 0 documents, were shown to doctors. This letter 1 doesn't refer to any of those documents. 2 The second thing he did was 3 Mr. Trammell put up a memorandum, which referred to 4 other warning letters, specifically. It was in the 5 context of that very important distinction in the 6 FDA regulations between warning letters and other 7 kinds of communications, including this. 8 This is not a warning letter. This is 9 what's called an untitled letter or sometimes a 0 notice of violation, but it is on the -- 1 Mr. Trammell put up that pyramid. It's on the very 2 lowest rung of that. It is not at all a warning 3 letter. 4 And Mr. Murphy, in responding to that 5 document that was up on the screen, very carefully

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1 limited his question to other warning letters in an 2 effort to dispel the misimpression that had been 3 left by the document. So he didn't open the door 4 and the document is not and never has been 5 relevant. 6 MR. TRAMMELL: Your Honor, further for 7 the record, I think we should be talking about the 8 exact questions that were asked. 9 On Page 894 Mr. Murphy asked: And now 0 that gets us back to the question that I first 1 asked you. Have you seen anything -- not a warning 2 letter, not an untitled letter, anything -- that 3 indicates and shows that Janssen sales reps 4 actually went out and promoted off-label pursuant 5 to a training document or a business plan that 6 you're now relying on. 7 The business plan is talking about 8 geriatric marketing. He said anything. Not 9 warning letters, Your Honor. 0 She wasn't able to answer that question 1 because it's not in evidence. For no other reason 2 than fairness, this letter has to come in. 3 THE COURT: This trial is also becoming 4 a trial, I think, concerning corporate reputation, 5 corporate intentions, things of that nature, which	1 (The jury enters the courtroom.) 2 THE COURT: All right, the record will 3 reflect that the jury has returned to the 4 courtroom. 5 I have overruled the objection. You 6 may proceed. 7 MR. TRAMMELL: Thank you, Your Honor. 8 Um, permission to approach briefly, 9 Your Honor? 0 THE COURT: You may. 1 BY MR. TRAMMELL: 2 Q. Doctor, I have handed you just now 3 Exhibit 1700, Exhibit 1681, Exhibit 1558, 4 Exhibit 8, Exhibit 170, Exhibit 208, 228, Exhibit 5 815, and Exhibit 571. 6 Do you have those before you, Doctor? 7 A. Yes. 8 Q. Those documents you've reviewed in 9 preparation to testify? 0 A. Let me just flip real quick again, but 1 I'm almost positive that I have seen or used all of 2 them. Yes, these are all documents that I have 3 reviewed. 4 MR. TRAMMELL: Your Honor, Plaintiffs 5 offer Exhibits 208, 228, 571, 815, 170, 8, 1558,
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1 has been -- that's the argument that the defense 2 has made. 3 And the questions that Mr. Trammell 4 refers to, in my opinion, do open it. I'll allow 5 you to go ahead. 6 MR. TRAMMELL: Thank you, Your Honor. 7 MR. POSNER: Your Honor, you will note 8 our objection. 9 THE COURT: Oh, absolutely. Your 0 objection is noted. 1 MR. POSNER: Not only on relevancy 2 grounds, but also on hearsay grounds and Rule 403 3 grounds. 4 THE COURT: The question is whether she 5 has seen it or is aware of it and whether or not 6 she has used it in formulating her opinions. We'll 7 find out about that. We haven't had a chance to 8 have her questioned about that. 9 Hearsay does not necessarily apply to 0 documents that she may have been aware of or used 1 in formulating her opinions. 2 MR. POSNER: Not necessarily, I agree 3 with that. 4 THE COURT: We'll see how that works 5 out. All right. Let's bring the jury back.	1 1681, 1700. 2 MR. MURPHY: No objection, Your Honor. 3 THE COURT: Without objection they'll 4 be received and marked into evidence. 5 (PLF. EXH. 208, a document, was 6 admitted into evidence.) 7 (PLF. EXH. 228, a document, was 8 admitted into evidence.) 9 (PLF. EXH. 571, a document, was 0 admitted into evidence.) 1 (PLF. EXH. 815, a document, was 2 admitted into evidence.) 3 (PLF. EXH. 170, a document, was 4 admitted into evidence.) 5 (PLF. EXH. 8, a document, was admitted 6 into evidence.) 7 (PLF. EXH. 1558, a document, was 8 admitted into evidence.) 9 (PLF. EXH. 1681, a document, was 0 admitted into evidence.) 1 (PLF. EXH. 1781, a document, was 2 admitted into evidence.) 3 MR. TRAMMELL: Thank you, Your Honor. 4 BY MR. TRAMMELL: 5 Q. Doctor, have you reviewed Plaintiff's

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EXHIBIT C

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July, 2009

EMPLOYMENT

Title and Company

From - To

Independent Consultant

9/08 - Present

Johnson & Johnson Pharmaceutical Research & Development, LLC
Titusville, NJ 08560

Senior Vice President and Member, Board of Directors
CNS, Pain, and Translational Medicine

12/04 - 9/08

Vice President, CNS and Pain Therapeutic Areas

7/03 - 12/04

Merck & Company, Inc., West Point, PA

Vice President, Neuroscience, Ophthalmology and
Gastroenterology, Clinical Research

11/96 - 7/03

Vice President, Neuroscience and Ophthalmology
Clinical Research

6/96 - 11/96

Executive Dir., Clinical Neuroscience/Ophthalmology

12/90 - 5/96

E.R. Squibb & Sons, Princeton, New Jersey

Vice President International Medical Affairs/
Central Nervous System Clinical Research

8/87 - 11/88

Warner-Lambert/Parke-Davis Company, Ann Arbor, Michigan

Vice President, Clinical Therapeutics

8/86 - 8/87

Merck & Company, Inc., West Point, PA

Executive Director, Clinical Neuroscience

11/88 - 12/90

Associate / Director, Clinical Research Domestic

7/79 - 8/86

Naval Research Laboratory, Washington, D.C.

Research Chemist

3/69 - 6/70

Exhibit
Reines - 1
08.25.09

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July, 2009

ACADEMIC AND OTHER EXPERIENCE

Co-Chair, Neuroscience Steering Committee 11/06 – 8/08
Foundation for NIH Biomarkers Consortium
Member, National Drug Abuse Advisory Council 9/99 - 8/04
Washington, DC

Associate Professor 10/79 - 8/86
Department of Psychiatry and Human Behavior
Jefferson Medical College
Philadelphia, Pennsylvania

Post-doctoral Research Associate 9/74 - 9/76
Developmental Biology & Cancer
Albert Einstein College of Medicine
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EDUCATION

<u>School</u>	<u>Date</u>	<u>Major/Minor/Courses</u>	<u>Degree</u>
Cornell University Ithaca, New York	1968	Chemistry	A.B. Magna cum Laude
Columbia University New York, New York	1973	Bio/Organic Chemistry	Ph.D.
Albert Einstein College of Medicine Bronx, NY	1976	Medicine	M.D.
Montefiore Hospital and Medical Center Bronx, New York	1976-1979 1978-1979		Psychiatric Residency Chief Resident

LICENSURE and BOARD CERTIFICATION

Pennsylvania State Board of Medicine #MD022925E

National Board of Psychiatry and Neurology

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July, 2009

ADDITIONAL TRAINING

<u>Source</u>	<u>Type</u>	<u>Date</u>
Cornell University Ithaca, New York	Strategic Decision Making and Critical Thinking	5/94
University of Rochester Rochester, New York	Drug Development	11/79

SOCIETY MEMBERSHIPS

National Advisory Council on Drug Abuse
American Psychiatric Association
Pennsylvania Psychiatric Association
American College of Neuropsychopharmacology
Assoc. for Research in Vision and Ophthalmology (ARVO)
Institute of Medicine Neuroforum

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JUL 15 2009
ALBANY, N.Y.

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July, 2009

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**REGULATORY
PROCEDURES MANUAL**
August 1997

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Department of Health and Human Services
U.S. Food & Drug Administration
Office of Regulatory Affairs
Office of Enforcement
Division of Compliance Policy



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INTRODUCTION

PURPOSE

The purpose of the Regulatory Procedures Manual (RPM) is to provide a convenient and organized system for statements of FDA regulatory procedures for use by FDA personnel. The statements made in the RPM are not intended to create or confer any rights, privileges, or benefits on or for any private person, but are intended merely for internal guidance.

BACKGROUND

The RPM was designed in 1958 to replace the L. S. Manual. In 1971 and again in 1995 the RPM underwent major revisions.

CURRENT

This is the second edition of the RPM published in a bound format. The purpose of the RPM remains primarily as a manual on "how to" proceed in regulatory matters, both domestic and import. Additional information on the emergency procedures, regulatory structure, name and telephone numbers of Agency contacts have been added to make the process of obtaining information easier.

CLEARANCE

The Division of Compliance Policy (HFC-230) within the Office of Enforcement has the responsibility for the RPM. The Division coordinates and obtains clearance as appropriate within the Agency.

UPDATES

The RPM content is always subject to revisions and additions. All revisions and additions will always be reflected in the electronic copy of the RPM on the Internet (www.fda.gov/ora/compliance_ref/rpm/rpm_hom.html). The Internet site will also show separate updates which can be printed for those needing to update their bound copy of the RPM. The RPM in bound format is scheduled to be republished in 1999.

DISTRIBUTION

For FDA personnel:

Copies of the RPM are provided to all FDA field and headquarters offices. Additional copies may be obtained by contacting the Division of Compliance Policy at (301) 827-0420.

For state and local government officials:

State and local government officials may obtain copies of the RPM and updates by contacting the Division of Federal-State Relations (HFC-150), 5500 Fishers Lane, Rockville, Maryland, USA 20857, telephone number (301) 443-6200.

Public:

The FDA Internet home page is www.fda.gov and the hyperlink address for the RPM is www.fda.gov/ora/compliance_ref/rpm/rpm_hom.html.

A hard copy of the RPM or any of its updates may be obtained for a fee by contacting the National Technical Information Services (NTIS), U.S. Department of Commerce, 5285 Fort Royal Road, Springfield, Virginia, USA 22161 or telephone number 703/487-4680.

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CHAPTER 4

ADVISORY ACTIONS

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SUBCHAPTER WARNING LETTERS

PURPOSE

The purpose of this chapter is to specify the agency's enforcement procedures governing the use of Warning Letters.

BACKGROUND

Various forms of letters containing warnings of violations have been used throughout the history of FDA. However, such letters were sparingly used until 1967, when District Directors were authorized to issue such correspondence. A proposed regulation was published in 1978 that would have formally defined the agency's procedures and prescribed the use of two forms of Warning Letters (Notice of Adverse Findings Letters and Regulatory Letters).

The proposal was withdrawn in 1980; however, the criteria for such letters were placed in the RPM and used by the agency until May 1991. On May 23, 1991, the agency implemented the single Warning Letter system to replace the two letter warning system. The Warning Letter system placed more authority, responsibility, and flexibility at the district level concerning enforcement strategy decisions than previous procedures.

Warning Letter - A written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal FD&C Act, or other acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation, may result in administrative and/or regulatory enforcement action without further notice.

PROCEDURES

When it is consistent with the public protection responsibilities of the agency and depending on the nature of the violation, it is FDA's practice to afford individuals and firms an opportunity to voluntarily take appropriate and prompt corrective action prior to the initiation of enforcement action. Warning Letters are issued for the purposes of achieving this voluntary compliance and establishing prior notice (see definitions in RPM Chapter 10 and the RPM section on "Prior Notice"). The use of the Warning Letter and the prior notice policy are based on the expectation that a majority of individuals and firms will voluntarily comply with the law. The agency position is that Warning Letters should only issue for violations of regulatory significance; i.e., those violations that may actually lead to enforcement

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action if not promptly and adequately corrected.

The Warning Letter was developed and initiated to correct violations of the statutes or regulations. Also available to the agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, and/or prosecution to achieve correction. Despite the significance of the violations, there are a number of circumstances which may preclude the agency from pursuing any further enforcement action following the issuance of a Warning Letter. For example, the violation may be serious enough to warrant the issuance of a Warning Letter and subsequent seizure; however, if the seizable quantity fails to meet the agency's threshold value, the agency may choose not to pursue a seizure. In this instance, the Warning Letter would appropriately document prior warning if adequate corrections are not made and enforcement action is warranted at a later time.

Responsible officials in positions of authority in regulated firms have a legal duty to implement whatever measures are necessary to ensure that their products, practices, processes, or other activities are in compliance with the law. Under the law such individuals are presumed to be fully aware of their responsibilities. Consequently, responsible individuals should not assume that they will receive a Warning Letter, or other prior notice, before FDA initiates enforcement action.

FDA is under no legal obligation to warn individuals or firms that they or their products are in violation of the law prior to taking enforcement action, except in a few specifically defined areas. When acting under the authority of the Radiation Control for Health and Safety Act (RCHSA), FDA is required by law to provide a written notification to manufacturers when the agency discovers products that fail to comply with a performance standard or that contain a radiation safety defect. Due to the legal requirements of the RCHSA, minor variations on the procedures specified below may occur.

A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action. For these reasons, the agency does not consider Warning Letters to be final agency action on which FDA can be sued.

There are instances when issuance of a Warning Letter is not appropriate, and, as previously stated, issuance of such a letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation is a repeat of a similar or substantially similar nature during which time the individual and/or firm have been notified of a similar or substantially similar violation.
2. The violation is intentional or flagrant.
3. The violation presents a reasonable possibility of injury or death.
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred, cannot be retracted; also such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters.

In certain situations, the agency may also take other actions as an alternative to, or concurrently with, the issuance of a Warning Letter. Additional instructions concerning the issuance of Warning Letters in specific product areas are located in various agency compliance programs and compliance policy guides.

AGENCY POLICY ON THE ISSUANCE OF WARNING LETTERS

Warning Letters should be issued only for violations of "regulatory significance." The threshold for determination of what constitutes "regulatory significance" is that failure to adequately and promptly achieve correction to the Warning Letter may be expected to result in enforcement action. It is recognized that despite the seriousness of the violations there are a number of circumstances which may mitigate against the Agency pursuing further regulatory action following the issuance of a Warning Letter. For example, the violation may be serious enough to warrant the Warning Letter and subsequent seizure. If, however, the seizable quantity fails to meet the Agency's threshold value, the Warning Letter would be appropriate to document prior warning if adequate corrections aren't made and subsequent enforcement action is warranted, i.e., injunction or prosecution.

WARNING LETTERS TO OTHER GOVERNMENT AGENCIES

All government establishments should be held to the same standards as non-governmental establishments. However, although the public health standards are identical, the process utilized to ensure compliance with these standards may vary. The Agency believes that government establishments will achieve and maintain a higher rate of voluntary compliance with FDA regulations compared to non-government establishments. Therefore, the most efficient use of our limited enforcement resources is

to utilize the enforcement process described below:

Prior to the issuance of a Warning Letter to any government agency, the issuing office should make a documented effort to obtain correction by discussing the violations with the responsible government officials. If this discussion with the responsible officials does not result in assurances of correction, a Warning Letter should be promptly issued to the government establishment's headquarters/office as discussed below.

If assurances of correction are provided at the meeting, a follow-up inspection should be scheduled, within a reasonable time frame consistent with the noted violations, to confirm that correction of the violations has occurred. If during the follow-up inspection, the previously reported deviations continue to exist, a Warning Letter should be issued as discussed in the following section.

FEDERAL AGENCIES

Federal agencies whose violations meet all the requirements for Warning Letters, and for which administrative sanctions (e.g. license suspensions, etc.) are available as enforcement follow-up, should be issued Warning Letters addressed to the government establishment's headquarters office.

For violative inspection of Federal agencies that meet all of the requirements for warning letters, and for which the only viable enforcement follow-up actions are seizure, injunction, or prosecution, warning letter recommendations should be referred by the appropriate Center to the Division of Compliance Policy for review and concurrence prior to issuance.

STATE AND LOCAL GOVERNMENTS

State and local governments whose violations meet all of the requirements for warning letters should be issued warning letters addressed to the government establishment's headquarters office.

ISSUANCE

The Warning Letter is the agency's principal means of notifying regulated industry of violations (prior notice) and of achieving prompt voluntary correction. Warning Letters can be issued at the discretion of the district director without center or other headquarters review or concurrence, except in specific program areas that require prior center concurrence. (See Center Concurrence.) Because the circumstances in each case will vary, and district directors may reach different decisions on the issuance of Warning Letters in similar circumstances, it is recognized that Warning Letters may not be issued with rigid consistency.

In reaching a decision to issue a Warning Letter directly, district directors should consider the following basic factors:

1. Evidence indicates that a firm, product, and/or individual is in violation of the law or regulations and that failure to adequately and promptly achieve correction may result in enforcement action.
2. The agency policy is clear concerning the violation(s) and the violation(s) are determined to be of regulatory significance.
3. There is a reasonable expectation that prompt correction will occur.
4. The nature of and the circumstances surrounding the violation(s) are appropriate to issuance of a Warning Letter.
5. The violation does not fall within the specific program areas listed in Center Concurrence.

CENTER CONCURRENCE

The following specific areas require center concurrence for the district director to issue Warning Letters, or Warning Letters are issued directly by the center.

ALL CENTERS

1. Labeling violations - except areas where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guides, Drug Health Fraud Bulletins.
2. Computer application and software violations.
3. Bioresearch monitoring program violations.
4. Product advertising violations.

Note: Warning Letters will continue to be issued directly by the centers in certain areas such as product advertising, OTC drug monographs and Bioresearch Monitoring Program.

CENTER FOR DRUG EVALUATION AND RESEARCH

1. New drug charges - includes unapproved changes in processes or formulations and recommendations to withhold approvals of applications or supplements.
2. Narcotic treatment program violations.
3. Adverse drug reaction reporting violations.
4. Novel and unusual temper-resistant packaging violations.
5. Prescription Drug Marketing Act violations.
6. Investigational drug use violations.
7. GMP charges involving bulk drugs.

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

1. Donor re-entry violations (e.g., HBsAg,

- anti-HIV-1).
- 2. Violations relating to drug GMPs.
- 3. Violative inspections of federal government agencies.
- 4. Viral marker test run deficiencies.* (See below)
- 5. Violations in areas where specific guidance has not been provided.* (See below).
- 6. Human tissue transplantation - the issuance of a Warning Letter to a firm following the issuance of an Order for Recall, Retention, and Destruction is not usually appropriate since enforcement action will have already been taken. If a district identifies circumstances in which a Warning Letter seems to be appropriate, the recommendation should be submitted to CBER for review.

*Viral marker testing violations: The districts no longer need Center concurrence regarding viral marker testing violations. However, Center concurrence is required for Warning Letters based on invalidation of viral marker test run deficiencies since Center guidance on this issue is relatively recent.

*Violations in areas where specific guidance has not been provided: The Center would not be in a strong position to issue a Warning Letter when there is no policy or agency policy on an issue that is not clear. Therefore, before recommending a Warning Letter to the Center, we encourage the district to contact the policy team within CBER's Office of Compliance to discuss issues where specific guidance has not been provided. Contact: CSO Steve Ripley, HFM-635, (301)594-3074.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

1. All 502(d) danger to health violations.
2. Medical device reporting violations which cite either failure to report unanticipated (temporary) serious injuries as defined in 803.3(h)(3)(ii) or malfunctions as defined in 803.3(c). Center medical/technical expertise is necessary to make these evaluations.
3. Restricted device violations.
4. Radiation Control for Health and Safety Act violations - except sunlamp products and x-ray assemblies.
5. Violation of requirements for post market surveillance studies.
6. Any violation of device tracking regulation requirements other than failure of the firm to implement any form of a tracking system.
7. All suspected violations of the user reporting regulations.
8. Failure to submit a 510(k)/PMA supplement for

modifications of a previously cleared device.

CENTER FOR VETERINARY MEDICINE

1. Product approval violations.
2. Tissue residue violations where no tolerance has been established, and/or which involve the use of compounded products.
3. Feed contaminant violations where no tolerance has been established.
4. Adverse drug reaction reporting violations.
5. Low acid canned pet food violations requiring technical review.

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

1. Pesticide and chemical contamination violations where no action level or tolerance has been established.
2. Special dietary food violations - includes medical foods, infant formula, and vitamin/mineral supplements.
3. Low acid canned food violations requiring technical review.
4. Food and color additive violations where no specific guidance has been provided.
5. Nutrition violations.

MULTIPLE CENTER REVIEW

When the districts are aware that the issues in a warning letter will require multiple center review, the warning letter recommendation should be submitted to each Center involved. However, when the district is unaware that the issues involve more than one Center, then the centers will review the warning letter serially. Each center's 15 working day review time limit will begin at the time the submission is received at that Center.

TIME FRAMES

Within fifteen (15) working days after completion of the inspection, or, if applicable, sample analysis, district should issue a Warning Letter directly or submit a Warning Letter recommendation to the center for concurrence.

Within fifteen (15) working days after receipt of the Warning Letter recommendation, the center should review and approve the issuance of a Warning Letter and notify the district office of its decision. If the warning letter is to be disapproved, the center will so notify the district office of its decision within 15 days of receipt, and will issue a memorandum stating its reasons within 30 days or as soon thereafter as possible.

FOLLOW-UP

The issuing district or center will evaluate the response and determine its adequacy. If the response is inadequate, or if no response is received, the district/center will initiate follow-up action as necessary to achieve correction. If the response appears adequate, the district/center will verify that the commitments have been fulfilled and that correction has been achieved, and will notify other appropriate agency units.

PROFILE UPDATE

The District or Center must promptly update the firm profile system when a drug or medical device Warning Letter is issued. The profile system is also to be updated again when it is determined that correction has been achieved, or when further enforcement action is recommended or taken. In the case of Warning Letters issued under Bioresearch Monitoring Program, corrective actions may not be verified until the next inspection as requested by the Center.

FORMAT

Warning Letters can vary in form, style, and content to provide the flexibility needed to accurately and effectively state the nature of the violation(s) encountered and the response expected of the recipient of the Warning Letter. Nevertheless, the elements listed below are common to Warning Letters:

1. Titled "WARNING LETTER."
2. Issued by the district director, division director, or higher agency official. Some program areas will require Center concurrence prior to issuance.
3. Issued to the responsible individual who, based on currently available evidence, appears to be most closely related to the violation, to that person's superior, and to the highest known official (original of letter) in the organization. Each person in the organization issued a copy is identified on the Warning Letter.
4. The dates of the inspection and a description of the violative condition, practice, and/or product in brief but sufficient detail to provide "prior notice" and permit the respondent to take corrective action. Citation of the section of the law and/or regulation violated is not required.
5. A request for correction and a written response

within a specific period of time after date of receipt of the letter, usually fifteen (15) working days. At the discretion of the district, the recipient may be offered an opportunity to discuss the content of the letter with district officials or, when appropriate, with Center officials.

6. A statement in drug and medical device Warning Letters (except warning letters issued to IRBs; clinical investigators, sponsors, and/or monitors involved in clinical trials) that: "Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts."
7. Instructions, as appropriate, that the response include (1) each step that has been or will be taken to completely correct the current violation(s) and to prevent the recurrence of similar violations; (2) the time within which correction will be completed; (3) any reason why the corrective action has not been completed within the response time; and (4) any documentation necessary to show that correction has been achieved.
8. A warning statement that failure to achieve prompt correction may result in enforcement action without further notice. Examples of such actions may be cited. It will not contain a commitment to take enforcement action (promise to sue).
9. A designated district or center official to whom the response should be addressed.
10. Delivered promptly (usually by certified mail, return receipt requested) with receipt documented.

DISTRIBUTION

Warning Letters should be distributed as follows:

1. Original - Addressee(s)
2. One redacted copy to HFI-35 for public display in accordance with FOI regulations.
3. One copy each to:
 - Each person identified on the Warning Letter
 - HFA-224
 - Division of Compliance Management and Operations (HFC-210)
 - Center Compliance unit (via special mail or fax)
 - CDER - HFD-300
 - CDER - HFM-620
 - CDRH - HFZ-300
 - CVM - HPV-236
 - CFSAN - HFS-605

DIOP - HFC-170 (Imports only)

- Appropriate district office, for all Center issued Warning Letters.
 - District offices for all establishment locations which receive either original or copy of warning letter.
 - Medical Products Quality Assurance Staff (HFC-240) (Copy HFC-120 with all drug and medical device Warning Letters regardless of whether GWQAP issues are involved).
 - Local Distribution, as required (i.e., factory file, W/L file, resident post and appropriate federal and state agencies).
4. Offices or individuals identified as blind copies (bce) on credit page (note: credit page with drafting, clearance record, and blind copies must not be sent to HFI-35).

Delivery - Warning letters should be sent to ensure overnight delivery and receipt of delivery (return receipt requested) should be documented.

Acknowledgement of Response to a Warning Letter - It is the Agency's general policy that responses received to warning letters should be acknowledged with an appropriate written response by the district or center that issued the warning letter.

Follow-up Enforcement Action - Once a firm has been issued a warning letter, provided the firm continues to operate out of compliance, districts/centers should evaluate further enforcement options. A second warning letter should not be issued for the same violation.

CLASSIFICATION

A Warning Letter constitutes official agency action and all inspections will be classified Official Action Indicated (OAI) when a Warning Letter is issued. This procedure provides greater consistency and uniformity in our classification system and our regulatory policy. Inspections should not be down classified from OAI due to failure to meet the 16 working day requirement for issuance of a Warning Letter. It is recognized that some OAI classifications should not have mandated follow-up without additional violations, such as issue residue violations.

WARNING LETTERS TO IMPORTERS AND FOREIGN FIRMS**IMPORTER WARNING LETTERS**

Warning letters for import violations may be issued at the discretion of the District Director without Center or other headquarters review or concurrence, except in certain program areas that require prior Center concurrence.

Warning letters may also be issued to importers of FDA regulated products who engage in business practices that appear designed to evade the lawful regulation of imports. The "Priority Enforcement Strategy for Problem Importers," chapter offers guidance for the proper use of warning letters, and other enforcement actions, against importers.

Generally, it is not appropriate to take enforcement action against a customs broker. The owner/consignee/importer is normally the responsible party for imported goods. However, if the broker is the owner/consignee/importer identified on the import documents, or has authority over the product through prior arrangement with the importer, it may be appropriate to issue a warning letter to the broker. Assurance must be made that the broker is responsible for the violation.

On March 6, 1992, the Director of the Division of Import Operations and Policy (DIOP, HFC-170) issued a memo that included three examples of warning letters that could be used for importer violations. Districts were also requested to send copies of all warning letters issued to importers to DIOP so that a master list can be generated. This list is maintained in Import Alert #00-17 and is updated as importer responses or new warning letters are received.

Questions regarding the issuance or use of a warning letter involving an importer, consignee, owner, or broker of imported goods should be directed to DIOP, Policy & Enforcement Branch (HFC-172) at (301) 443-6553.

IMPORT BROKERS

By statute (19 U.S.C. Section 1841), the United States Customs Service (Customs) has the responsibility for ensuring that brokers comply with the law. Customs, not FDA, has the authority to follow through on any threats of further regulatory action against violators. It is inappropriate for FDA to issue a warning letter, per se, to customhouse brokers. In those cases in which a broker fails to fulfill his statutory obligations as a broker, and FDA concludes that a warning is appropriate, the most that FDA should do is send an untitled letter to the broker informing him of the violation and warning that any future violation will be reported to Customs. However, there are some cases in which it may be appropriate to send a warning letter to a broker. Where the broker is functioning as the importer of

record and violates a provision of the FD&C Act, then a warning letter may be appropriate. In such a case, the warning letter is issued to the broker in his capacity as importer of record of the imported merchandise.

It is often difficult to distinguish between a broker performing his duties as a broker or as an importer of record. The only guidance the FD&C Act or its implementing regulations offers on the definition of owner or consignee is found in 21 CFR Section 1.83(a). That section defines an owner or consignee as "the person who has the rights of the consignee under the provisions of Sections 483, 484, and 485 of the Tariff Act of 1930, as amended (19 U.S.C. Sections 1483, 1484, and 1485)." (21 CFR Section 1.83(a)). Section 483 of the Tariff Act was repealed in 1983. Under Sections 484 and 485, a consignee's rights consist primarily of filing any documentation required to allow foreign merchandise entry into the United States. (19 U.S.C. Sections 1484, 1485).

The former Section 483 of the Tariff Act provided that the consignee of imported merchandise was the consignee declared on the bill of lading or air waybill, unless the consignee conferred its rights to other persons through endorsements on such documents. (19 U.S.C. Section 1483 (repealed 1983)). The current Section 484(a)(2)(C) provides that the documentation required to make entry of merchandise "shall be filed either by the owner or purchaser of the merchandise or, when appropriately designated by the owner, purchaser, or consignee of the merchandise, a person holding a valid license under Section 1641 of this title." (19 U.S.C. Section 1484(a)(2)(C)). While the person "appropriately designated" (i.e., a custom broker licensed under 19 U.S.C. Section 1641) is often the importer of record, Sections 484 and 485 of the Tariff Act recognize, as did the former Section 483, that neither the consignee nor the importer of record is necessarily the true owner of the imported merchandise. Thus, under Sections 484 and 485, Customs entry may be made only by the importer of record (i.e., the owner or purchaser, or a broker/designee). (Id., 19 U.S.C. Section 1485 (e)).

In most cases, the broker will not be the party responsible for causing the violation of the import provisions of the FD&C Act. While the broker files the entry documentation, he exercises little, if any, control over the merchandise itself. The owner/consignee/importer usually controls the movement of the merchandise and, therefore, bears the legal responsibility for complying with the FD&C Act.

A safe and easy approach to determining the proper addressee of a warning letter is to direct the letter to the person or entity identified on the entry

documents as the importer. Under Sections 484 and 485 of the Tariff Act, the importer of record always has the rights of the consignee. In other words, one must be an owner, consignee, or the authorized agent of either (e.g., the customs broker engaged to make entry) to be the importer of record. If there are other individuals with an interest in the merchandise but FDA is unsure of the extent of the interest, the importer of record should be able to identify those individuals and/or notify them of the violation. If FDA is aware of other persons or entities with an interest in the merchandise, the Agency should send courtesy copies of the warning letter to them as well as the broker.

FOREIGN FIRMS

With regard to foreign companies, the same principle discussed above applies. A warning letter may be appropriate if FDA maintains some kind of regulatory control over the company and is prepared to exercise that control, if necessary. Firms are placed on automatic detention because of repeatedly offering violative products for import. Unless the foreign firm is under the regulatory purview of the FDA, as declared in the applicable sections of the FD&C Act, issuing warning letters should be discussed with our Chief Counsel. For foreign manufacturers of drugs and drug products, CDER/OC issues Warning Letters based on their review and concurrence with recommendations by FDA investigators in the foreign inspection reports.

FREEDOM OF INFORMATION (FOI)

Warning letters will be on public display at the Freedom of Information Staff office.

RELEASE OF WARNING LETTERS

District and centers should use the following procedures prior to the release of a warning letter through FOI request:

1. Do not accept telephone requests for warning letters. FOI requests for warning letters should be sent to the FOI Staff (HFI-35) for response. Under exceptional circumstances the district may want to release a warning letter. In these cases the letter can be released by the district/center however, there must be assurance that the original letters have been received by the addressee and the FOI request sent to HFI-35.
2. Send a purged copy of all warning letters to (HFI-35) at the time the letter issues. Note: The Director, Freedom of Information Staff has asked that the person purging the letter place their name or initials and the date the letter was

purged for release directly on the purged copy for future reference.

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

The following are applicable CBER programs:

1. CP 7342.001 - INSPECTION OF LICENSED AND UNLICENSED BLOOD BANKS
2. CP 7342.002 - INSPECTION OF SOURCE PLASMA ESTABLISHMENTS

Part VI of both of these programs provides numerous references, contacts, and attachments applicable to these products, and Attachment B on both programs lists deviations which may warrant consideration of regulatory/administrative follow-up, e.g., warning letter.

The organizational unit in the CBER Office of Compliance which handles warning letter recommendations is the Regulatory Actions Team, HFM-810. They can be reached at (301) 594-2006.

Warning Letters

1. All correspondence to licensed establishments must be addressed to the Responsible Head with a copy sent to the highest official in the establishment. For unlicensed establishments, correspondence should be addressed to the most responsible individual, e.g., blood bank director or hospital administrator.
2. The lists of significant deviations (following) serve as guides for determining the recommended course of action. Any significant deviation, if well documented and representative of a continual pattern of operation, as opposed to an occasional deviation, may warrant the issuance of a warning letter. Additionally, warning letters may be indicated when there are deviations which may not affect the donor's health or the integrity of the product, but because they continually occur, may reflect an overall inadequately operated establishment.
3. The following specific areas require center concurrence for the District Director to issue a warning letter, otherwise, the warning letters are issued directly by the district: Donor re-entry violations; invalidation of viral marker test run deficiencies; labeling violations (except areas where specific guidance has been provided, e.g., Compliance Programs, Compliance Policy Guide (CPG), Drug/Health Fraud Bulletin); computer application and software violations; product advertising violations, and violative inspections

of federal government agencies.

In areas where a specific guidance has not been provided, we encourage the district offices to contact the policy team within CBER's Office of Compliance before recommending a Warning Letter to the Center. Please contact: Stephen Ripley, HFM-835, 301-594-3074.

Schedule a follow-up inspection approximately 30 days after the response to the warning letter is received to determine the adequacy of the reported corrective actions. When corrective action has not been effected or the firm has failed to respond, the district should consider appropriate follow-up.

4. Submit copies of all warning letters and any correspondence between the firm and the district to Division of Case Management (HFM-610).
5. Districts should routinely provide copies of Warning Letters to the appropriate state agency or agencies. If the state regulatory structure for these products is not known, contact the ORA Division of Federal-State Relations (HFC-150) at (301) 443-3360 for assistance. NOTE: The letter should be redacted appropriately to protect confidential commercial information unless the state officials are appropriately commissioned as discussed in RPM Chapters three and ten.

Violations must be evaluated to determine if they warrant administrative or regulatory action or both. To assist in this determination, Attachments A and B of CP 7342.001 are lists of significant deviations from the GMP regulations. These two lists contain deviations which are sufficiently serious that if they are allowed to continue, might jeopardize donor health or might compromise product safety or integrity. The deviations on these lists apply to both unlicensed and licensed establishments. Any deviation listed has the potential to become a health hazard, and all deviations must be corrected as quickly as possible after responsible personnel have been made aware of them.

Federal/State Relations

Currently, the Agency has no formal cooperative program with state or local jurisdictions for the inspection or regulation of blood banks. Cooperation with these authorities is, however, encouraged; especially where it is known that a state or local jurisdiction has a regulatory program. Exchange of information should occur with all levels of State government whenever feasible.

Deviations Which May Warrant Consideration of Regulatory/Administrative Follow-Up

General

- A. Changing or altering blood labels or records so as to falsify, but not constituting a danger to health or is not a current practice. [606.160]
- B. Shipment of unlicensed blood or blood products in interstate commerce for sale, barter, or exchange. [42 U.S.C. 282(a)]
- C. Inadequate or filthy facilities. [608.40; 640.4(b)]
- D. Personnel inadequately trained or supervised in the operations they perform but not to an extent that constitutes a danger to health. [608.20(b); 640.3(a); 640.4(a)]
- E. Records of the performance of any significant step in the collection, processing, compatibility testing, storage and distribution of each unit of product are significantly incomplete or inaccurate. [606.160(e)(b)(c) end (a)]
- F. A history of similar or substantially similar deficiencies about which the manufacturer has been advised.

Specific

A. Donor Suitability:

1. Specific deviations from the regulations or non-adherence to Standard Operating Procedures (SOP) Inc (1) providing donors with the AIDS educational material; (2) medical history questions to be asked of donors; (3) determining what makes a donor unacceptable for donation; and/or (4) not performing hemoglobin, blood pressure, or temperature determinations. [640.3; 606.20(b)]. Note: Autologous donations that will not be for allogeneic (homologous) use or further manufacturing may differ from donor suitability determinations applied to allogeneic donations, however, the personnel must follow the firm's SOP established for autologous donations.
2. No written procedures for determining donor suitability, including the exclusion of high-risk donors in regard to AIDS. [608.100(b)(1) and (2); 640.3(b)(c)(e)(f)]
3. Donor suitability records are incomplete or inaccurate. [606.160(a)(1) and (b)(1)]
4. No records available from which unsuitable donors may be identified so that products from such individuals will not be distributed. [606.160(e)]

B. Blood Collection:

1. Arm preparation technique is inadequate or deviates significantly from the firm's SOP. [640.4(f)]
2. Container not permanently sealed in an acceptable manner. [640.2(c)]
3. Container, pilot, and laboratory samples are

incompletely identified so as to relate them to the individual donor. [606.140(c); 606.160(c); 640.4(e) and (g)(3)]

4. Unapproved container used for collection of whole blood. [640.2(c); 640.4(c)]

C. Processing:

1. Laboratory tests for the determination of ABO, Rh, HBsAg and other viral markers not performed on laboratory samples collected from the donor at the time of filling final container, except in unusual situations. [640.5; 610.40(b)]
2. Anti-HIV and/or HBsAg test(s) not performed with an approved (licensed) test kit or as otherwise allowed in Sections 610.40 and 610.46.
3. Deviations in the performance of tests of interpretation of results according to manufacturer's directions and specifications, e.g., use of out-dated reagents; mixing reagents from different master lots; failure to run the proper number of controls concurrently with the test; failure to conduct necessary retests. [610.40; 610.45; 606.65(e)]
4. Records of test results significantly incomplete or inaccurate. [606.160(b)(2)(iii)]

Note: Refer to Compliance Program 7342.001 for a list of licensed manufacturers of HBsAg and anti-HIV test kits.

D. Storage:

1. Blood or blood components not stored at proper temperatures. [606.100(b)(10)]
2. Failure to maintain daily temperature records when blood and blood components are in storage. [606.160(b)(3)(iii)]
3. Failure to have or follow a system which would prevent the issuance of any products not suitable for use. [606.40(e)(6)]

E. Components (Red Blood Cells, Plasma, Platelets, Cryoprecipitated AHP):

1. Components prepared by a method which deviates significantly from the regulations or the firm's SOP. [640.16(b); 640.24(a); 640.30(a); 640.62(a)]
2. Records of component preparation are significantly incomplete or inaccurate. [606.160(e)(1), (b)(2)(iii), (b)(2)(iv)]

F. Compatibility Testing:

Records of test results are significantly incomplete or inaccurate. [606.160(b)(4)(ii)]

G. Adverse Reactions and Fatalities:

1. Failure to investigate adverse reactions and maintain appropriate records. [606.170(e)]
2. The Center for Biologics Evaluation and Research not advised of death(s) resulting from complications related to blood

collecting or transfusion. [606.170(b)].

H. Errors or Accidents:

Errors or accidents in the manufacture of blood and/or blood products (licensed facilities) which might affect their safety, purity, and/or potency not reported to CBER. [600.14(a)].

I. Distribution and Receipt:

Distribution and receipt procedures (system) of each unit can not be readily determined to facilitate its recall if necessary. [606.185(e)].

J. Computerization:

Contact CBER (HFM-610 or HFM-650) for guidance.

Use of Current Good Manufacturing Practice (CGMP): Regulations for Finished Pharmaceuticals for Regulatory Actions for Blood Establishments

Since the workshop concerning General Principles of Quality Assurance for Blood Establishments (January 21-22, 1982), there has been considerable discussion as to the applicability of the drug CGMPs (21 CFR Part 211) to manufacturing operations and systems within blood establishments. CBER and ORA partially addressed the issues through clarification statements contained in the recently reissued CP 7342.001 (Inspection of Licensed and Unlicensed Blood Banks) and a new section to the Investigations Operations Manual (IOM) Chapter 560 - Biologics.

The Part 211 CGMPs are applicable to blood establishments. We recognize that with the increase in complexity of blood establishment operations due to the implementation of additional testing procedures for viral markers and to automated or computerized operations, blood establishments must place more attention on process and systems controls during the manufacture of blood and blood components. As a result, CBER and ORA issued the "Draft Guideline for Quality Assurance in Blood Establishments" addressing the specific process and system control expectations for blood establishments. These process control expectations will be based on requirements contained in both 21 CFR Parts 211 and 606.

In order to provide for uniform application and enforcement regarding deficiencies from 21 CFR Part 211 CGMPs, CBER review and concurrence is required for warning letters relating to deviations from Part 211. Direct reference authority does not include citing blood establishments for deviations from Part 211 CGMPs in warning letters.

Advertising and Promotional Labeling Staff
Procedural Guide

The Advertising and Promotional Labeling Staff (APLS) may initiate regulatory action if the

advertising and promotional labeling are not consistent with the approved labeling (package insert), clinical data used to approve the product, or applicable sections of the FD&C Act and regulations for labeling and advertising by notifying the manufacturer in writing of the violations. If significant problems in the advertising or promotional labeling are discovered that could pose a potential health hazard, or if other violations persist, APLS will work with the Office of Compliance to implement appropriate compliance action as necessary.

Warning Letters to Tissue Establishments

Since enforcement action will have already been taken, it is not usually appropriate to issue a warning letter for violations involving human tissue for transplantation when an Order for Recall, Retention, and Destruction has been issued. If a district identifies circumstances in which a warning letter seems to be appropriate, the recommendation should be submitted to CBER for review.

Direct Warning Letter recommendations to the attention of:

Office of Compliance
Division of Case Management, HFM-610
Steven Mastello, Director
301-584-2008

Direct Warning Letter questions to the attention of:

Regulatory Actions Team, HFM-610
Cecily Kols Kaufman, Team Leader
301-584-2006

CENTER FOR DRUG EVALUATION AND RESEARCH

GLOSSARY OF STANDARD CHARGES

PREAPPROVAL INSPECTIONS/PENDING APPLICATIONS - WITHHOLD APPROVAL

Warning letters are not to be used by the districts as a follow-up to a preapproval inspection of pending drug or device applications (Antibiotic Form 6, ANDAs, NDAs, PMAs) if no other FDA regulated products are marketed by the firm.

Warning letters may be used by the districts for preapproval inspections of drug and device facilities when other FDA regulated products are marketed by the firm. These letters should include a disapproval statement stating "due to the deficiencies listed on the attached FDA-483 we are recommending to the Center that approval of the application(s) be withheld," and a statement that "federal agencies are advised of the issuance of all warning letters about drugs so that they may take

this information into account when considering the award of contracts."

GRANDFATHER NEW DRUG CHARGE - usually for drug which claims to have been on the market pre-1938 or pre-1982.

605(a) The articles are new drugs within the meaning of Section 201(p) of the Act and approval of an application filed under Section 605(b) is not effective for such drugs and a Notice of Claimed Investigational Exemption under Section 605(n) and Part 312 of the Code of Federal Regulations (CFR) is not on file for such drugs, and documentation in support of such drugs, and "grandfather" exemption has not been submitted per 21 CFR 314.200(a)(2) which constitutes a waiver of such claims.

BACK DOOR NEW DRUG CHARGE: When the new drug charge (605) cannot be used because of lack of interstate movement of the article to be seized but we have documented the interstate movement of a component as a 301(k) sample then we may charge that the product was misbranded while held for sale.

602(f)(1) The article of drug, (DRUG NAME), is misbranded in that its labeling fails to bear adequate directions for the use for which the article is represented or suggested (as described above), and it is not exempt from this requirement under regulation 21 CFR 201.116, since the article is a new drug within the meaning of Section 201(p) and no approval of an application filed pursuant to Section 605(b) is effective for this drug.

A 602(f)(1) charge may be used for any OTC drug if the product fails to bear adequate directions for use and the product is also a new drug.

When the product is not a new drug, the simple misbranding charge should read:

602(f)(1) "The article of drug, (Drug Name) is misbranded in that its labeling fails to bear adequate directions for use for which the article is represented or suggested."

PRESCRIPTION DRUG WHERE YOU HAVE NO LABELING BEARING DIRECTIONS FOR USES.

602(f)(1) The article(s), (DRUG NAME), is subject to the provisions of Section 603(b)(1) and it is not exempt from 602(f)(1) in that its labeling fails to bear information required

by regulation 21 CFR 201.100, providing adequate directions for use under which a practitioner licensed by law can use the drug safely and for the purposes for which it is intended, including indications; effects, dosages, routes, methods, frequency and duration of administration, relevant hazards; contraindications, side effects, and precautions.

REGISTRATION AND LISTING: The charge is misbranding under section 602(a) but the violation is failure to register and list.

602(c) The articles, (DRUG NAMES), are misbranded in that they were manufactured in an establishment not duly registered under Section 510 of the Act and the articles have not been listed as required by Section 510(j).

Prescription Drugs

Section 503(b)(1) provides criteria for determining if the article is a prescription drug. Section 603(b)(1) is not a violation charge:

603(b)(1) The article, (DRUG NAME), because of its toxicity or other potential for harmful effect, or the method of use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, and is misbranded because it is not dispensed upon prescription by a licensed practitioner.

The charge is as follows:

For prescription drug:

603(b)(4) The article of drug, (DRUG NAME), is subject to 603(b)(1) and is misbranded in that its label fails to bear the statement, "Caution: Federal law prohibits dispensing without prescription."

For an OTC drug that is not entitled to bear the Federal caution (prescription) statement. The article of drug, (Drug name), is not subject to 603(b)(1) and is misbranded in that its label bears the statement "Caution: Federal law prohibits dispensing without a prescription" and it is not entitled to bear such statement.

The above charge is applicable to articles marketed with prescription legend when in fact they are OTC drugs.

The following straight UNAPPROVED NEW DRUG charge may be used when there is interstate movement of the finished labeled drug product.

605(a) The article of drug, (DRUG NAME), is a

drug within the meaning of Section 201(g) of the Act which may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Federal Food, Drug, and Cosmetic Act, since it is a new drug within the meaning of Section 201(p) of the Act and no approval of an application filed pursuant to Section 505(b) is effective for such drug.

Notes: The Nontraditional Drug Compliance Branch (HFD-304) has distributed at least 19 Health Fraud Bulletins and District Offices should refer to them for guidance and contact points.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

For Level 1 noncompliances, the issuance of a Warning Letter for a facility inspection does not necessitate the district submitting the letter to CDRH for concurrence. Under other circumstances, where numerous Level 3 noncompliances are found, but no single noncompliance is severe enough to warrant a Warning Letter, a Warning Letter may be sent with CDH concurrence. A Warning Letter will also be sent when an uncertified facility has been found to be operating without a certificate. When Warning Letters are to be issued for any situation not specifically identified as a Level 1 noncompliance, the draft Warning Letter should be submitted to the Office of Compliance, CDH for concurrence with a recommendation memorandum. If a facility has been shown to be operating uncertified, a Warning Letter can be issued to the facility and will not require CDH concurrence. If a Warning Letter is being considered for failure to correct Level 2 noncompliances after a follow-up reinspection, a recommendation should be submitted to CDH for concurrence. (See Compliance Program 7382.014 for other case guidance.)

RECOMMENDED WORDING FOR CHARGES

Below is a listing of charges that we commonly use, which should be used by all compliance officers to achieve uniformity. Please note the change made to the Section 502(o) charge concerning removal of the order required by Section 513(f)(1)(A) for premarket notifications. OCC is of the opinion that this reference is to support a Section 501(i)(1) charge for lack of a PMA.

Adulteration Charges

Section 501(f)(1)(B) [21 U.S.C. 351(f)(1)(B)] in

that it is Class III device under Section 513(f) [21 U.S.C. 360(f)] and does not have an approved application for premarket approval in effect pursuant to Section 515(a) [21 U.S.C. 360(a)] or an approved application for an investigational device exemption under Section 520(g) [21 U.S.C. 360(g)].

Section 501(c) [21 U.S.C. 351(c)] in that its strength, purity, or quality falls below that which it purports or is represented to possess.

Section 501(h) [21 U.S.C. 351(h)] in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, CFR Part 820.

Misbranding Charges

Section 502(a) [21 U.S.C. 351(a)] in that the labeling for the device, namely (state the name of the labeling, i.e., the ABC Catalog) contains statements which represent or suggest that the device is adequate and effective (quote the misbranding statement), which representations or suggestions are false or misleading or otherwise contrary to fact because the device is not adequate or effective for such purposes.

Section 502(b) [21 U.S.C. 352(b)] in that the device is in package form and its label fails to contain (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

Section 502(f)(1) [21 U.S.C. 352(f)(1)] in that the labeling for the device fails to bear adequate directions for the purposes for which it is intended, because adequate directions cannot be written for (i.e., such purposes, etc.).

Section 502(f)(2) [21 U.S.C. 352(f)(2)] in that the labeling for the device fails to bear adequate warnings against use in those pathological conditions where its use may be dangerous to health.

Section 502(j) [21 U.S.C. 352(j)] in that the device is dangerous to health when used in the manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof. (NOTE: this charge cannot be used if the device does not have any labeling.)

Section 502(o) [21 U.S.C. 352(o)] in that the device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under Section 510 [21 U.S.C. 360], was not included in a list required by Section 510(j) [21 U.S.C. 360(j)], and a notice or other information respecting the device was not provided to the FDA as required by Section 510(k) [21 U.S.C. 360(k)].

Section 502(o) [21 U.S.C. 352(o)] MODIFICATION OF THE DEVICE - a notice or other information respecting the modification to the device was not provided to the FDA as required by 21 CFR 807.81(a)(3)(i).

Section 502(o) [21 U.S.C. 352(o)] NEW INTENDED USE OF THE DEVICE - in that a notice or other information respecting new intended use of the device was not provided to the FDA as required by 21 CFR 807.81(a)(3)(ii).

Section 502(i)(2) [21 U.S.C. 352(i)(2)] in that your firm failed to submit information to the Food and Drug Administration as required by the Medical Device Reporting (MDR) Regulation, as specified in 21 CFR Part 803.

A simplified version of a Warning Letter (Exhibit 4-12) was developed to clearly convey to small businesses the applicable violations associated with the marketing of a device in the absence of a substantially equivalent premarket notification (510(k)). This was necessary because some firms, especially small businesses, are unfamiliar with the FDA and the statutory legal jargon. By reading this letter, the recipient can more easily understand what the legal violations are and what action is necessary to resolve the problem.

For examples of model GMP/MDR Warning Letters, see Compliance Program 7382.830 - Inspection of Medical Device Manufacturers.

UNTITLED LETTERS TO X-RAY ASSEMBLERS

CDRH and ORA have decided that individual x-ray test letters to x-ray assemblers should now be issued only as untitled letters and not as warning letters. Individual x-ray test letters are a requirement of the Radiation Control for Health and Safety Act and must be issued regardless of whether the Agency is prepared to take follow-up enforcement action. Warning letters may be issued to x-ray assemblers for "pattern of violations" situations where the Agency is prepared to take enforcement action if the violations continue. If you have specific cases to discuss or need further information on this change contact the Office of Compliance, HFZ-300, 301-594-4692.

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOODBORNE BIOLOGICAL HAZARDS

CITATIONS TO VIOLATIONS UNDER FOOD ECONOMICS (Requirement and Citation(s))

Type size of mandatory information - 21 CFR 101.2(c), 101.105(i), 403(i) FD&C

101.2(c), 101.105(i), 403(i) FD&C

Statement of Identity on PDP - 21 CFR 101.3, 403(g), 403(i)(1) FD&C

Ingredient statement: common or usual name and order of predominance - 21 CFR 101.4, 403(i)(2) FD&C

Name and POB of manufacturer, packer/distributor - 21 CFR 101.5(a), 403(e)(1) FD&C

Nutrition labeling - 21 CFR 101.9, 403(e)(1) and 201(n) FD&C

English labeling - 21 CFR 101.5(c), 403(f) FD&C

Statement of presence of artificial flavors, colors, and preservatives - 21 CFR 101.22(c), 403(k) FD&C

Conformity to standard of identity standardized food - 21 CFR Applicable Standard, 403(g)(2) FD&C

Labeling of optional ingredients - 21 CFR Applicable Standard, 403(g)(2) FD&C

Product substitution - 402(b)(2) FD&C

Short weight - 403(e)(2) FD&C

Quantity of contents statement separately stated on PDP - 4(a)(2) FPLA, 21 CFR 101.105

Serving size statement - 4(a)(4) FPLA 21 CFR 101.8

Quantity of contents statement in avoid dupes pounds and ounces - 4(a)(3)(A)(i) FPLA, 21 CFR 101.105

NUTRITION LABELING AND EDUCATION ACT (NLEA) (SECTION 403 OF THE FD&C ACT)

Regulatory/Administrative Action

The Agency has stated that a firm will have made a "Good Faith Effort" to comply when its label complies with the January 6, 1993 regulations and in so doing may deviate from a requirement placed in the regulations by the August 18, 1993 technical amendments. A firm will not be required to change its label if it complies with the January 6 regulations, but deviates from the effective regulations due to changes made in the August 18 technical amendments.

All recommendations for regulatory actions except for failure to bear nutrition labeling (Criterion A below) must be submitted to CFSAN, Division of Enforcement (HFS-607) for review and concurrence prior to issuance. Include three (3) original product labels with each recommendation.

Districts should recommend issuance of warning letters to firms whose product(s) meets one or more of the following criteria:

1. non-exempt products that fail to bear nutrition labeling;
2. products bearing health claims or nutrient content claims that have not been authorized by FDA; and
3. products that fail to bear information required by NLEA that was not required previously, e.g., ingredient declaration on standardized foods, percent juice, names of certified colors.

Warning letters for these types of violations should consist of a description of the type of major violation and a disclaimer paragraph stating that there may be other violations other than those indicated in the letter. This type of warning letter should not include a description of any other violation that may be on the label.

Warning letter recommendations should be submitted for product labels with format deviations on the Nutrition Facts Panel. Label deficiencies for non-NLEA requirements should also be included in this warning letter.

Warning letter recommendations based on nutrient analysis in support of charges for violations of health claims or nutrient content claims requirements must include a copy of the collection report, three (3) original product labels, and the analytical worksheet. Warning letter recommendations should be submitted for violations of non-NLEA requirements, provided they are egregious, such as lack of an ingredient listing or significantly misleading product name.

STANDARD LANGUAGE FOR WARNING LETTERS FOR NLEA VIOLATIONS

Incorporate one or more of the following five paragraphs as appropriate. This is agreed upon language for issuing abbreviated warning letters:

1. This product is considered to be misbranded in that it fails to bear nutrition labeling as required by 21 U.S.C. 343(q)(1) and 21 CFR §101.9 and is not exempt under 21 U.S.C. 343(q)(5) from this requirement and has been labeled on or after May 8, 1994.
2. This product is misbranded under 21 U.S.C. 343(q)(1)(B) (or (A) in the case of nutrient content claims) in that it bears the health claim (nutrient content claim) "____" which has not been authorized by FDA. See 21 CFR §101.14 and Subpart E of Part 101 for authorized health claims; and 21 CFR §101.13 and Subpart D of Part 101 for authorized nutrient content claims.
3. This product is misbranded under 21 U.S.C.

343(i) in that it is fabricated from two or more ingredients, one of which is a standardized food but fails to bear the common or usual name of each ingredient in the standardized food as set forth in 21 CFR §101.4(b).

4. This product is misbranded under 21 U.S.C. 343(i) in that it is a food which purports to be a beverage containing vegetable or fruit juice and fails to bear a statement with appropriate prominence on the information panel of the total percentage of such fruit or vegetable juice contained in the food.
5. This product is misbranded under 21 U.S.C. 343(i) in that it contains a color or colors required to be certified without naming each.

Incorporate the following paragraph in each warning letter:

The above violations concern certain new labeling requirements and are not meant to be an all inclusive list of deficiencies on your labels. Other label violations can subject the food to legal action. It is your responsibility to assure that all of your products are labeled in compliance with all applicable statutes enforced by FDA.

CENTER FOR VETERINARY MEDICINE

CP 7371.004 - MEDICATED FEEDS

CGMP Deviations

Recommend formal administrative action, and regulatory action, if appropriate, when CGMP violations demonstrate that the methods, facilities, or controls being used present an actual or probable adverse impact on the safety, identity, strength, quality, or purity of the finished product. These are significant CGMP violations that support an Official Action Indicated (OAI) inspection classification. The following course of follow-up action should be considered:

1. On the initial CGMP inspection classified OAI, issue a warning letter. The district has the discretion to determine whether a warning letter is appropriate based on the circumstances of the specific case. In accordance with the delegation of authority, each letter concerning OAI inspections must contain a statement that the letter constitutes official notice of CGMP violations as required under Section

512(m)(4)(B)(i) of the Federal Food, Drug, and Cosmetics Act.

2. If the CGMP re-inspection is violative and classified OAI, recommend regulatory action, (e.g., injunction and/or mass seizure of medicated feeds and *** drug components).

*NOTE: Issuance of the official notice under Section 512(m)(4)(B)(i), item 1. above, is a prerequisite of this action.

Examples of significant CGMP violations that warrant OAI classification and the above course of follow-up action include:

- o Failure to conduct adequate clean-out procedures which have or could result in unsafe contamination of the finished product.
- o Scales or metering devices used to determine the amount of drug ingredient in the product are inaccurate or are operating in a manner that has caused or could be expected to cause incorrect or erratic drug levels in the medicated feed.
- o Lack of daily drug inventory records or failure to make a daily comparison between the actual amount of drug used and the theoretical amount of drug used or failure to take corrective action when significant discrepancies are detected.
- o A pattern of failure to perform medicated feed assays according to the schedule in 229.58.
- o Lack of follow-up action to determine and correct the cause of medicated feeds not meeting assay specifications.
- o Failure to properly label medicated feeds; for example, lack of withdrawal instructions on labeling or operating in a manner that would favor a label mix-up.
- o Failure to have master records or production records, or such records are lacking elements that can reasonably be expected to cause an adverse effect on the finished product.

If CGMP deviations are identified which do not support an OAI classification, the district has the discretion to determine what type of follow-up (e.g., meeting with the firm) is appropriate and who should be delegated the responsibility for conducting such follow-up activity.

Non-CGMP Violations

Below are several examples of non-CGMP violations that warrant issuance of warning letters as the initial action:

1. Use of unapproved drugs, or unapproved combinations or levels of approved drugs.
2. Illegal distribution of Type A medicated articles.

These violations fall within the specific areas that require center concurrence prior to issuance of a warning letter.

Import

Detain or refuse entry of medicated feeds which appear to be in violation of the Act and regulations. Release, with comments, feeds with minor violations.

Inspection Classification and MFA Approval/Denial

Firms with CGMP deviations as described under Administrative/Regulatory Sanctions, will be classified under PAC 71004 as Official Action Indicated (OAI).

Firms with CGMP deviations as described under Item C, Voluntary Action Indicated (CP 7371.004), will be classified under PAC 71004 as either NA, or VA.

GUIDANCE FOR SALMONELLA IN ANIMAL FEED

In 1990 when CVM announced a goal of salmonella negative in animal feed and feed ingredients, we realized that salmonella contamination was a widespread problem in the feed industry. Further, we realized that because of the nature of the business and the source of some of the ingredients that the stated goal would not be easily achieved.

A recent FDA survey of 154 animal protein and vegetable protein processors (less than 50% of this one segment of agribusiness) indicated that on the day of sampling over 70 (45%) of the firms had product on hand that was salmonella positive. Deciding which firm(s) should be identified for regulatory action and what action to take is obviously difficult, as is the matter of dealing with adulterated product on the market.

To address this problem, while permitting a vital part of agribusiness to operate and still move toward a salmonella negative goal, CVM is working with the United States Animal Health Association, academia, and industry to develop and implement Hazard Analysis Critical Control Point (HACCP) based quality assurance programs within the feed industry. It is the Center's hope that industry will embrace HACCP and begin systematically reviewing their manufacturing processes to address the source(s) of salmonella contamination. Our desire, for the implementation of HACCP programs does not mean that the Center is opposed to regulatory action at this time, rather it means we should be selective in choosing the cases.

CVM is revising the regulatory action guidance regarding salmonella contamination in feed. CPGs 7126.07 and 7126.13 have been revoked. While guidance has not been finalized, we can state that we will be giving considerable weight to a firm's efforts to remedy production and handling problems to decrease the incidence of salmonella. Prime candidates for regulatory attention will be those

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UNTITLED LETTERS ISSUED TO INDUSTRY ON ILLEGAL PROMOTIONAL ACTIVITIES

If a center is willing to support further Agency regulatory action if the violative practice doesn't cease, a warning letter and not an untitled letter should be issued for illegal promotional activities such as the promotion of a device or drug which has not been approved by FDA for commercial distribution and making representations that the device or drug is safe or effective for such purposes. If the center is not prepared to support regulatory action should a firm ignore a letter issued for illegal promotional activities, neither a warning letter nor an untitled letter should be used. An alternate approach would be to alert the district office of the violation and request that they bring the promotional activity to the attention of the firm on the next scheduled visit. This way if the district inspection reveals additional problems, this violation may be included as part of their regulatory action plan, should the firm fail to make appropriate corrections. If the problem is deemed to be more urgent the district could also request a meeting with the firm to discuss the violations.

R. 8592

FILED
OCT 23 1997
SPATIAL AND TEMPERATURE
CONTROL DIVISION
U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
WASHINGTON, D.C. 20201
H. ROSE BLACKLEY

firms that show a high incidence of positives and little regard for identifying problems and making improvements. [Concerning salmonella positive protein on the market, the field should notify firms in writing to review their operation in an effort to identify and correct possible contamination sources. CVM is developing example letters fitting various situations and including a 704(d) notification of analytical results.]

CVM will continue to support regulatory action against feed, ingredients, or pet food presenting a hazard to human or animal health. The strongest cases can be made for salmonella contamination of retail size containers which can be expected to be taken into the home where contamination could be expected to extend to cooking utensils and food preparation surfaces, thereby exposing humans to the contaminant. Imports found positive for salmonella may be detained without Center concurrence.

QUALITY ASSURANCE FOR WARNING LETTERS

IDENTIFICATION OF WARNING LETTERS

To facilitate the tracking of warning letters, it is suggested that every warning letter issued by a district or center office should bear a sequential code number. This code number should identify the fiscal year issued, the district or center issuing, and the appropriate sequential number for warning letters issued by that office.

WARNING LETTER MONITORING

To monitor and evaluate the effectiveness of warning letters it is suggested that the following information, at a minimum, be maintained by each district and center office for all warning letters issued.

General Information

1. Name of firm (and CFN #)
2. Location of firm (city & state)
3. Date warning letter issued
4. Date establishment inspection (EI) concluded

Time Frame Information

1. (Number) working days (WD) after completion of the inspection or, if applicable, a sample analysis for the district or the center to issue the warning letter directly, or for the district to submit the warning letter to the center for concurrence.

Note: When a warning letter is issued in response to an inspection, test, or other action not conducted by the district issuing the warning

letter, the 16 working day time frame for the issuing district begins upon receipt of the inspection report or other document which is the basis for the issuance of the warning letter. Examples of this situation are warning letters issued by a district based on inspectional or other activities conducted by cooperating state agencies (e.g., medicated feed inspections) or warning letters issued at the request of a center.

2. (Number) working days (WD) after receipt of the warning letter for the center to review and concur or not concur in the issuance of a warning letter, and notify the district of its decision.

Compliance Information

1. Response

Yes (Y), No (N), or Pending (P)

Use pending (P) for situations such as:

- The firm's response time has not yet expired.
- The firm's response was inadequate and continuing to correspond.
- The firm's response is under review by the center.

2. Correction adequate

Yes (Y), No (N), or Pending (P)

Use pending (P) for situations such as:

- Scheduled reinspection has not occurred.
- Sample analysis or analysis is pending.
- Met with firm and awaiting response.

3. Follow-up action on no response or inadequate correction

- (a) If follow-up action is completed, briefly state the type of action taken (i.e., seizure, injunction, civil penalty, disqualification).

- (b) If follow-up action is in-process or has not been initiated, briefly state the type of action in-process or planned.

4. Provide any additional information, if necessary to explain the follow-up action completed or planned, or to clarify particular circumstances involved in handling the case.

The above information will be periodically requested by the Division of Compliance Policy (HFC-230).

QUALITY AUDITS

In order to improve quality control/quality assurance of regulatory actions such as warning letters, it is important for the Agency to define quality standards and institutionalize the process to

allow assessment of quality. To assist in this standardization of quality for warning letters, the Division of Compliance Policy has developed 17 criteria points.

The audit form, see Exhibit 21, can assist in insuring uniformity in the issuance of warning letters. Through use of an audit, strengths and weaknesses can be addressed and plans for correction implemented.

EXHIBITS

Imports

- 4-1 Sample Warning Letter (WL) - Violative Shipments
- 4-2 Sample WL Language (WLL) - Failure to Hold Entry Misrepresentation
Sample WLL - Distribution Prior to Release
Sample WLL - Misrepresentation
Sample WLL - Standard of Identity/Foreign Language

Biologics

- 4-3 Sample WL - Blood or Plasma
- 4-4 Sample WLL - Computer Software
Sample WLL - Source Plasma

Drugs

- 4-5 Sample WL - Misbranded
- 4-6 Sample WL - Temper-Resistant Packaging
- 4-7 Sample WLL - Sterile drugs/CGMP
Sample WLL - DESI Drug/NDAs and ANDAs
Sample WLL - Homeopathic Drugs

Devices

- 4-8 Sample WL #8 - X-Ray Assemblers
- 4-9 Sample Warning Letter Language
- 4-10 Sample Warning Letter Language
- 4-11 Sample Directed Plan of Correction
- 4-12 Sample WL - Plain English

Feeds

- 4-13 Sample WLL - Standard of Identity
Sample WLL - Undeclared Additive
Sample WLL - Seafood Misbranding
Sample WLL - Labeling
Sample WLL - Sulfites in Potatoes
Sample WLL - Infant Formula
Sample WLL - Interstate Sanitation
Sample WLL - Insanitary Conditions
Sample WLL - NLEA

Cosmetics

- 4-14 Sample WLL - Color Additives

Veterinary Medicine

- 4-15 Sample WL - Medicated Feed Mill
- 4-16 Sample WLL - GMP Veterinary Drug
Sample WLL - Producer Warning Letter
Sample WLL - Misbranding
Sample WLL - Dealer Warning Letter

Other

- 4-17 WL Audit Report Form

SUBCHAPTER UNTITLED LETTERS

AGENCY POLICY ON ISSUANCE

There are some specific circumstances in which the agency has a need to communicate with regulated industry about documented violations that do not meet the threshold of regulatory significance. Therefore, when circumstances warrant the issuance of an untitled letter to a member of an FDA-regulated industry, the letter should be in a format that clearly distinguishes it from a Warning Letter. The essential elements of this untitled letter are:

1. Not titled;
2. May be issued by any appropriate agency compliance official;
3. No statement that FDA will advise other federal agencies of the issuance of the letter so that they may take this information into account when considering the awarding of contracts;
4. No warning statement that failure to take prompt correction may result in enforcement action;
5. No mandated district follow-up;
6. Time frames for correction are not specified; and
7. A written response may be an option, but is not necessary.

The following types of correspondence should be issued as untitled letters and not as warning letters:

1. Letters sent to an entire industry, such as the letter on excessive glazing of seafood. Letters issued to put an entire industry "on notice" should be untitled letters;
2. The district may issue a brief untitled letter with the FDA-483 attached to assure that top management of a firm (i.e., president, CEO, etc.) has a copy of the FDA-483 when the original FDA-483 was not issued to top management during the inspection. Since this correspondence is only a brief transmittal letter it is not considered a warning letter. If significant deviations are found, a warning letter should be sent and not an untitled letter.

EXHIBIT E

FILED
CLERK OF DISTRICT COURT
JANUARY 15 1936
AT HOPE BLAINE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Re: NDA #s 20-272 and 20-588
Risperdal® (risperidone)
MACMIS # 12195

WARNING LETTER

Dear Dr. Shetty:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a "Dear Healthcare Provider" (DHCP) Letter for Risperdal® (risperidone) disseminated by Janssen Pharmaceutica, Inc. on November 10, 2003. DDMAC has concluded that the DHCP letter is false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a) and 321(n)) because it fails to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the approved product labeling (PI), minimizes the risk of hyperglycemia-related adverse events, which in extreme cases is associated with serious adverse events including ketoacidosis, hyperosmolar coma, and death, fails to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible, and misleadingly claims that Risperdal is safer than other atypical antipsychotics. The healthcare community relies on DHCP letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers is a serious public health issue.

Background

According to the approved product labeling (PI), Risperdal is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Risperdal is indicated for the treatment of schizophrenia and for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Risperdal is also indicated in combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

Previously, information concerning the risks of hyperglycemia and diabetes appeared in the Adverse Reactions section of the PI under the subheading "Other Events Observed During the Premarketing Evaluation of RISPERDAL®." This section identified diabetes mellitus as an infrequent event (occurring in 1/100 to 1/1000 patients) and polyuria/polydipsia as a frequent event (occurring in at least 1/100 patients). In addition, the Adverse Reactions section of the PI

Plaintiff Ex. 1729

CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

R. 8594

EXHIBIT	17
WIT:	BRANN
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Ajit Shetty, M.D.

Page 2

Janssen

NDA #s 20-272 and 20-588 (MACMIS #12195)

had a subheading titled "Postintroduction reports" and described hyperglycemia and diabetes mellitus aggravated, including diabetic ketoacidosis, as temporally (but not necessarily causally) related to Risperdal.

In response to post-marketing reports of diabetes mellitus, including some cases that resulted in hospitalization and/or death, FDA evaluated the risk of the development of diabetes mellitus in patients treated with atypical antipsychotics. This evaluation included a thorough review from a number of sources, including clinical trial data, spontaneous post-marketing reports, epidemiological studies, published case series, published clinical pharmacology studies, published preclinical studies, and unpublished studies for clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Based on this review, and given the severity of the events reported and the potential to identify those events at an earlier stage with additional monitoring, FDA determined to require the addition of language to the Warnings section of the PI for all atypical antipsychotics regarding the risk of hyperglycemia and diabetes. By letter dated September 11, 2003, FDA notified Janssen (through Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) of the new warning requirement. On November 6, 2003, Janssen submitted supplemental NDAs covering addition of the following information to the Warnings section of the PI for Risperdal:

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of treatment emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

FDA subsequently approved these supplements, and requested that Janssen issue a DHCP letter communicating the important new risk information. FDA also asked Janssen to submit a copy of the letter to the NDA and to the MedWatch program, and reminded Janssen of its reporting requirements under 21 CFR 314.80 and 314.81.

Omission of Material Information

The DHCP letter fails to communicate the fact that information regarding the potential consequences of hyperglycemia and the recommendation of regular glucose control monitoring was added to the PI for Risperdal. Instead, as discussed below, the letter minimizes risks associated with Risperdal and claims that Risperdal is safer than other atypical antipsychotics, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risks/Misleading Comparative Claim

The DHCP letter states:

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research^{1,2,3,4,5,6,7,8} suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

This statement suggests that Risperdal does not increase the risk of diabetes, contradicting the Warning in the revised PI and minimizing the risks associated with the drug including hyperglycemia-related adverse events such as ketoacidosis, hyperosmolar coma, and death, and minimizing the importance of blood glucose control monitoring.

The references cited in the letter do not represent the weight of the pertinent scientific evidence. That evidence, as explained above, indicates an increased risk of hyperglycemia-related adverse events and diabetes with Risperdal. In addition, this statement does not accurately describe the results of the cited studies. Two of the studies^{1,3} actually show an increased risk of diabetes and hyperglycemia with Risperdal. In the first study, investigators found that the risk for diabetes in the risperidone cohort was higher than in the haloperidol cohort (HR 1.23, 95% 1.01 - 1.5). In

¹ Duse JB, Cavazoni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiology* 2003;56:164-170.

² Caro JJ, Ward A, Levinton C and Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry* 2002;63:1135-1139.

³ Fuller MA, Shermock KM, Seale M and Grogg AL. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. *Pharmacotherapy* 2003;23(8):1037-1043.

⁴ Gianfrancesco F, White R, Wang RH and Nasrallah HA. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. *J Clin Psychopharmacol* 2003;23(4):328-335.

⁵ Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Therapeutics* 2003;25(4):1150-1171.

⁶ Gianfrancesco FD, Grogg AL, Mahmoud RA et al. Differential effects of risperidone, olanzapine, clozapine and conventional antipsychotics on type II diabetes: findings from a large health plan database. *J Clin Psychiatry* 2002;63:920-930.

⁷ Koro CE, Fedder DO, L'Italiani GI et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-245.

⁸ Sernyak MJ, Leslie DL, Alarcon RD et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry* 2002;159:561-566.

Ajit Shetty, M.D.

Janssen

NDA #s 20-272 and 20-588 (MACMIS #12195)

Page 4

the second study, for patients less than forty years old, olanzapine, clozapine, quetiapine and risperidone were all associated with a statistically significant increase in risk for diabetes. Thus, the cited studies as well as the complete "body of evidence" supporting the labeling change are misrepresented in the DHCP letter.

FDA is not aware of substantial evidence or substantial clinical experience to support Janssen's claim that "Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics." If you have data to support this claim, please submit them to FDA for review. FDA is unable to conclude, based on unpublished and published studies, whether the differences in results represent true differences in risk for diabetes mellitus among drugs or are due to limitations in the study designs or in some cases, the limited sample sizes examined. FDA's conclusion regarding the lack of evidence to support a ranking of risk among the atypical antipsychotics is reflected in the following statement from the Warnings section of the PI for Risperdal: "Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

Failure to Submit Post-Marketing Reports

The DHCP letter was not submitted to FDA on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81 (b)(3)(i)).

Conclusions and Requested Actions

The DHCP letter misleadingly omits material information about Risperdal, minimizes potentially fatal risks associated with the drug, and claims superior safety to other drugs in its class without adequate substantiation, in violation of Sections 502(a) and 201(n) of the Act (21 U.S.C. §§ 352(a) and 321(n)).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Risperdal that contain claims the same as or similar to those described above and provide a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials. Please submit a written response to this letter on or before May 3, 2004, describing your intent to comply with this request, listing all promotional materials for Risperdal that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12195 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Risperdal, and may determine that additional measures will be necessary to fully correct the false or misleading messages resulting from your violative conduct. It is your responsibility to ensure that your promotional materials for Risperdal comply with each applicable requirement of the Act and FDA implementing regulations.

Ajit Shetty, M.D.

Janssen

NDA #s 20-272 and 20-588 (MACMIS #12195)

Page 5

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.

Director

Division of Drug Marketing,

Advertising and Communications

FILED
CLERK OF COURT
SOUTHERN DISTRICT
OF NEW YORK
JAN 11 2005
KIMBERLY BLAUGLEY

Cc: William C. Weldon
CEO
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Abrams
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APPROPRIATE
M. HOPE BLACKLEY
APR 19 2004

STATE OF SOUTH CAROLINA)
COUNTY OF SPARTANBURG)

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.)
Alan Wilson, in his capacity as Attorney)
General of the State of South Carolina,)

Civil Action No. 2007-CP-42-1438

Plaintiff,

v.

JANSSEN PHARMACEUTICA, INC.,)
JANSSEN, L.P. and JOHNSON &)
JOHNSON, INC.,)

Defendants.)

**DEFENDANTS' MOTION
FOR A DIRECTED VERDICT**

FILED
IN THE COURT
OF COMMON PLEAS
SEVENTH JUDICIAL CIRCUIT
SPARTANBURG COUNTY
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M. HOPE MASONLEY

TO: JOHN B. WHITE, JOHN S. SIMMONS, AND FLETCHER V. TRAMMELL
ATTORNEYS FOR PLAINTIFF

Pursuant to Rule 50(a) of the South Carolina Rules of Civil Procedure, Defendants Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby move this Court for a directed verdict as to the claim of Plaintiff, the State of South Carolina (the "State"), under the South Carolina Unfair Trade Practices Act ("SCUTPA"). The State's SCUTPA claim is based on: (1) a November 10, 2003 mailing from Janssen to South Carolina physicians (the "November 2003 mailing"); and (2) the distribution of the U.S. Food and Drug Administration ("FDA")-approved package insert for Risperdal® ("Risperdal package insert").

Despite years of litigation and sweeping allegations of misconduct directed at Janssen, the State's claim lacks both evidence and legal support. A directed verdict is appropriate for a number of independent reasons.

First, the State's SCUTPA claim based on the November 2003 mailing fails in its entirety because it is expressly preempted by federal law. As this Court and many others

have previously recognized, the U.S. Food, Drug, and Cosmetic Act (the "FDCA" or the "Act") does not permit private causes of action based on violations of the Act. Indeed, federal law provides that *only* the federal government may enforce the FDCA. 21 U.S.C. § 337(a). Nevertheless, the State's evidence that the November 2003 mailing was "deceptive," including the testimony of its expert witnesses, is based only on the FDA's characterization of the November 2003 mailing as "false and misleading in violation of Sections 502(a) and 201(n) of the [FDCA]." As counsel for the State noted, this question is one "for the FDA to decide." Trial Tr. vol. V, 1183:3-9, Mar. 11, 2011.

Second, the State's SCUTPA claim based on the FDA-approved Risperdal package insert fails in its entirety because it is barred by SCUTPA's regulated activity exemption. S.C. Code Ann. § 39-5-4(a). The testimony of the State's experts, that the Risperdal package insert was "inadequate" at the time of product launch, places the Risperdal package insert claim squarely within the regulated activity exemption as enunciated by this Court. Not only federal regulations but also common sense dictate that a pharmaceutical manufacturer cannot have a duty to update the package insert on the very first day it is issued, when the FDA approved every single word of the initial label, which was required to be used "verbatim."

Third, the State's deceptive trade practice claim cannot be submitted to the jury because:

- (1) the November 2003 mailing and the Risperdal package insert do not contain any actionable representations – opinions accompanied by all the support for them are not actionable;
- (2) the State has no evidence – factual, expert, or otherwise – that: (a) Janssen did not have a reasonable basis for the opinions set forth in either the November 2003 mailing or the Risperdal package insert; or (b) either the November 2003 mailing or the Risperdal package insert had a tendency to deceive or was likely to deceive the relevant audience, South Carolina physicians; and

- (3) the State has no evidence – factual, expert, or otherwise – that either the November 2003 mailing or the Risperdal package insert was material to South Carolina physicians' decisions to prescribe Risperdal for their patients.

Fourth, the State's belated claim that the November 2003 mailing and the Risperdal package insert constitute "unfair" trade practices also cannot be submitted to the jury because:

- (1) the State has no evidence – factual, expert, or otherwise – that satisfies the essential elements of a claim for an unfair trade practice; and
- (2) alleged violations of public policy alone are not a basis for a finding that an act or practice is "unfair."

Fifth, the State's SCUTPA claim, whether based on a deceptive trade practice or an unfair practice fails because the State did not introduce sufficient evidence to satisfy the element that the alleged unfair or deceptive trade practice adversely affected the public interest.

Sixth, the State's claim of unfair and/or deceptive trade practices also fails because the State has not introduced sufficient evidence for the jury to find willful conduct – as "willfulness" is defined by South Carolina law.

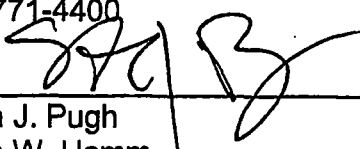
Seventh, the State's claim is barred by SCUTPA's three year statute of limitations.

Finally, there are no facts of record that would support any claim or effort to disregard the separate corporate existence of defendant Johnson & Johnson, a separate legal entity that functions solely as a holding company. Accordingly, a judgment must be entered in favor of Johnson & Johnson and against the State on the State's SCUTPA claim.

WHEREFORE, for the reasons stated herein and in the accompanying memorandum of law, the Court should grant Defendants' Motion in its entirety.

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March 14, 2011.

FILED
U.S. DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
2011 MAR 14 PM 4:49
M. HOPE BACILEY

STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.
Alan Wilson, in his capacity as Attorney
General of the State of South Carolina,

Civil Action No. 2007-CP-42-1438

Plaintiff,

v.

**MEMORANDUM OF LAW IN SUPPORT
OF DEFENDANTS' MOTION
FOR A DIRECTED VERDICT**

JANSSEN PHARMACEUTICA, INC.,
JANSSEN, L.P. and JOHNSON &
JOHNSON, INC.,

Defendants.

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby submit this Memorandum of Law in support of their Motion for a Directed Verdict.

I. INTRODUCTION

Plaintiff, the State of South Carolina (the "State"), has chosen to pursue a single claim against Defendants – a claim under the South Carolina Unfair Trade Practices Act ("SCUTPA"). As its sole remaining claim, the State asserts that Defendants engaged in certain allegedly unfair or deceptive trade practices: (1) the dissemination of a November 10, 2003 mailing by Janssen to South Carolina physicians (the "November 2003 mailing"); and (2) the distribution of a package insert, or product label, for Risperdal® (the "Risperdal package insert" or the "package insert"), which was approved repeatedly by the U.S. Food and Drug Administration ("FDA") over a fifteen-year period.

The State does not challenge either the November 2003 mailing or the Risperdal package insert in its entirety. Rather, the State only asserts that: (1) three sentences of the

cover letter to the November 2003 mailing are purportedly "deceptive" or "unfair"; and (2) several sentences of the multi-page FDA-approved Risperdal package insert are also purportedly "deceptive" or "unfair," and then only as to certain limited potential risks as to Risperdal.

After four years of litigation, however, the State has offered *no* material facts in support of its SCUTPA claim. Instead, the State has only offered as "evidence" the personal opinions of two experts. Neither South Carolina law nor applicable federal decisions (applicable to the determination of the State's claim by the express terms of SCUTPA) allow such speculative evidence to be submitted to a jury in support of a claim for either a deceptive or an unfair trade practice. Defendants' motion for a directed verdict should be granted because the factual and legal grounds upon which the State's SCUTPA claim fails are not only numerous but also insurmountable.

II. THE STATE'S "EVIDENCE"

A. As To The November 2003 Mailing.

In its case in chief, the State's only "evidence" that the November 2003 mailing was "unfair" or "deceptive" in violation of SCUTPA was: (1) the opinions of its experts, Laura M. Plunkett, Ph.D. (a toxicologist and pharmacologist, not a physician or an epidemiologist) and William C. Wirshing, M.D. (a psychiatrist); and (2) an April 2004 "warning letter" from the Director of the Division of Drug Marketing, Advertising, and Communications ("DDMAC") of the FDA.

B. As To The Risperdal Package Insert.

The State's "evidence" that the Risperdal package insert was "unfair" or "deceptive" again consisted only of the testimony of experts. One of the State's experts, Dr. Wirshing, testified that the label from 1994 to 2004 did not adequately disclose the risk of diabetes; the label from 1997 to 2006 did not adequately disclose the risk of death in the elderly; and

the label from 1994 to 2007 did not adequately disclose the risk of hyperprolactinemia. Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011. The State's other expert, Dr. Plunkett, testified that from 1994 to 2007 the label did not adequately warn of the dangers of hyperprolactinemia and from 1994 to 2004 the label did not adequately warn of the risk of diabetes. Trial Tr. vol. IV, 935:3-936:22, Mar. 10, 2011.

III. DIRECTED VERDICT STANDARD

"In deciding whether to grant or deny a directed verdict motion, the court is concerned only with the existence or nonexistence of evidence." *Ecclesiastes Prod. Ministries v. Outparcel Assocs., Inc.*, 374 S.C. 483, 491, 649 S.E.2d 494, 498 (Ct. App. 2007) (citation omitted). Further, although "[t]he issue must be submitted to the jury whenever there is material evidence tending to establish the issue in the mind of a reasonable juror," *id.* at 490, 656 S.E.2d at 407 (internal quotations and citations omitted), it is clear that "this rule does not authorize submission of speculative, theoretical, and hypothetical views to the jury," *Parrish v. Allison*, 376 S.C. 308, 319-20, 656 S.E.2d 382, 388 (Ct. App. 2007). Thus, "[a] directed verdict should be granted where the evidence raises no issue for the jury as to the defendant's liability." *Guffey v. Columbia/Colleton Reg'l Hosp., Inc.*, 364 S.C. 158, 163, 612 S.E.2d 695, 697 (2005). In addition, a directed verdict also is proper "where there is no evidence on any one element of the alleged cause of action." *Id.*

IV. ARGUMENT

A. The State's SCUTPA Claim Based On The November 2003 Mailing Is Preempted By Federal Law.

As the State presented its case, the SCUTPA claim as to the November 2003 mailing is based entirely on Janssen's alleged violations of federal law. Time and again, the State introduced or based its expert witnesses' testimony on the 2004 warning letter sent by

the FDA and merely had its experts agree with the statements in the letter. See, e.g., Trial Tr. vol. V, 1058:1-1059:15, Mar. 11, 2011 (Plunkett's opinion that the November 2003 mailing was false and misleading is "based upon the FDA standard"). In fact, the State presented testimony from a Janssen sales representative seemingly to prove the point that "it's for [the FDA] to decide." *Id.* at 1183:3-9 (testimony of Alderman).

This Court, like many others, previously acknowledged that preemption would clearly apply to a claim like this, based on an alleged violation of federal law. See *State ex rel. McMaster v. Eli Lilly & Co.*, No. 2007-CP-42-1855, slip op. at 23, 2009 WL 6058384 (S.C. Ct. Com. Pl. Sept. 22, 2009) (Couch, J.) ("*Lilly*") (recognizing that "to the extent that the Plaintiff in this case might be seeking to bring a private cause of action based on the [Food, Drug, and Cosmetic Act (the 'FDCA' or the 'Act')] the motion [for summary judgment] would be granted"); see also *Weston v. Kim's Dollar Store*, 385 S.C. 520, 537, 684 S.E.2d 768, 778 (Ct. App. 2009) (holding that the circuit court correctly applied the doctrine of federal preemption in determining that state law claims "dependent on warning, labeling, design, marketing, misbranding, or other similar claims" are preempted by federal law "because a jury's acceptance of the disputed claims could result in different or additional requirements from the federal requirements").

Indeed, federal law provides that *only* the federal government may enforce federal drug labeling law and expressly prohibits attempts to use state law to enforce federal drug labeling law. The FDCA provides that any "proceedings for the enforcement, or to restrain violations, of this chapter [of the FDCA] shall be by and in the name of the United States." 21 U.S.C. § 337(a). There can be no uncertainty as to the primacy of the FDA because, as the United States Supreme Court has explained, Section 337(a) "leaves no doubt that" the federal government has the exclusive authority to "file suit for noncompliance" with FDA

regulations. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4 (2001); accord *Lilly*, No. 2007-CP-42-1855, slip op. at 23, 2009 WL 6058384 (Couch, J.).

The State's entire claim as to the November 2003 mailing is inextricably intertwined with the April 2004 DDMAC warning letter, the centerpiece of the State's claim. But that warning letter speaks only of purported violations of the FDCA. Thus, the State's claim is that the November 2003 mailing was "deceptive" because it was, in DDMAC's view, "false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act." Trial Ex. P232. The State, then, is improperly attempting to impose liability based on alleged violations of the FDCA. *Id.*

This is particularly inappropriate in the present case because DDMAC investigated all aspects of the November 2003 mailing and took no further steps after Janssen issued its July 2004 letter. Trial Tr. vol. IV, 838:13-23, Mar. 10, 2011. That is, DDMAC made a conscious decision not to pursue any of the panoply of remedies available to it. See generally FDA Regulatory Procedures Manual § 4-1-1 ("The Warning Letter was developed to correct violations of the statutes or regulations. Also available to the agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution to achieve correction."). See also Trial Tr. vol. III, 838:13-23, Mar. 10, 2011 (If Janssen had not complied, the FDA could have pursued administrative enforcement actions).¹

¹ The State's claim also is preempted to the extent that it is based on: (1) the alleged failure to disclose to the FDA the results of two studies (referred to by the State as "RIS-113" and "ERI"); and (2) the supposed "off-label promotion" of Risperdal. See, e.g., Trial Tr. vol. III, 633:16-634:2, Mar. 9, 2011 (Wirshing testifying that results of "RIS-113" should have been disclosed to the FDA); Trial Tr. vol. V, 1074:21-1075:12, Mar. 11, 2011 (Plunkett testifying that results of "RIS-113" and "ERI" should have been disclosed to the FDA); Trial Tr. vol. IV,

(continued...)

Thus, Defendants are entitled to a directed verdict as to the State's claim based on the November 2003 mailing because such a claim is preempted by federal law.

B. The State's SCUTPA Claim Based On The FDA-Approved Risperdal Package Insert Fails Because The Evidence Presented Does Not Support An "Ability to Update" Exception To The Regulated Activity Exemption.

This Court declined, at the summary judgment stage, to apply the regulated activity exemption provided under S.C. Code Ann. § 39-5-40 as a bar to the State's claim based on the FDA-approved Risperdal package insert. The Court explained:

This Court has previously noted that drug manufacturers have a continuing duty to update its labels so as to include new more stringent warnings concerning the use and efficacy of its drugs and the warning associated therewith. See 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C). It is clear to this Court that the FDA does not allow or permit deceptive activities in the marketing and labeling of drugs, and further, it requires that drug manufacturers are required to up-date their warnings based on available information.

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Slip op. at 7-8 (Feb. 25, 2011).

(...continued)

861:5-22, Mar. 10, 2011 (Plunkett agreeing with State's counsel upon review of internal Janssen document that it appears as if Janssen was engaging in "off-label promotion"). The first simply is a "fraud on the FDA claim," which is barred by *Buckman* and this Court's decision in *Lilly*. See *Buckman*, 531 U.S. at 348; *Lilly*, slip op. at 23, 2009 WL 6058384; see also Trial Tr. vol. I, 56:10-12, 58:5, Mar. 7, 2011. The second is expressly preempted by the FDCA as an impermissible attempt to pursue a private cause of action for alleged violations of the FDCA. Trial Tr. vol. IV, 757:24-25, 758:1-25, 1101:14-17, 1102:1-25, 1103:1-10, Mar. 11, 2011 (Plunkett agreeing with State's counsel that "off label" promotion is against "FDA rules," which "have the force of law"; FDA supposedly "caught" Janssen engaging in off-label promotion (in 1999), which is "against the law"). The off-label promotion claim should also be barred by the representation of the State's counsel, on the first day of trial, that "we're not making a claim based on any of that," i.e., alleged off-label promotion; there would only be "some evidence" of the delivery of package inserts to physicians. Trial Tr. vol. I, 134:6-14, Mar. 7, 2011; see also *id.* at 77:22-24 (State's counsel: "We'll never come to the Court and say, on November 5th, 1999, ten sales reps said this, which we think violates the statute.").

In support of its decision denying summary judgment on the regulated activity exemption, this Court cited 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C). Under this regulation, known as a changes being effected ("CBE") regulation, a pharmaceutical manufacturer is *not* required – or even permitted – to update a package insert based simply on "available information." Rather, a pharmaceutical manufacturer may *only* update a package insert when it has (i) "newly acquired information" that (ii) constitutes "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter." *Id.*

Under 21 C.F.R. § 201.57(c)(6)(i), "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. In its 2008 revisions to the CBE regulation, the FDA made abundantly clear that use of a CBE submission is appropriate "only to reflect newly acquired information . . . [and then] only if there is sufficient evidence of a causal association with the drug, biologic, or medical device." 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008). The FDA's revision was "intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, *and to prevent overwarning*, which may deter appropriate use of medical products, or overshadow more important warnings." *Id.* at 49605-06 (emphasis added); *see also id.* at 49603 (CBE regulation was meant to "codify the agency's longstanding view concerning when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change.").

The FDA also made clear that what constitutes "newly acquired information" sufficient for application of the CBE regulations is very limited:

The definition of "newly acquired information" has been revised to clarify that data, whether derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) needs to be of a "different type or greater severity or frequency than previously included in submissions to FDA".

Id. at 49604.

Thus, to show that Janssen had an obligation at some point in time after approval of the initial package insert by the FDA to update its package insert under the CBE regulation, the State was required to provide specific evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" between Risperdal and the risks of hyperglycemia, diabetes, weight gain, hyperprolactinemia, and alpha toxicity. Neither of the State's experts could identify with any specificity exactly what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence of a causal association," or exactly "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). Dr. Wirshing actually testified that at the time of the FDA-mandated class label change, the evidence did not support a conclusion of a "causal" connection between Risperdal and diabetes. Trial Tr. vol. III, 496:25-497:10, Mar. 9, 2011 (evidence was "not conclusive" and it was "not causal"). Dr. Plunkett conceded she was not retained to form a failure to warn opinion related to the Risperdal label. Trial Tr. vol. IV, 932:9-933:21, Mar. 10, 2011.

Both of the State's experts also testified that the Risperdal package insert was "inadequate" at the time of product launch. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). As a matter of law, logic, and common sense, a pharmaceutical manufacturer

cannot have a duty to update the package insert on the very first day it is issued, when the FDA had just approved every word of the initial label, which was required to be used "verbatim" by Janssen. Trial Ex. P571 (Initial approval letter). The State's expert testimony thus falls far short of establishing any obligation by Janssen to update its package insert as to the risks of diabetes, hyperprolactinemia, and alpha toxicity.

The State attempted to satisfy its burden by repeatedly offering "evidence" as to Janssen's "awareness" of the risks of hyperglycemia, diabetes, weight gain, and hyperprolactinemia. See, e.g., Trial Tr. vol. III, 623-15-626:13, Mar. 9, 2011 (testimony of Wirshing). As the FDA regulations, and the FDA itself make clear, general awareness and knowledge of risks of the use of a prescription medicine are insufficient to require a manufacturer to update its package insert – and will not support the use of the BE procedures. See 21 C.F.R. 314.70(c)(6)(iii)(A),(C); *id.* § 201.57(c)(6)(i); 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008).

Finally, neither of the State's experts provided any testimony as to exactly "what" would cure the alleged inadequacy of the Risperdal package insert. See, e.g., Trial Tr. vol. V, 994:17-24, Mar. 11, 2011 (Plunkett testifying that she has not re-written the label as to the risk of hyperprolactinemia). This lack of clarity is another reason the Court should not allow a jury to decide the State's package insert claim. *Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.*, 586 F. 3d 500, 508 (7th Cir. 2009) ("But Schering has been coy about what it thinks the disclaimer should say, and its coyness makes us doubt that this is a matter that can be resolved intelligently without a decision by the FDA.").

Although the Court permitted the State's "package insert" claim to proceed beyond summary judgment, the State's evidence at trial confirms that: (1) at all times, the Risperdal package insert was approved and permitted by the FDA; (2) the FDA has never determined that the Risperdal package insert was not properly updated by Janssen; (3) the FDA has

never determined that the Risperdal package insert was false or misleading; (4) the Risperdal package insert was updated and revised multiple times by Janssen with the approval and permission of the FDA; and (5) the State did not present sufficient evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" as to any of the risks which the State alleged were inadequately disclosed. Rather, the State continues to maintain that the Risperdal package insert was "inadequate" from Day One of the sale of Risperdal, a position unsupported by logic, fact, or the law. As the State has not introduced any evidence that Janssen was required to – or permitted to – update its label with a CBE submission, this Court's prior holding and SCUTPA's regulated activity exemption bar the State's package insert claim.

C. The State Has Failed To Introduce Sufficient Proof Of Each Of The Elements Of Both Its Deceptive Trade Practice Claim And Its Unfair Trade Practice Claim.

The express terms of SCUTPA require South Carolina courts to be guided by decisions and interpretations of the Federal Trade Commission ("FTC"), including, obviously, policy pronouncements of the FTC itself. *Plowman v. Bagnol*, 316 S.C. 283, 287, 450 S.E.2d 36, 38 (1994) ("In section 39-5-20(b), the Legislature specifically instructs state courts to be guided by the decisions of the Federal Trade Commission (FTC) and the Federal Courts construing the Federal Trade Commission Act, 15 U.S.C. [§] 45(a)(1), in interpreting section 39-5-20(a)[.]"). This direction is significant because, as outlined below, these sources not only establish the necessary elements of the State's claim of an unfair or deceptive practice or act but also establish the insufficiency of the evidence offered by the State.

Stated another way, these standards set forth the applicable evidentiary burden for the State. And it is a burden that cannot be satisfied with opinion testimony alone as to whether a particular act or practice is "unfair" or "deceptive"; instead, the State is required to

present *facts* supporting each of the elements of its SCUTPA claim. As the State's evidence fails to establish the essential elements of either a deceptive trade practice claim or an unfair trade practice claim, judgment in favor of Defendants is mandated. *Guffey*, 364 S.C. at 163, 612 S.E.2d at 697 (directed verdict is proper "where there is no evidence on any one element of the alleged cause of action").

1. **The State Lacks Sufficient Evidence As To The Essential Elements Of Its Deceptive Trade Practices Claim.**

Well-settled law provides that to establish liability for a deceptive trade practice, "the FTC must establish that (1) there was a representation; (2) the representation was likely to mislead customers acting reasonably under the circumstances; and (3) the representation was material." *FTC v. Tashman*, 318 F.3d 1273, 1277 (11th Cir. 2003) (citations omitted). The State equally, therefore, is required to establish these elements.

a. **Lack Of An Actionable Representation.**

The November 2003 mailing expressed Janssen's opinion as to the conclusions that could be drawn from a certain "body of evidence from published peer-reviewed epidemiology research." See Trial Ex. P1736 (November 10, 2003 mailing). Equally significant, the November 2003 mailing also cited to each of the published epidemiological peer-reviewed studies, thereby fully disclosing the entire scientific basis for the opinion. *Id.* Because Janssen's statement of its opinion was accompanied by a disclosure of the sources upon which the opinion was based – allowing any reader of the November 2003 mailing to draw his own conclusions about the scientific evidence – the mailing cannot be considered deceptive. See *Bruette v. Stokes, Kia, Isuzu, Subaru, Inc.*, No. 2001-CP-10-1800, slip op. at 9, 2002 WL 34128304 (S.C. Ct. Com. Pl. Nov. 6, 2002) ("When the alleged unfair trade practice 'is a misrepresentation, the claimant is not entitled to recover if he had an equal and ample opportunity to ascertain the truth but failed to exercise proper diligence

to do so.” (citation omitted)); see also *Pizza Hut, Inc. v. Papa John’s Int’l, Inc.*, 227 F.3d 489, 496 (5th Cir. 2000) (holding, under analogous Lanham Act, 15 U.S.C.A. § 1125(a): “Bald assertions of superiority or general statements of opinion cannot form the basis of Lanham Act liability.” Rather the statements at issue must be a ‘specific and measurable claim, capable of being proved false or of being reasonably interpreted as a statement of objective fact.” (citations omitted)); *Cytoc Corp. v. Neuromedical Sys., Inc.*, 12 F. Supp. 2d 296, 300 (S.D.N.Y. 1998) (“In the actual statement, contained in a press release, Cytoc identified the specific screening site, and the numbers of positive cases diagnosed with the pap smear and with ThinPrep. The inclusion of such specific evidence means that this statement could not be found to be misleading.”). This is especially true where the opinions relate to scientific and medical research. See, e.g., *McDonagh v. Bergan*, No. 03 C 446, 2003 WL 21798735, at *3 (N.D. Ill. July 25, 2003) (“disagreements of this type among medical professionals should be settled by discussion and research in the medical community, not by the courts”).

The statements in the Risperdal package insert, like the statements in the November 2003 letter, reflect judgments, by Janssen and/or the FDA, about the meaning and significance of the scientific evidence. As to the package insert, neither of the State's experts even attempted to argue that the statements about diabetes, hyperprolactinemia, etc. were based on anything other than extensive medical research and information as to the use of Risperdal for over a decade, although they took issue with the significance of some of that research and with decisions about the wording of certain parts of the package insert and the prominence of the “risk” information in it. See generally Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). And this is dispositive of the State's deceptive trade practice claim.

The present case illustrates precisely the logical problem and, equally important, the constitutional problem, with the entirety of the State's SCUTPA claim – the State improperly seeks to punish reasonable expressions of scientific opinions by Janssen. To proceed on that claim, the State erroneously believes that the jury may choose among the different experts' positions in the scientific debate and then have the Court punish Janssen for having a different – yet scientifically supported – view. Nothing under applicable law supports this conclusion or result. Thus, the complete absence of a provably false factual representation that could “deceive” the persons to whom it was made precludes the State's deceptive trade practice claim in the first instance.

b. **Absence Of Evidence That The November 2003 Mailing Or The Risperdal Package Insert Had A “Tendency To Deceive” Or Was “Likely To Deceive” South Carolina Physicians.**

Under South Carolina law, the test for SCUTPA liability is whether the challenged statement or act “has a tendency to deceive.” *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (Ct. App. 2000). Whether an act has a “tendency to deceive” or is “likely to deceive” “depends upon the surrounding facts and the impact of the transaction on the marketplace.” *Id.* As directed by the express terms of SCUTPA, this Court must look to the FTC’s Policy Statement on Deception, which similarly provides that the knowledge and sophistication of the relevant audience is to be considered when determining whether a company’s trade practice is deceptive or misleading. See 2 Fed. Trade Comm’n App. D-2 (2009). Pursuant to the Policy Statement, “a practice or representation directed to a well-educated group, such as a prescription drug advertisement to doctors, would be judged in light of the knowledge and sophistication of that group.” *Id.* (emphasis added). The relevant audience, or “marketplace,” for the State's SCUTPA claim necessarily is South Carolina physicians because: (1) Risperdal can only be obtained by

prescription; (2) the November 2003 mailing was sent to physicians; and (3) the package insert is written for physicians.

As part of its proof, therefore, the State was required to present evidence that the November 2003 mailing and the Risperdal package insert actually had a "tendency to deceive" or were "likely to deceive" South Carolina physicians. See *TC X, Inc. v. Commw. Land Title Ins. Co.*, 928 F. Supp. 618, 625 (D.S.C. 1995), *aff'd without op.*, 86 F.3d 1152 (4th Cir. 1996) (granting summary judgment for the defendant on a SCUTPA claim, stating that "[t]here is no evidence that Commonwealth deceived TC X or anyone else regarding its interpretation of the policy").

The State's claim fails because the State did not to prove that either the November 2003 mailing or the Risperdal package insert had a tendency to deceive or were likely to deceive. The State's experts took the position that the November 2003 mailing was somehow inherently "deceptive" and that the Risperdal package insert was "inadequate" as to certain risks. See *generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). But they provided no testimony whatsoever about the knowledge and sophistication of South Carolina physicians, and no testimony as to whether the November 2003 mailing or the Risperdal package insert, with their statements as to the scientific evidence, actually deceived or were "likely to deceive" those physicians. See *generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). Without supporting facts, the speculation of experts as to whether a statement is actually "deceptive" is insufficient to satisfy the State's evidentiary burden.

c. **Lack Of Evidence Of Materiality.**

A material claim is one that is "likely to affect" a party's "conduct or decision with regard to a product or service." FTC Policy Statement on Deception at 2. As the State has

introduced no evidence that either the November 2003 mailing or the Risperdal package insert was material to a single prescribing decision by a South Carolina physician, its deceptive trade practice claim fails for this reason as well.

2. The State Also Lacks Sufficient Facts As To Its Unfair Trade Practices Claim.²

The State's alternative claim that the November 2003 mailing and the Risperdal package insert are "unfair" acts or practices also cannot be submitted to the jury. "Unfair" acts or practices cannot be "inferred." *Wingard v. Exxon Co., U.S.A.*, 819 F. Supp. 497, 506 (D.S.C. 1992) ("Additionally, an unfair or deceptive trade practice cannot be inferred from the conduct of Exxon. Generally, an unfair trade practice involves a misrepresentation made to a consumer. In this case there is no element of misrepresentation." (citations omitted). Further, "[t]he SCUTPA does not prohibit all business activities that someone may consider 'unfair', however." *Miller v. W.H. Bristow, Inc.*, 739 F. Supp. 1044, 1055 (D.S.C.1990). Thus, the State is required to prove the essential elements of an unfair trade practice, which can easily be determined by reference to both the Federal Trade Commission Act as well another FTC long-standing Policy Statement. See 15 U.S.C.A. § 45(n) (FTC Act); FTC Policy Statement on Unfairness (1980).

a. Lack Of Evidence Of The Essential Elements Of An Unfair Trade Practices.

In construing SCUTPA, the South Carolina Supreme Court has found decisions from Tennessee courts persuasive authority. See, e.g., *Ward v. Dick Dyer Assocs., Inc.*, 304

² Defendants previously filed a motion to limit, among other things, the State's claim to "deceptive" trade practices, consistent with the State's numerous discovery responses to that effect. As the Court has not ruled explicitly on that aspect of the motion to limit, Defendants address here the insufficiency of the State's evidence as to its purported "unfair" trade practices claim.

S.C. 152, 156, 403 S.E.2d 310, 312 (citing *Skinner v. Steele*, 730 S.W.2d 335 (Tenn. App. 1987)). In defining what constitutes an unfair trade practice, Tennessee courts have adopted the elements set forth in 15 U.S.C. § 45(n) (part of the Federal Trade Commission Act). *Tucker v. Sierra Builders*, 180 S.W.3d 109 (Tenn. App. 2005). As held by the court in *Tucker*:

In the 1994 legislation reauthorizing the Federal Trade Commission, Congress undertook to codify the Commission's policy statement on unfairness by stating that an act or practice should not be deemed unfair "unless the act or practice causes or is likely to cause substantial injury to consumers which is not reasonably avoidable by consumers themselves and not outweighed by countervailing benefits to consumers or to competition." 15 U.S.C.A. § 45(n). Following the mandate of Tenn. Code Ann. § 47-18-115, we will use this description of unfairness to guide our interpretation of Tenn. Code Ann. § 47-18-104(a).

Id. at 116-117. As further explained by the court:

To be considered "substantial," consumer injury must be more than trivial or speculative. Substantial injury usually involves monetary injury or unwarranted health and safety risks. Consumer injury will be considered substantial if a relatively small harm is inflicted on a large number of consumers or if a greater harm is inflicted on a relatively small number of consumers. Even if an act or practice causes or is likely to cause substantial injury, it will not be considered unfair unless the injury is not reasonably avoidable by consumers themselves. Consumers cannot reasonably avoid injury when a merchant's sales practices unreasonably create or take advantage of an obstacle to the free exercise of consumer decision-making. Practices that unreasonably interfere with consumer decision-making include (1) withholding important information from consumers, (2) overt coercion, or (3) exercising undue influence over a highly susceptible class of consumers.

Id. at 117 (citations omitted).

The State's evidence for its unfair trade practice claim falls far short of meeting any of these essential elements. First, any alleged "substantial" injury to consumers from either the November 2003 mailing or the Risperdal package insert is nothing more than

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speculation. Second, any alleged "substantial" injury is more than outweighed by the undisputed benefits to South Carolina residents from the availability and use of Risperdal. The State's expert, Dr. Wirshing, in particular testified in great detail as to the substantial medical benefits of Risperdal. Trial Tr. vol. III, 561:7-568:2, 624:7-14, Mar. 9, 2011. Finally, the State introduced no evidence whatsoever from which a jury could conclude that any aspect of the November 2003 mailing or the Risperdal package insert "unreasonably interfered" with either a consumer's or a physician's decision to choose Risperdal.

b. **Alleged Violations Of Public Policy Alone Are Not A Basis Upon Which The Jury Can Make A Finding That An Act Or Practice Is "Unfair."**

Ever since they were first advanced, only a few weeks ago, the State's "public policy" arguments have been unclear – shifting depending on the particular issue raised. See, e.g., Pl.'s Opp'n to Defs.' Mot. In Limine To Preclude Irrelevant And Unfairly Prejudicial Evidence at 18 ("the State is entitled to introduce evidence of loss and harm sustained by the South Carolina Medicaid program to show that Defendants' labeling of Risperdal prescriptions paid or reimbursed by the State violated S.C. Code § 39-5-20(a) because it was unethical, immoral, and offensive to South Carolina's public policy of not defrauding public agencies that protect the health and welfare of its citizens."); Pl.'s Opp'n To Defs.' Mot. For Summ. J. As To Pl.'s Unfair Trade Practices Claim Based On The November 2003 Mailing at 21 ("In its April 2004 Warning Letter to Janssen, the FDA recognized the significant and detrimental impact of the November 2003 "Dear Doctor" letter on the South Carolina public: 'The healthcare community relies on [Dear Doctor] letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers is a *serious public health issue*.'").

Regardless of the State's public policy argument *du jour*, the State has nothing but speculative public policy concerns as the basis of its unfairness claim. The FTC Act, as well as the FTC's "unfairness" policy statement unequivocally confirm, however, that a violation of public policy alone is not a basis upon which the jury can find that the November 2003 mailing or the Risperdal package insert was an unfair trade practice. 15 U.S.C.A. § 45(n); FTC Policy Statement on Unfairness (1980). Similarly, a violation of public policy cannot be the primary basis upon which the jury can find that the November 2003 mailing was an unfair trade practice. 15 U.S.C.A. § 45(n). Because, after all the State's evidence is in, the State has nothing more than vague, conclusory assertions of a violation of an unspecified "public policy," the State's unfair trade practice claim may not be submitted to the jury.

D. Absence Of Sufficient Evidence To Establish That The Alleged Unfair Or Deceptive Trade Practices Adversely Affected The Public Interest.

The State is required to show that the challenged practice has the potential for repetition. Slip op. at 4 (Feb. 25, 2011). The potential for repetition may be proven by showing: (1) the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) the defendant's procedures created a potential for repetition of the unfair and deceptive acts. See, e.g., *Singleton v. Stokes Motors, Inc.*, 358 S.C. 369, 595 S.E.2d 461 (2004).

1. The November 2003 Mailing.

As to the November 2003 mailing, the State did not introduce any evidence that any similar kind of action occurred in the past. Nor did the State introduce any evidence that any procedure of Defendants created a potential for repetition. Indeed, the State introduced no evidence that any prior or subsequent letter to physicians ever has been challenged by anyone, including the FDA. In over a decade of communications with physicians as to the

risks of Risperdal, the single piece of correspondence challenged by the State is insufficient to establish that the November 2003 mailing "has the potential for repetition."

The January 5, 1999 DDMAC letter, which raised a concern, in the view of a DDMAC reviewer, about "a campaign that markets Risperdal for geriatric patients," Trial Ex. P200, is not sufficient evidence to satisfy SCUTPA's "capable of repetition" element under the decision of *Burbach v. Investors Management Corp.*, 326 S.C. 492, 484 S.E.2d 119 (Ct. App. 1997). Under *Burbach*, the January 5, 1999 DDMAC letter is insufficient – and inadmissible – evidence to satisfy the "capable of repetition" element because: (1) it was issued over five years before the 2004 warning letter; (2) there is no similarity whatsoever between the two letters; the 1999 letter concerned certain marketing materials in connection with geriatric patients and the 2004 warning letter concerned a mailing to healthcare professionals as to changes to the Risperdal package insert as to the risks of diabetes, hyperglycemia, and weight gain; and (3) in over sixteen years, these are the only two isolated instances where the FDA ever raised any concern as to Janssen's activities in relation to Risperdal. *Id.* at 498 n.3, 484 S.E.2d at 122 n.3.

2. The Risperdal Package Insert.

The State's Risperdal package insert claim suffers from the same lack of evidence. The evidence shows that, for more than sixteen years, the agency charged with determining the sufficiency and accuracy of the label, the FDA, never took any issue with the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. The State also could not identify a single Janssen "procedure" that purportedly would result in an unfair or deceptive Risperdal package insert in the future.

The mere fact that the challenged act or practice remains in effect, i.e., the Risperdal package insert remains in use, is insufficient to establish the essential element that the challenged practice be capable of repetition. See *Jefferies v. Phillips*, 316 S.C. 523, 529,

451 S.E.2d 21, 23-24 (Ct. App. 1994) ("In the course of human endeavor, every action has some potential for repetition. The mere proof that the actor is still alive and engaged in the same business is not sufficient to establish this element."); *see also Wilson Group, Inc. v. Quorum Health Res., Inc.*, 880 F. Supp. 416, 428 (D.S.C. 1995) ("There is no evidence in this case of other similar acts and, therefore, no basis to conclude that Quorum's alleged acts have the potential for repetition." (footnote omitted)).

In the absence of a showing that the challenged conduct has the potential for repetition, to establish a SCUTPA violation, the alleged unfair act or deceptive practice must affect the public interest. That is, the State also "must establish, *by specific facts*, that members of the public were adversely affected by the defendants'" alleged unfair trade practice. *Bessinger v. Food Lion Inc.*, 305 F. Supp. 574, 584 (D.S.C. 2003), *aff'd*, 119 F. App'x 636 (4th Cir. 2004) (emphasis added). But the mere invocation of such words as "public interest," "public policy," and "public health issue" by the State's experts, without specific facts supporting such conclusory statements, is insufficient. *Orangeburg Pecan Co. v. Farmers Inv. Co.*, 869 F. Supp. 2d 359, 362 (D.S.C. 1994) ("Plaintiff here has done little more than chant phrases like 'public interest' and 'public impact' without producing a shred of evidence that such alleged wrongdoing is capable of repetition, or was, in fact, repeated."); *see, e.g., Trial Tr. vol. IV, 760:7-9, Mar. 10, 2011* (Plunkett merely agreeing with State's counsel that DDMAC's 2004 letter says November mailing "creates a serious public health issue").

A SCUTPA claim cannot be speculative. Yet, the State presented no factual evidence that either the November 2003 mailing or the Risperdal package insert had an *actual* adverse affect on the public or on physicians. *See Trial Tr. vol. V, 993:16-994:8, 995:10-17, 999:3-8, 1024:21-1025:10* (Plunkett testifying that she had no contact with any South Carolina physicians regarding the Risperdal label or any of the matters that are the

subject of the lawsuit; no specific knowledge of any South Carolina resident experiencing hyperprolactinemia or diabetes after receiving Risperdal). At most, one of the State's experts testified that the November 2003 mailing it "potentially" was a serious public health issue. Trial Tr. vol. III, 473:17-20, Mar. 9, 2011 (testimony of Wirshing). As such, the failure of the State to establish the required SCUTPA element of an adverse impact on the public also precludes the submission of the State's case to the jury. See, e.g., *Omni Outdoor Adver. Inc. v Columbia Outdoor. Adver. Inc.*, 974 F.2d 502, 507 (4th Cir. 1992) ("Omni suggests that the practice of double billing inflates costs to the advertisers and hence to consumers. Omni, however, cites no evidence in the record to support this proposition. It offers no basis other than sheer speculation to conclude that the total advertising costs of the affected companies rose as a result of the alleged COA practices. South Carolina courts have consistently rejected speculative claims of adverse public impact and required evidentiary proof of such effects.") (citations omitted).

E. The State Has Failed To Introduce Sufficient Facts For The Jury To Find Willful Conduct.

The State also lacks sufficient evidence as to the essential element of a "willful" violation of SCUTPA. Under SCUTPA, a violation is willful only "when the party committing the violation knew or should have known that his conduct was a violation of [the South Carolina Unfair Trade Practices Act]." S.C. Code Ann. § 39-5-140(d). As held by South Carolina courts, conduct is willful for purposes of a SCUTPA violation only "[i]f in the exercise of due diligence, a person of ordinary prudence engaged in trade or commerce could have ascertained that his conduct violates the Act." *State ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 290 S.C. 124, 128, 348 S.E.2d 381, 384 (Ct. App. 1986) ("*Nest Egg*").

According to the State, to satisfy this requirement, "it is merely necessary to show that Defendants knew or should have known that the labeling was unfair or deceptive." See

Pl.'s Opp'n to Defs.' Mot. For Summ. J. As To Pl.'s Unfair Trade Practices Claim Based On The FDA-Approved Risperdal Package Insert at 18. But the limited South Carolina decisions interpreting this element of SCUTPA have interpreted the element of a willful violation far more narrowly – a violation is willful only where the defendant's conduct violated a specific South Carolina statute that expressly prohibits the precise practice that the Attorney General alleges is a violation of SCUTPA. See *Nest Egg*, 290 S.C. at 124, 348 S.E.2d at 381 (willful conduct was a pyramid scheme expressly proscribed by S.C. Code Ann. § 39-5-30). See generally *Gentry v. Yonce*, 337 S.C. 1, 12, 522 S.E.2d 137, 143 (1999) (“Advertising a jackpot over the statutory \$125 limit [set forth in S.C. Code Ann. § 39-5-30] is offensive and has a tendency to deceive a person into thinking that a jackpot over \$125 is legal.”). Even more significant, the South Carolina Supreme Court has made clear that a defendant's conduct is not willful if the conduct challenged as unfair or deceptive is not prohibited and there is evidence that the conduct challenged as unfair or deceptive is a common practice in the defendants' trade or business. *Haley Nursery Co., Inc. v. Forrest*, 298 S.C. 520, 525, 381 S.E.2d 906, 908 (1989) (“[Defendant's] conduct is not prohibited and there is evidence it is in accord with the common practice of the trade. Applying the statutory definition, we hold the record supports the trial judge's finding the violation was not willful.”).

The State presented no evidence that the Risperdal package insert was ever “prohibited” by the FDA or anyone else. The State's expert, in fact, acknowledged the contrary; the FDA has never taken any action as to the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. Further, not only is the use of a package insert in accord with the “common practice of the trade,” but it is required for prescription medicines such as Risperdal. See 21 U.S.C.A. § 355 (b)(1)(F) (new drug application shall include “specimens of the labeling proposed to be used for such drug”). Accordingly, the State has not

introduced any evidence from which a jury could find that Defendants committed a willful violation of SCUTPA in connection with the Risperdal package insert.

As to the November 2003 mailing, the State failed to introduce any evidence that Janssen knew or should have known that the statements in the mailing were false. States with statutes similar to SCUTPA that also impose a "willfulness" requirement have held that, at a minimum, a plaintiff must establish that a defendant knew or should have known that the representations challenged as deceptive were false. See, e.g., *Adamson v. Worldcom Commc'ns, Inc.*, 78 P.3d 577, 583 (Or. App. 2003) (for unlawful trade practices claim, for a willful violation, "it suffices that the defendant knew of the falsity of a representation, without knowing that the representation violated the law"); *State ex rel. Corbin v. United Energy Corp. of Am.*, 725 P.2d 752, 758-59 (Ariz. App. 1986) ("The evidence presented [as to willfulness] was sufficient for the jury to have concluded that appellants knew or should have known that the performance representations were false.").

Neither of the State's experts testified that the materials cited by Janssen in the November 2003 mailing did not support the statements made by Janssen. The testimony in fact was to the contrary. See Trial Tr. vol. III, 457:20-458:4, 613:15-614:4, Mar. 9, 2011 (Wirshing admitting that it was fair to say that the primary conclusion from the eight articles cited in the mailing were supportive "to a degree" of the middle paragraph of the November 2003 mailing; six of the eight articles support the statement that Risperdal has a lower diabetes risk than Zyprexa; and, while the word "infrequently" may not be the best word used in the November 2003 mailing to describe the occurrence rate for hyperglycemia, expert admitted that "it wasn't really common at any rate"). As such, any conduct as to the November 2003 mailing also was not "willful." Thus, the State also failed to introduce sufficient evidence for the jury to find that Defendants committed a willful violation of

SCUTPA in connection with either the Risperdal package insert or the November 2003 mailing.

F. The State's Entire SCUTPA Claim Is Barred By The Statute Of Limitations.

A SCUTPA claim must be filed no more than three years after discovery of the unlawful conduct. S.C. Code Ann. § 39-5-150. Any alleged "deception" as to the November 2003 mailing would have been apparent to any reader of the November 10 "Dear Healthcare Provider" letter, as the letter states *both* (1) Janssen's opinion as to the conclusions "suggest[ed]" by a certain "body of evidence from published peer-reviewed epidemiology research," *and* (2) the identification of – and citations to – that published peer-reviewed epidemiology research." See Trial Ex. P1736 (November 2003 mailing). Certainly, any of the physicians and other prescribers to whom the letter was addressed – and the State – had the ability to review the publicly available published studies to which Janssen pointed them and to "discover" any alleged deception in the opinion Janssen offered about them.³ As such, the limitations period began to run at the time of

³ In its February 25, 2011 Opinion, the Court stated that "the essential question before this Court is when the State Attorney General's Office would have become aware of 'unfair or deceptive acts or practices' in the Defendant's marketing and labeling actions relative to the sale of Risperdal." Slip op. at 6 (Feb. 25, 2011). The only South Carolina court to address the issue, however, held that the State is subject to the same principles governing the application of the statute of limitations as anyone else. *Willcox v. Stroup*, 358 B.R. 824 (D.S.C.), *aff'd*, 467 F.3d 409 (4th Cir. 2006). Similarly, another state court interpreting its consumer protection statute found that an attorney general is not entitled to preferential treatment in connection with stale claims. See *State of Delaware ex rel. Brady v. Pettinaro Enters.*, 870 A.2d 513, 532 (Del. Ch. 2005) ("Given the public policy underlying statutes of limitation in general – to compel timely pursuit of claims and to avoid the adjudication of stale claims – and these apt criminal law analogies, in particular – I cannot accept the State's strange argument that the [statute's] limitation period did not start to run until the Attorney General received complaints from consumers. To do so would be to condone torpor on the part of consumers, as well as the State itself."); *id.* at 533 ("I realize, of course, that as a practical matter, state agencies may be reliant on citizen complaints to trigger their investigations as to even blatantly unlawful conduct. But that reality does not allow the

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dissemination of the November 2003 mailing. See *Prestwick Golf Club, Inc. v. Prestwick Ltd. P'ship*, 331 S.C. 385, 393, 503 S.E.2d 184, 188 (Ct. App. 1998) (limitations period began to run on SCUTPA claim when defendant "announced its intention"); see also *Gibson v. Bank of Am., N.A.*, 383 S.C. 399, 407-08, 680 S.E.2d 778, 782-83 (Ct. App. 2009) (limitations period began to run at time of receipt of bank statements showing withdrawals that were the subject of claim). As the State did not file its original Complaint until April 23, 2007, the SCUTPA claim based on the November 2003 mailing is time-barred.

The State's package insert claim also is time-barred. According to the State's experts, the Risperdal package insert was "inadequate" from day one in 1994. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). Also according to the State's experts, the inadequacy of the Risperdal package insert as to the precise risks which the State alleges were inadequately disclosed could be predicted and were *known* based on: (1) the chemical compound of Risperdal itself; and (2) instances of weight gain, hyperglycemia, and hyperprolactinemia that were seen in the *pre-marketing clinical studies* of Risperdal. Trial Tr. vol. IV, 687:22-687:25, 691:16-23, 689:19-690:6, Mar. 10, 2011 (testimony of Plunkett); Trial Tr. vol. III, 475:24-477:23, 528:14-25 (Wirshing testifying that weight gain warning should have been made earlier based on pre-marketing clinical trials; risk of alpha toxicity "inherent in the molecule"; risk was known "[i]n the 80s"). The statute of limitations, therefore, began to run on the State's package insert claim at the time of the initial Risperdal package insert in 1994. *Prestwick Golf Club, Inc.*, 331 S.C. at 393, 503 S.E.2d at 188; see also *Gibson*, 383

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State the luxury to recline in a leather chair, believing that the statute of limitations will only run once some aggrieved citizen gets around to making a complaint." (footnote omitted)).

S.C. at 407-08, 680 S.E.2d at 782-83.⁴ As the alleged deceptive conduct occurred more than three years prior to the initiation of this action, the State's entire package insert claim is time-barred.

G. The State Has Failed To Introduce Sufficient Evidence For The Jury To Determine That Johnson & Johnson Is Liable For The Purported Violations Of SCUTPA.

Defendant Johnson & Johnson is named as, and is in fact, a separate corporate entity. See Second Am. Compl. Caption & ¶ 23. Johnson & Johnson is a holding company; it owns operating companies. Thus, the State has no evidence that Johnson & Johnson did anything that could give rise to liability. To impose liability on Johnson & Johnson for the acts of its subsidiary, defendant Janssen, the State would have to pierce the corporate veil. Application of the doctrine of piercing the corporate veil, however, is "not to be applied without substantial reflection" because "[i]f any general rule can be laid down, it is that a corporation will be looked upon as a legal entity until sufficient reason to the contrary appears." *Sturkie v. Sifly*, 280 S.C. 453, 457, 313 S.E.2d 316, 318 (Ct. App. 1984) (citation omitted).

A plaintiff who seeks to avoid the protections generally afforded corporations must satisfy a two-prong test. First, a number of eight factors must weigh in favor of piercing the veil; they are: (1) whether the subordinate corporation was grossly undercapitalized;

⁴ South Carolina courts consistently have rejected any argument that a statute of limitations is tolled based on alleged continuing conduct by a defendant. See *Epstein v. Brown*, 363 S.C. 372, 610 S.E.2d 816 (2005) (rejecting "continuous representation" argument to toll statute of limitations); *Harrison v. Bevilacqua*, 354 S.C. 129, 580 S.E.2d 109 (2003) (rejecting "continuous treatment" rule to toll statute of limitations); see also *Maher*, 331 S.C. 371, 384, 500 S.E.2d 204, 211 (Ct. App. 1998) ("The objective test in South Carolina's discovery rule is sufficient to allow plaintiffs the opportunity to discover and act upon the original breach, without need for application of the 'continuing wrong' doctrine in this situation.").

(2) whether the parent corporation observed corporate formalities; (3) whether the subordinate corporation paid dividends; (4) whether the subordinate corporation was insolvent at the time; (5) whether the parent corporation siphoned the funds of the subordinate corporation; (6) whether the subordinate corporation had non-functioning officers or directors; (7) whether the subordinate corporation maintained corporate records; and (8) whether the subordinate corporation was a facade for the operations of the parent. *Dumas v. InfoSafe Corp.*, 320 S.C. 188, 192, 463 S.E.2d 641, 643-44 (Ct. App. 1995) (citations omitted).

Second, the plaintiff must prove that "an element of injustice or fundamental unfairness [will be done] if the acts of the corporation be not regarded as the acts of the individuals [or parent]." *Id.*, 463 S.E.2d at 644 (internal quotations and citation omitted). "To prove fundamental unfairness, the plaintiff must establish that (1) the defendant was aware of the plaintiff's claim against the corporation, and (2) thereafter, the defendant acted in a self-serving manner with regard to the property of the corporation and in disregard of the plaintiff's claim in the property." *Id.* (citation omitted).

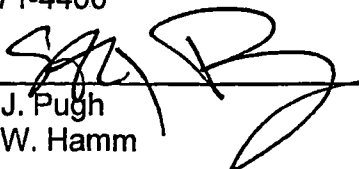
Here, the State has not attempted to introduce evidence that would satisfy even one of the initial eight factors that must be considered. In addition, the State did not introduce any evidence that an injustice or fundamental unfairness would be worked if Johnson & Johnson were not held liable for the purported violations of SCUTPA by Janssen – the sole defendant against whom the State has even attempted to introduce any "evidence."

V. CONCLUSION

For the foregoing reasons, Defendants respectfully request that this Court enter an Order granting a directed verdict in favor of Defendants and against Plaintiff on its sole remaining claim.

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March 14, 2011.

STATE OF SOUTH CAROLINA

COUNTY OF SPARTANBURG

STATE OF SOUTH CAROLINA
ex. rel. Alan Wilson, in his capacity
as Attorney General of the State of
South Carolina,

PLAINTIFF,

v.

ORTHO-MCNEIL-JANSSEN
PHARMACEUTICALS, INC., f/k/a
JANSSEN PHARMACEUTICA, INC.,
and/or JANSSEN, L.P., AND
JOHNSON & JOHNSON, INC.

DEFENDANTS.

IN THE COURT OF COMMON PLEAS

FOR THE SEVENTH JUDICIAL CIRCUIT

Civil Action No.: 2007-CP-42-1438

PLAINTIFF THE STATE OF SOUTH
CAROLINA'S RESPONSE IN
OPPOSITION TO DEFENDANTS'
MOTION FOR A DIRECTED VERDICT

RECEIVED
MAR 18 2011
BY: _____

TO: STEVEN J. PUGH, KENNETH A. MURPHY, EDWARD M. POSNER, AND
THOMAS F. CAMPION, ATTORNEYS FOR DEFENDANTS

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson,¹ in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Response in Opposition to the Motion for a Directed Verdict ("Motion") filed by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc. (collectively, "Janssen" or "Defendant"), and would respectfully show the Court as follows:

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J. HOPE BLACKLEY

¹ Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

I.
SUMMARY

As further described herein, the State has proven all elements of its claim under the South Carolina Unfair Trade Practices Act ("SCUTPA"), including the public impact and willful nature of Defendants' unfair and deceptive conduct in their product labeling. Further, the State's claim is not preempted by federal law nor is its labeling exempted from SCUTPA as actions or transactions permitted under laws administered by a regulatory body or officer acting under statutory authority of the United States. Moreover, the State's claim is not barred by the applicable statute of limitations. Additionally, the State has offered sufficient evidence to impose liability on all Defendants, including Johnson and Johnson. For the reasons outlined herein, the Court should deny Defendants' Motion in its entirety.

II.
PROCEDURAL HISTORY & FACTUAL BACKGROUND

A. Statement of the Case.

On April 23, 2007, the State initiated this action against Janssen, manufacturer of the atypical antipsychotic drug Risperdal, to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for Janssen's willful, deceptive, and unfair course of conduct in its product labeling. On March 19, 2010, the State filed its Second Amended Civil Action Complaint (hereinafter, "Amended Complaint"), petitioning the Court to assess against Janssen such penalties in an amount up to five thousand dollars for each "method, act or practice declared unlawful by § 39-5-20" and the willful use thereof. S.C. Code Ann. § 39-5-110(a). The State's Amended Complaint alleges, in brief, that Janssen: (1) "willfully engaged in a protracted, deceptive and unfair course of conduct in violation of SCUTPA" through its "labeling of Risperdal, which willfully, deceptively, and unfairly minimized, misrepresented, and/or

concealed the drug's dangerous side effects"; (2) "had actual knowledge that Risperdal causes weight gain" and "other severe adverse effects" upon product launch, but "failed to include a warning of the potential for weight gain and the possible development of diabetes as a result of the use of Risperdal in its U.S. labeling for many years," and "failed to warn adequately of these adverse effects," in all subsequent label changes; (3) was "chastised by the FDA for being brazenly 'false' and 'misleading'" in its Dear Doctor Letters by "[f]ailing to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the labeling; [m]inimizing the risks of potentially fatal hyperglycemia-related adverse events; [f]ailing to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible; and [m]isleadingly claiming that Risperdal is safer than other atypical antipsychotics"; and, (4) "made, and continue[s] to make, orally and in writing, false, misleading or deceptive representations," and "continue[s] to disseminate false, misleading, or deceptive information to the public . . . regarding the health risks and benefits associated with using Risperdal." (Pl.'s Second Am. Compl. ¶¶ 8, 13, 24, 26, 45, 46, 57, 58.)

III. ARGUMENT AND AUTHORITIES

"In ruling on a motion for directed verdict, the trial court must view the evidence and all its reasonable inferences in the light most favorable to the nonmoving party." *Wright v. Craft*, 640 S.E.2d 486, 501 (S.C. Ct. App. 2006); see *Long v. Norris & Assocs. Ltd.*, 538 S.E.2d 519 (S.C. Ct. App. 2000). A directed verdict in favor of the moving party is proper *only* when the evidence yields a single inference. *Id.* Alternatively, "the trial court *must* deny a motion for a directed verdict when the evidence yields more than one inference or its inference is in doubt." *Wright*, 640 S.E.2d at 501 (emphasis added); see *McMillan v. Oconee Mem'l Hosp., Inc.*, 626 S.E.2d 884, 886 (S.C. 2006); *Bailey v. Segars*, 550 S.E.2d 910, 913 (S.C. Ct. App. 2001); *Steinke*

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v. S.C. Dep't of Labor, Licensing & Regulation, 520 S.E.2d 142, 148 (S.C. 1999). Thus, “[i]f more than one inference can be drawn from the evidence, a jury issue is created and the motion should be denied and the case must be submitted to the jury.” *Id.*; see *Jinks v. Richland County*, 585 S.E.2d 281, 283 (S.C. 2003); *Long*, 538 S.E.2d at 9; *Adams v. G.J. Creel Sons, Inc.*, 465 S.E.2d 84, 85 (S.C. 1995).

A. The State’s SCUTPA Claim Stands On Its Own Under South Carolina Law and the Evidence Presented; It is not Preempted by Federal Law.

Defendants continue to misconstrue (intentionally so) the State’s statutory claim under South Carolina law as instead an impermissible private action brought to enforce the federal Food, Drug and Cosmetic Act (“FDCA”). *The Court will be overwhelmingly familiar with this argument as it has rejected it time* (Order of Sept. 22, 2009 (*South Carolina v. Eli Lilly & Co.*, 2007-CP-42-1855) at 20-23 (hereinafter “*Lilly Order*,” attached as Exhibit A)) *and time again* (Order of Feb. 25, 2011 at 19).

As did the defendant in *Lilly*, Defendants argue that the State’s SCUTPA claim is really a claim to enforce the labeling and promotional regulations of the FDCA, arguing (in particular) that the State’s evidence of the November 10, 2003 “Dear Doctor” letter is “inextricably intertwined” with the April 2004 FDA DDMAC warning letter. (Mot. at 5; *Lilly Order* at 20-23 (Ex. A).) Defendants rely on an out-of-context excerpt from the *Lilly Order*, which is surprising in light of this Court’s ultimately rejecting this very argument in *Lilly*. (Mot. at 4; *Lilly Order* at 23 (Ex. A).) Indeed, in *Lilly* the Court rightly recognized that “[t]o the extent that the Plaintiff[] allege[s] that the defendant[] made false statements or deliberately concealed material facts in order to mislead health care professionals and consumers about the safe[t]y of [the drug at issue], those claims are viable” (*Lilly Order* at 23 (quoting *In re Epogen & Aranesp Off-Label Mktg. & Sales Practices Litig.*, 590 F. Supp. 2d 1282, 1291 (C.D. Cal. 2008) (Ex. A).) The

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Court “refuse[d] to find that Plaintiff is seeking to bring a private cause of action under the U.S. Food[,] Drug and Cosmetics Act.” (*Lilly* Order at 23 (Ex. A).)

As in *Lilly*, the State here was entitled to and did present evidence of Defendants’ conduct in relation to their knowledge and notice of Risperdal’s safety risks, which goes to Defendants’ “willfulness” under S.C. Code Ann. 39-5-110(a). Proof of willfulness includes documents from or relating to their federal regulator, the FDA. Still, the State does not contend that those documents in and of themselves trigger a SCUTPA violation. Take the November 2003 “Dear Doctor” letter, for example:

1. The FDA informed Janssen no later than January 4, 1994, that any claims it made that Risperdal was safer or more effective than “other marketed antipsychotic drug product[s]” would be considered false and misleading. (Pl. Ex. 571.)
2. In September 1999, Janssen received the “Topline Results” of a randomized, double-blind, “gold standard,” year-long clinical study comparing Risperdal and Zyprexa to determine which drug was linked to greater incidence of diabetes and clinically significant weight gain. (Pl. Ex. 442.) The results showed no difference between Risperdal’s and Zyprexa’s respective diabetes and weight gain liabilities at the end of a year. (*Id.*; Trial Tr. at 434-35, 438-39 (attached as Exhibit B).) Trial 113 was never published. (Trial Tr. at 419 (Ex. B); Trial Tr. at 1318-1319 (Caers Dep. Cut at 403 (Ex. B)).)
3. In August 2000, Janssen had in its possession the results of the “ERI” study, showing increased incidence of diabetes and weight gain in Risperdal over Zyprexa. (Pl. Ex. 167; Trial Tr. at 721-24 (Ex. B)). Those unfavorable results of the ERI study were intentionally not disclosed. (Pl. Ex. 167; Trial Tr. at 725-27(Ex. B).)
4. In September 2003, the FDA informed Janssen of its intent to request that the manufacturers of antipsychotic drugs adopt a class label. (Pl. Ex. 520.)
5. Janssen responded to that request by issuing, in part, the November 10, 2003 “Dear Doctor” letter containing the following statements that were contrary to the facts set forth above: “Hyperglycemia-related adverse events have infrequently been reported in patients receiving Risperdal. Although confirmatory research is still needed, a body of evidence from peer-reviewed epidemiology research suggests that Risperdal is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotic drugs. Evidence also suggests that Risperdal is associated with a lower risk of diabetes than some other studied atypical antipsychotic drugs.” (Pl. Ex. 1836.)

Even without considering the April 2004 FDA DDMAC Warning Letter, the State has shown through competent evidence that the representations made in Janssen's November 10, 2003 "Dear Doctor" letter were deceptive and unfair under SCUTPA. Janssen had in its possession data from at least two studies—Trial 113 (Pl. Ex. 442) and ERI (Pl. Ex. 167)—that showed that Risperdal's association with diabetes was not infrequent (Trial Tr. (Mar. 9, 2011) at 457-58 (Ex. B).) Dr. William Wirshing, the State's psychiatrist and clinical studies expert, who was familiar with the Risperdal label at all times and had prescribed the drug hundreds of times each year, testified that the implication of the second sentence above—no association with an increased risk of diabetes as compared to untreated patients—was that Risperdal was "actually devoid of diabetic risk potential." (Trial Tr. at 350-51, 354, 458, 623.) But that implication was also deceptive and unfair based on what Janssen knew at the time about the results of Trial 113 and the ERI study, which it kept to itself. (*See* Nos. 2, 3, *supra*.) And, the suggestion that Risperdal had a lower risk of diabetes than other studied antipsychotic drugs only told half the story—Trial 113 and the ERI study showed that Risperdal had an equal or greater risk of diabetes and weight gain than Zyprexa. (*See* Nos. 2, 3, *supra*; Trial Tr. at 459 (Ex. B).) Based on that evidence alone, the representations about Risperdal in the November 10, 2003 "Dear Doctor" letter are deceptive and unfair under SCUTPA—they either tend to deceive, or they are offensive to public policy, immoral, unethical, or oppressive. *State ex rel. McLeod v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984); *Wright*, 640 S.E.2d at 500. The April 2004 Warning Letter is simply additional evidence that the "Dear Doctor" letter was deceptive—but it is far from the State's only evidence. Additionally, the fact that the FDA initially instructed Janssen not to compare Risperdal to its competitors (No. 1, *supra*), and that the FDA intended the 2004 label to cover "all atypical antipsychotics" (No. 4, *supra*) contributes to the evidence of willfulness of

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Janssen's conduct—i.e., whether Janssen knew or should have known not to make such statements and comparisons in the “Dear Doctor” letter in light of those circumstances.

In any event, Janssen's incredible statement—that “federal law provides that *only* the federal government may enforce federal drug labeling law and expressly prohibits attempts to use state law to enforce federal drug labeling law” (Mot. at 4)—is expressly contrary to the United States Supreme Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), which Defendants' Motion entirely ignores. The High Court ultimately held that state law offers an additional, and important, layer of consumer protection that complements FDA regulation. *Id.* at 1202-04. As importantly, the Court held that “it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.” *Id.* at 1197-98.² Defendants' reliance on *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001), does not dictate a different result because this is not a case in which the State asserts or relies on evidence of “fraud on the FDA”—i.e., fraud claims based solely on the disclosure requirements of the FDCA—as shown above. Indeed, proof of common law fraud is not required under SCUTPA, which “creates new substantive rights by making conduct unlawful that was not actionable under the common law.” *McLeod*, 313 S.E.2d at 338. Further, *Buckman* recognized that *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) carved out “state-law causes of action that parallel federal safety requirements.” *Buckman*, 531 U.S. at 353, which accords with *Wyeth v. Levine*.³

² In addition, this Court ruled in *Lilly* that “[b]ased upon Lilly's ability to make unilateral amendments to its labeling [under 21 C.F.R. §§ 201.57(e) and 314.70(c)(6)(iii)(A), (C), as well as *Wyeth v. Levine*] . . . this Court finds as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA.” (*Lilly* Order at 22-23 (Ex. A).)

³ For the same reasons, the State's claim based on evidence of the nondisclosure of the Trial 113 results is not preempted, as Defendants assert. (Mot. at 5 n.1.) Quite obviously, as illustrated in the discussion above,

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The State does not seek to punish Defendants for violating the FDCA or any federal law or regulation. The State's evidence on which the jury will decide Defendants violated SCUTPA depends not on the violation of federal laws, but on the application of South Carolina law to all the facts. Defendants' Motion should be denied.

B. Defendants Ignore Established Precedent of the United States Supreme Court, the South Carolina Supreme Court, and this Court in Maintaining That S.C. Code Ann. § 39-5-40 Establishes a "Safe Harbor" for Their Unfair and Deceptive Conduct in the Labeling of Risperdal.

Defendants brazenly seek to have this Court ignore established precedent of the United States Supreme Court and the South Carolina Supreme Court—as well as to overrule this Court's own orders and rulings—in arguing that their unfair and deceptive labeling practices are exempt from SCUTPA as actions or transactions *permitted* under laws administered by a regulatory body or officer acting under statutory authority of the United States. *See* S.C. Code Ann. § 39-5-40(a). In doing so, Defendants improperly rely on the FDA's August 22, 2008 revision to the applicable regulations enacted *after* the period for which the State is seeking civil penalties under SCUTPA. (*See* Mot. at 7.)

The South Carolina Legislature has specifically required that such actions or transactions be "permitted" under law in order to qualify for SCUTPA's narrow exemption, and it is unarguable that Defendants' misconduct does not fall within that category. Moreover, this Court refused to admit into evidence the very regulation on which Defendants now rely on relevance and unfair prejudice grounds, implicitly basing its ruling not only on the fact that the revision

Janssen's hiding the Trial 113 results most significantly demonstrates the knowledge that only Janssen possessed about the true nature of Risperdal's side-effect profile. Similarly, the State's allegations and evidence regarding marketing for non-approved ("off-label") uses is not focused on FDCA violations, but on the deceptive and unfair representations under SCUTPA made in marketing plans and materials themselves as compared to Janssen's knowledge of Risperdal's risks. Further, there is no such "off-label promotion claim" to bar based on any representations of counsel (*id.*)—i.e., the State does not seek to have the Court assess penalties for the number of times Defendants promoted Risperdal off-label.

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was adopted outside the relevant time period, but also in consideration of the High Court's rejection of this lesser standard in *Wyeth v. Levine*.⁴

Defendants, nevertheless, attempt to impose artificial limitations on SCUTPA enforcement powers established under South Carolina law through their unsubstantiated argument that Risperdal's deceptive labeling was essentially authorized by the FDA, and thus evades the reach of the State's legal enforcement powers, in that they had no "newly acquired information" or requisite "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under § 201.57(c)" sufficient to *permit* their use of a CBE submission to update their package insert. (Mot. at 7 (citing 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008).) Contrary to Defendants' assertions, the FDA's revision is not retroactive, but even assuming that it was, the High Court's reasoning in *Wyeth v. Levine* forecloses Defendants' position.

In *Wyeth*, the Court emphasized that despite recent amendments to the FDCA and to FDA regulations, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times," and "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." 129 S. Ct. at 1197-98. "Indeed, the 'complex and extensive' regulatory history and background relevant to this case . . . undercut the FDA's recent pronouncements of pre-emption, as they reveal the longstanding coexistence of state and federal law and the FDA's traditional recognition of state-law remedies." *Id.* at 1203. As in the case of Wyeth's Phenergan label, this recognition was in place each time the agency reviewed Defendants' Risperdal label. *See id.* Defendants, thus, had the opportunity to strengthen the warnings in their labeling *at any time* that they determined there was a reasonable association

⁴ See Trial Tr. at 1046-1051 (Ex. B.).

between Risperdal consumption and a serious hazard but continuously failed to take advantage of that regulatory self-help provision. *See* 21 C.F.R. § 201.57(e) (2006).

Therefore, it is unquestionable that *Wyeth* rejected Defendants' argument that because their prescription drug labeling was FDA-approved and regulated, the company could not comply with conflicting state law. And, this Court has found "***as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA.***" *Lilly*, slip op. at 23 (emphasis added) (Ex. A).

Based on the foregoing, Defendant's contentions are plainly unmeritorious and do not comport with controlling decisions by this and higher Courts. Consistent with that controlling precedent, the Court should deny Defendants' Motion.

C. The State Has Proven All Elements of Its SCUTPA claim.

Apparently abandoning their flawed, former attempts to convince this Court of "reliance" and "causation" elements purportedly required by SCUTPA § 39-5-110(a) in light of federal court interpretations of the Federal Trade Commission ("FTC") Act, Defendants nevertheless rely exclusively on a lone FTC case from the United States Court of Appeals for the Eleventh Circuit to establish the elements of a SCUTPA penalties claim. (Mot. at 11 (citing *FTC v. Tashman*, 318 F.3d 1273, 1277 (11th Cir. 2003).) Defendants then virtually ignore all other applicable South Carolina precedent, preferring to cite federal FTC cases to support their arguments that the State has not satisfied its evidentiary burden for proving deceptive and unfair trade practices under SCUTPA. Defendants' arguments fail, as discussed below.

1. The State Offered Ample Evidence Supporting Its Deceptive Trade Practices Claim.

Defendants then assert (1) that the State lacks an actionable representation under the cited FTC elements; (2) that the State has not shown the representation was likely to mislead (as

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opposed to having a “capacity” or “tendency to deceive” under South Carolina precedent, *McLeod*, 313 S.E.2d at 338); and (3) that the representation was material. (Mot. at 11.) Not only do Defendants improperly rely on federal as opposed to ample State precedent interpreting SCUTPA, each of the aforementioned elements is satisfactorily met.

(a) The Representations Offered by the State Are Actionable.

Although the State is only required to prove that a representation “had the capacity or effect or tendency to deceive,” *McLeod*, 313 S.E.2d at 338, the State also fulfilled the additional (overlapping) element Defendants impose in terms of identifying an “actionable representation.” The State has already demonstrated why the November 10, 2003 “Dear Doctor” letter is actionable under SCUTPA—i.e., that misrepresentations regarding Risperdal’s absence of diabetes risk in the “Dear Doctor” letter tended to deceive South Carolina physicians and patients. While Defendants disclosed some sources allegedly supporting their position that Risperdal was “devoid of diabetic risk potential” (Trial Tr. at 458), *Defendants nevertheless plainly omitted other information it had hidden from doctors, patients, the FDA, and the public at large that demonstrated a very real diabetes risk potential.* As this Court found in denying Defendants’ summary judgment motions, “[i]t appears from the November 2003 ‘Dear Doctor’ letter that Janssen may have actually taken affirmative action to confuse the issue, so as to hide the disparity between what was being told to the prescribing public and what its own professionals and experts knew.” (Order of Feb. 25, 2011 at 6.) The failure to disclose relevant information is actionable under SCUTPA. *See York v. Conway Ford, Inc.*, 480 S.E.2d 726, 727, 28 (S.C. 1997) (holding that the representation that a truck sold to plaintiff was a “like new” demonstrator that had never before been titled to an individual, while failing to disclose that the truck had a bent frame from a previous accident, was actionable under SCUTPA); *Inman v. Ken Hyatt Chrysler Plymouth, Inc.*, 363 S.E.2d 691, 692 (S.C. 1988) (selling repossessed vehicle as

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new without disclosure is a deceptive trade practice); *Estate of Carr v. Circle S Enters.*, 664 S.E.2d 83, 89 (S.C. Ct. App. 2008) (including in SCUTPA's ambit the "failure to disclose a material fact"); *Wright*, 640 S.E.2d at 499-500 (holding duty to disclose is applicable to a SCUTPA claim). Unlike the *Bruette v. Stokes, Kia, Isuzu, Subaru, Inc.* case Defendants cite, here there was no "equal and ample opportunity" for South Carolina doctors and their patients "to ascertain the truth" about the knowing, willful misrepresentations in the "Dear Doctor" letter because only Defendants possessed the relevant results of Trial 113 and the ERI study, which Defendants chose not to disclose.

The same holds true for Defendants' argument that the warnings in the package insert were not deceptive. For example, whether or not the label is based on judgments by Janssen and/or the FDA as to the significance of the scientific evidence, only Defendants had possession of the revealing Trial 113 and ERI results and opted to keep those results from public and regulatory view. The failure to disclose those results demonstrating a reasonable association with the serious hazards of diabetes/hyperglycemia and weight gain permitted Janssen to steer clear of strengthening Risperdal's warnings—a requirement that Janssen desperately sought to avoid. (*See, e.g.*, Pl. Ex. 254, 1105, 1264, 1552, 2651, Trial Tr. at 670-71, 778-81, 788-90, 791-95, 871-73 (Ex. B.).)

In sum, notwithstanding Janssen's characterizations that its November 10, 2003 "Dear Doctor" letter and labels were "reasonable expressions of scientific opinion," that argument wholly ignores the inherent deception in Janssen's failure to disclose fully what it knew to be the true attendant health risks of consuming Risperdal. This is not a matter of "scientific debate," as Janssen seeks to convince the jury and Court. This is a matter of a drug company withholding

vital safety information in order to maintain its market status. As such, the conduct is actionable under SCUTPA for the reasons shown above.

(b) The State Proved Tendency to Deceive.

Defendants again seek to convince this Court that in order to prove a tendency to deceive, the State must show, for example, that the November 10, 2003 “Dear Doctor” letter and the Risperdal labels “actually deceived or were ‘likely to deceive’” South Carolina physicians. (Mot. at 14.) That, however, is not the law in South Carolina, as the Court knows. “[T]here is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive.” *McLeod*, 313 S.E.2d at 338 (citing *Federal Trade Comm’n v. Algoma Lumber Co.*, 291 U.S. 67 (1934); *D.D.D. Corp. v. Federal Trade Comm’n*, 125 F.2d 679 (7th Cir. 1942)); *see also Dowd v. Imperial Chrysler-Plymouth, Inc.*, 381 S.E.2d 212, 213-214 (S.C. Ct. App. 1989) (“To recover for fraud, the familiar [sic] nine elements must be proved ‘by clear, cogent, and convincing evidence.’ No such proof is required to recover under [SCUTPA].”)

Further, contrary to Defendants’ assertions, the State’s psychiatrist expert, Dr. Wirshing, did not take “the position that the November 2003 mailing was somehow inherently ‘deceptive’ and that the Risperdal package insert was ‘inadequate’ as to certain risks.” (Mot. at 14.) Instead, Dr. Wirshing explained in great detail the bases for each of his opinions that the November 10, 2003 “Dear Doctor” letter and the package insert were deceptive and untrue. (*See, e.g.*, Trial Transcript at 358 (Dr. Haas’s statement that Janssen first warned of weight gain risk in 1994 label was untrue, no warning contained in that label); *id.* at 458 (Janssen statement that Risperdal has no increased risk of diabetes as compared to untreated patients was untrue because of potential for clinically significant weight gain, which axiomatically increases diabetes risk); *id.* at 459 (Janssen’s assertion that Risperdal was devoid of diabetes risk was untrue based on Trial 113 and

other evidence); *id.* (assertion that Risperdal had lower diabetes risk was untrue based on Trial 113); *id.* at 484 (Nov. 10, 2003 “Dear Doctor” letter omitting material information and reference list was “far from exhaustive”); *id.* at 521 (sales materials characterizing Zyprexa as having diabetes risk and Risperdal as not having that risk were untrue in light of Trial 113 results); *id.* at 525-26 (assertion that Risperdal has zero percent association with diabetes in double-blind trials was untrue given previously revealed 2.8% diabetes risk and Trial 113 results).) Such testimony is far from “speculation of experts,” as Janssen attempts to characterize it. There is sufficient evidence for the jury to determine finally whether Defendants’ representations regarding Risperdal had a tendency to deceive.

(c) Materiality Is Simply Not a Required Element of the State’s Claim.

Devoid of support in the South Carolina case law, Defendants’ three-sentence argument that the State failed to prove that the November 2003 mailing or the Risperdal package insert were “material” to any prescribing decision by any South Carolina doctor must fail. “Materiality” sounds like code language for “reliance” or “causation,” neither of which the State is required to prove, as shown above. All that need be shown is a “tendency to deceive,” as amply repeated above and in the State’s previous filings.

2. The State Offered Sufficient Evidence of its Unfair Trade Practices Claim.

Again choosing to rely on extra-jurisdictional case law, Defendants suggest that the Court follow Tennessee law to interpret SCUTPA, and ignore the State’s previously cited, applicable South Carolina precedents. The overriding concern of SCUTPA is not which person in particular (consumer or otherwise) received or was affected by a deceptive representation about a product, but is instead unfairness or deception “in the conduct of any trade or commerce . . .” *that affects the public interest generally.* S.C. Code Ann. § 39-5-20(a) (2009); *see Bessinger v. Food Lion, Inc.*, 305 F. Supp. 2d 574, 582 (D.S.C. 2003) (“[SCUTPA] is not available to redress

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a private wrong where the public interest is unaffected.”); *Noack Enters., Inc. v. Country Corner Interiors of Hilton Head Island, Inc.*, 351 S.E.2d 347, 349 (S.C. Ct. App. 1986) (“The legislature’s intent [was] to limit the application of the [SC]UTPA to only those unfair or deceptive acts or practices in the conduct of trade or commerce *that affect the public interest . . .*”) (emphasis added). To prove the unfairness of Defendants’ conduct, all the State need to have shown to recover penalties under section 39-5-110 is that Defendants willfully committed *unfair* trade practices that affected the public interest. See S.C. Code Ann. §§ 39-5-20, 39-5-110 (2009). “An unfair trade practice has been defined as a practice which is **offensive to public policy** or which is **immoral, unethical, or oppressive**.” *Wright*, 640 S.E.2d at 500 (emphasis added); see *Bessinger*, 305 F. Supp. 2d at 582 (construing SCUTPA—per section 39-5-20(b)⁵—in accordance with the Federal Trade Commission Act, under which courts have determined that a practice is *unfair* when it “offends established public policy and when the practice is immoral, unethical, oppressive, unscrupulous, or substantially injurious to consumers”); accord *Dowd*, 381 S.E.2d at 214 (holding that, in order to impact the public interest, unfair or deceptive acts or practices in the conduct of trade or commerce must simply have “the *potential* for repetition”) (emphasis added) (citations omitted).⁶

This Court, in fact, already recognized and upheld the critical public interests underlying these SCUTPA actions in *Lilly*:

⁵ It is the intent of the legislature that in construing paragraph (a) of this section the courts will be guided by the interpretations given by the Federal Trade Commission and the Federal Courts to § 5(a)(1) of the Federal Trade Commission Act (15 U.S.C. 45(a)(1)), as from time to time amended.

S.C. Code Ann. § 39-5-20(b).

⁶ “The potential for repetition may be demonstrated in either of two ways: (1) by showing the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) by showing the company’s procedures create a potential for repetition of the unfair and deceptive acts.” *Wright*, 640 S.E.2d at 502. Of course, “[those] two ways are not the only means for showing the potential for repetition or public impact, and each case must be evaluated on its own merits[.]” *Id.* A “plaintiff need not allege or prove anything further in relation to the public interest[.]” *Crary v. Djebelli*, 496 S.E.2d 21, 23 (S.C. 1998).

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I am surprised by the fact that most of the members of the public who are involved in this case are economically disadvantaged individuals who suffer from such debilitating conditions as schizophrenia, bi-polar mania, [and] [A]lzheimer[']s, [are] children, and [suffer from] dementia. They were in these [Medicaid] programs because they could not pay for or arrange their own care. In other words, they were unable to care for themselves.

When looking at the purpose of SCUTPA, one comes to the conclusion that the legislature intended [to] cast a wide net for causes of action in order to prevent and discourage deceit and fraud perpetrated on both the public at large and the business community of this state. It is clear that the legislature speaks in broad terms as to the activities that it seeks to make actionable and allows various avenues of enforcement of its prohibitions. Once a deceptive or unfair act in the commerce of this state is identified as affecting the public interest as a whole, and as such, the act is capable of repetition; then it would seem that the legislature seeks broad enforcement of the act.

In reviewing the above issues I found that the discussion in City of Charleston, S.C. v. Hotels.com, LP, 520 F.Supp.2d 757 (D.S.C. 2007) is relevant concerning the broad enforcement of SCUTPA. In that case the City of Charleston brought action against Hotels.com under the SCUTPA for charging consumers, on a national basis, a hospitality tax which it represented to be for a City tax. Instead of remitting the funds to the City (which it was under no apparent obligation to do in the first place) Hotels.com kept the funds and thus collected [them] as additional profit. Charleston was not a party to the transactions, had no right to collect the tax, and had no contractual connection with Hotels[.com]. In determining the legislative intent of SCUTPA and whether it would apply to this relationship, Judge Duffy held that the [d]efendants are clearly involved in trade and commercial activity of the type that legislators intended to regulate by enacting SCUTPA. He took this action in spite of the lack of a close connection between the city and the defendant and the fact that the victims could have protected themselves. *It appears he looked to the nature of the wrong and its relationship to public policy and considerations in find[ing] the City could proceed. In reviewing SCUTPA as a whole it is clear to me that the legislature intended to provide many avenues for the enforcement of its prohibitions.*

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(Lilly Order at 27-28 (Ex. A) (emphases added).) In line with Defendants' acknowledgement that "[p]ractices that unreasonably interfere with consumer decision-making include (1)

withholding information from consumers,” and (2) “exercising undue influence over a highly susceptible class of consumers” (Mot. at 16 (citation omitted)), this Court should find that the State has met its evidentiary burden for proving unfair conduct in violation of SCUTPA under relevant South Carolina case law.

D. The State Has Proven Public Impact of Defendants’ Unfair and Deceptive Trade Practices Under SCUTPA.

Despite Defendants’ claim that “the State did not introduce sufficient evidence to satisfy the element that the alleged unfair or deceptive trade practice adversely affected the public interest,” South Carolina law and applicable federal law do not require the State to prove “actual” impact, but, rather, that the alleged unfair or deceptive act or practice had the mere *potential* for repetition, at most—which the State has decidedly demonstrated. (Mot. at 3; *see also id.* at 18-21.) With respect to its impact on the public, this Court has already ruled that labeling, promotions, and other such communications by a pharmaceutical manufacturer to the public, including prescribing physicians, are of “considerable importance” to the State, the public and the medical community. *Lilly*, 2007-CP-42-1855, at *18-20. (*See* discussion, *supra* at III.C.2.) Beyond that, the State is not required to proffer evidence of the November 2003 “Dear Doctor” letter’s or the Risperdal package insert’s “actual” public impact for its dissemination to be actionable under SCUTPA.

Rather, and as Janssen acknowledges (despite its contemporaneous contention that the State’s claim must fail because it, allegedly, “presented no factual evidence that either, the November 2003 mailing or the Risperdal package insert had an *actual* adverse affect on the public or on physicians,” Mot. at 20), “[a]n impact on the public interest may be shown if the acts or practices have the potential for repetition.” *Wright*, 640 S.E.2d at 501; *accord Dowd v. Imperial Chrysler-Plymouth, Inc.*, 381 S.E.2d 212, 214 (S.C. Ct. App. 1989) (holding that, in

order to impact the public interest, unfair or deceptive acts or practices in the conduct of trade or commerce must simply have “the *potential* for repetition”) (emphasis added) (citations omitted). “The potential for repetition may be demonstrated in either of two ways: (1) by showing the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) by showing the company’s procedures create a potential for repetition of the unfair and deceptive acts.” *Id.* at 502. Of course, “[t]hese two ways are not the only means for showing the potential for repetition or public impact, and each case must be evaluated on its own merits[.]” *Id.*; accord *Crary v. Djebelli*, 496 S.E.2d 21, 23 (S.C. 1998). A “plaintiff need not allege or prove anything further in relation to the public interest[.]” *Crary*, 496 S.E.2d at 23.

Indeed, the purpose of the “public impact” requirement is simply to exempt actions for *private* wrong where the public interest is unaffected. See *Noack Enters., Inc. v. Country Corner Interiors of Hilton Head Island, Inc.*, 351 S.E.2d 347, 349-50 (S.C. Ct. App. 1986); see also *Wright*, 640 S.E.2d at 501 (“Since 1986, South Carolina courts have required that a Plaintiff bringing a private cause of action under UTPA allege and prove the defendant’s actions adversely affected the public interest.” (quoting *Daisy Outdoor Adver. Co. v. Abbott*, 473 S.E.2d 47, 49 (S.C. 1996))). Therefore, the South Carolina Supreme Court has “***expressly reject[ed]*** ***any rigid, bright line test*** that delineates in minute detail exactly what a plaintiff must show to satisfy the potential for repetition/public impact.” *Daisy*, 473 S.E.2d at 51 (emphasis added).

In that connection, the State has proffered “impact evidence” sufficient to show that the dissemination of the November 2003 “Dear Doctor” letter to thousands of South Carolina prescribing physicians⁷ and related deceptive labeling was offensive to and affected the public

⁷ See Trial Tr. at 1317 (“And the defendant stipulates that based upon their available distribution list there were 7,194 copies of [the November 2003 “Dear Doctor” letter] sent to addresses of physicians in South Carolina.”) (Ex. B.).

interest in misleading the public, and in particular the South Carolina medical community, by “fail[ing] to disclose the addition of information relating to hyperglycemia and diabetes mellitus to the approved product labeling”⁸; “minimiz[ing] the risk of hyperglycemia-related adverse events, which . . . is associated with serious adverse events including ketoacidosis, hypersmolar coma, and death”⁹; “fail[ing] to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible”¹⁰; and, “misleadingly claim[ing] that Risperdal is safer than other atypical antipsychotics,”¹¹ despite the FDA’s unequivocal instruction that all product labeling be updated to include information about diabetes mellitus adverse events.¹²

For example, in its April 2004 Warning Letter to Janssen, the FDA recognized the significant and detrimental impact of the November 2003 “Dear Doctor” letter on the South Carolina public:

The healthcare community relies on [“Dear Doctor”] letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers *is a serious public health issue*.¹³

Relative to the Risperdal labeling, or package insert, the State has also introduced evidence of the extent to which the South Carolina public was impacted by Defendants’ false and misleading labeling and the extent to which Defendants’ actionable conduct was repetitious. Through the testimony of Dr. David Patterson, for example, the State presented evidence of the

⁸ Pl. Ex. 1729.

⁹ *Id.*

¹⁰ *Id.*

¹¹ *Id.*

¹² Pl. Ex. 520.

¹³ Pl. Ex. 1729 (emphasis added).

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accurate number of Risperdal prescriptions filled in the State of South Carolina between 1994 and 2007, which included, *inter alia*, numerous prescriptions for particular patient populations to which Defendants most heavily promoted Risperdal through their labeling during the relevant time period, as described more fully above.¹⁴ With each such prescription, Defendants' false and misleading labeling was disseminated.¹⁵

The South Carolina Supreme Court has determined that evidence such as the foregoing is particularly responsive to the public impact requirement of SCUTPA. *See, e.g., Daisy*, 473 S.E.2d at 50. It has found that evidence of other instances of the alleged deceptive or unfair conduct at issue is "directly relevant to UTPA's public interest requirement" and "[establishes] a potential for repetition of the defendant's unfair and deceptive acts." *Id.* More specifically, the Supreme Court has held that the potential for repetition requirement is satisfied where the unfair or deceptive communication at issue has been repeated through publication to other consumers, as has Defendants' Risperdal labeling. *See Haley Nursery Co. v. Forrest*, 381 S.E.2d 906, 908 (S.C. 1989).

Thus, contrary to Defendants' arguments, SCUTPA does not condition the prosecution of a government enforcement action under section 39-5-110 upon demonstration of actual public impact, and the State has presented evidence sufficient to demonstrate that Defendants' Risperdal labeling, including the dissemination of the November 2003 "Dear Doctor" letter, had the potential for repetition, was repeated to numerous consumers and did impact the South Carolina public. *See Wright*, 640 S.E.2d at 501-02; *Dowd*, 381 S.E.2d at 214.

¹⁴ See Pl. Ex. 2670; Pl. Ex. 2671; Pl. Ex. 2672; Trial Tr. at 1292-1307 (Ex. B.).

¹⁵ See Trial Tr. at 1061-1075, 1084-85 (Ex. B.).

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E. Defendants' Conduct Was Willful.

The State has already demonstrated above how Defendants' actual or constructive knowledge that it was violating FDA regulations and instructions is proof of willfulness. (See discussion, *supra* at III.C.) Despite Defendants' persistent efforts to impose additional SCUTPA burdens of proof on the State, the express language of the applicable statute, S.C. Code Ann. § 39-5-110(c), requires only that Defendants "knew or should have known that [their] conduct was a violation of § 39-5-20." Defendants argue that the State must additionally show that the conduct was "prohibited." Yet, the flipside of that argument is that Defendants fail to explain satisfactorily how Risperdal's labeling would qualify as "permitted" for purposes of statutory exemption in light of their willful refusal to strengthen Risperdal's warnings section in the labeling, as they were required to do by the FDA, once they became aware of reasonable evidence of an association between Risperdal use and a serious hazard. 21 C.F.R. § 201.57(e) (2006). (See discussion, *supra* at III.B.) More specifically, Risperdal labeling contained false and misleading information, and omitted true information, since the drug's launch in the United States. (See, e.g., Pl. Ex. 1712, Trial Tr. at 357-58, 624-25, 708-710, 843-45 (Ex. B).) Defendants' conduct with respect to the representations in the labeling was "willful" under the statute because it is merely necessary to show that Defendants knew or should have known that the labeling was unfair or deceptive. S.C. Code Ann. §§ 39-5-20, 39-5-110(c). And, most importantly for purposes of this discussion, Defendants had the opportunity to strengthen the warnings in the labeling at any time that they determined there was a reasonable association between Risperdal consumption and a serious hazard. See 21 C.F.R. § 201.57(e) (2006). But, Defendants continuously failed to take advantage of that regulatory self-help provision.

Accordingly, this Court rejected defendant's virtually identical arguments in *Lilly* "[b]ased on [defendant's] ability to make unilateral amendments to its labeling and the further facts concerning [its] marketing and labeling methods which have been demonstrated to this Court as being in controversy." (*Lilly* Order at 22-23 (Ex. A).) The fact that the FDA had intermediately "approved" Zyprexa's labeling, therefore, did not absolve Lilly from its duty to update the labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." See 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); accord *Wyeth*, 129 S. Ct. at 1197 (2009). Janssen's failure to do so here, in view of overwhelming evidence in support of such a labeling change, was willful in that Janssen knew or should have known its conduct would violate SCUTPA.

F. The State's SCUTPA Claims Are Not Time-Barred by General or Anecdotal Knowledge of Risperdal's Side-Effect Profile.

Janssen misapprehends the State's claims and the appurtenant trigger that commences the running of the statute of limitations period. In attempts to divert this Court's attention from the State's actual or constructive knowledge of Janssen's wrongful conduct in South Carolina, which would start the limitations period, Janssen remarkably contends that the very publications for which the State seeks civil penalties under SCUTPA for being "false" and "misleading"—the November 2003 "Dear Doctor" letter and Risperdal labeling, more generally—commenced the running of the limitations period under SCUTPA, thus barring the State's claims. Janssen bases its unsuccessful argument on two flawed premises: that, allegedly, "any of the physicians and other prescribers to whom the letter was addressed—and the State—had the ability to review the publically-available published studies to which Janssen pointed them and to 'discover' any alleged deception in the opinion Janssen offered about them"; and, relative to Risperdal labeling,

more generally, that the State's experts—pharmacologist, toxicologist, and regulatory expert, Dr. Laura Plunkett, and psychiatrist, Dr. William Wirshing—could have known of the risks associated with Risperdal based on “the chemical compound of Risperdal itself,” and “instances of weight gain, hyperglycemia, and hyperprolactinemia that were seen in the pre-marketing clinical studies of Risperdal.” (Mot. at 24-25.) Janssen's arguments are unsound and belied by the fact that the publically-available published studies to which Janssen cited were admittedly flawed, company-sponsored, or otherwise unreliable, as well as the fact that even if industry experts or medical professionals could have had requisite knowledge, their knowledge is immaterial to what the *State* knew relative to Risperdal's safety profile prior to commencing this action.

Moreover, this issue has already been decided authoritatively by this Court. Denying Janssen's motions for summary judgment and concluding that the State is not barred from proceeding under the applicable statute of limitations, the Court distinguished the State's requisite knowledge of “[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce . . . in the Defendants' marketing and labeling relative to the sale of Risperdal,” from “medical professionals' . . . concern[s] about the side effects of the drugs in question.” (Order, Feb. 25, 2011, at 6.) The Court further emphasized that “the essential question . . . is when the State Attorney General's Office would have become aware of ‘unfair or deceptive acts or practices’ in the Defendants' marketing and labeling [of Risperdal]”—not when “the medical community nationally and in this State [would have become] aware.” (*Id.*) Additionally, the Court considered that “Janssen may have actually taken affirmative action to confuse the issue, so as to hide the disparity between what was being told to the prescribing public and what its own professionals and experts knew” relative to Risperdal's

true safety profile, and that “[t]his could in some situations even justify an equitable tolling of the Statute of Limitations.”¹⁶ (*Id.*)

Similarly, in the *Lilly* case, the Court opined that “[k]nowledge by the State that” a prescription drug “may have contributed to weight gain, diabetes, or related diseases . . . does not place the State on notice that [the defendant] is involved in any of the enumerated wrongful acts.” *Lilly*, slip op. at 10 (Ex. A.) More specifically, the Court detailed the applicable statute of limitations, attendant to the “discovery rule,” which runs from the date the injured party either knows or should have known by the exercise of reasonable diligence that *a cause of action arises from the wrongful conduct* of the defendant. *See id.* at *9 (citing S.C. Code Ann. § 15-3-535 (Supp. 2007); *Burgess v. Am. Cancer Soc’y, South Carolina Div., Inc.*, 386 S.E.2d 798, 800 (S.C. Ct. App. 1989); *Epstein v. Brown*, 610 S.E.2d 816, 818 (S.C. 2005)) (emphasis added). The Court emphasized that the State’s acquisition of bits and pieces of anecdotal information about Zyprexa prior to the filing of its Original Complaint is insufficient to trigger the running of the statute. *Lilly*, slip op. at 11. Without “facts concerning the . . . specified incidences of

¹⁶ As this Court acknowledged, even it could find that the State tardily filed its Complaint in this lawsuit—which for clear reasons amply described herein it did not—the doctrines of equitable estoppel and/or equitable tolling nevertheless permit the State to bring its claims. Because Janssen’s intentionally deceptive conduct was designed to avoid detection, Janssen is equitably stopped from asserting a limitations defense and/or the applicable limitations period is equitably tolled. *See Hooper v. Ebenezer Senior Servs. & Rehab. Ctr.*, 659 S.E.2d 213, 225 (S.C. Ct. App. 2008) (“A defendant will be estopped to assert the statute of limitations in bar of a plaintiff’s claim when the delay that otherwise would give operation to the statute has been induced by the defendant’s conduct.”). Moreover, “[s]ilence, when it is intended, or when it has the effect of misleading a party, may operate as equitable estoppel.” *Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 339 (S.C. Ct. App. 2001).

With respect to equitable tolling, the Court of Appeals of South Carolina observed that “[i]t has been held that equitable tolling applies principally if the plaintiff is actively misled by the defendant about the cause of action, or is prevented in some extraordinary way from asserting his or her rights.” *Hooper*, 659 S.E.2d at 221. “[T]he equitable tolling doctrine does not require wrongful conduct on the part of the defendant, such as fraud or misrepresentation.” *Id.*

Janssen’s false representations, concealment of material facts, and knowledge of the true facts, intending to mislead the State about any cause of action it may have had against Janssen, demands the application of the equitable estoppel or equitable tolling doctrines here. Given the scope of deceptive activities in which Janssen engaged as described herein, the Court should necessarily find that the applicable statute of limitations period is equitably tolled and/or that Janssen is equitably stopped from asserting its statute of limitations defense.

wrongdoing, of which the State was aware or should have been aware prior to February 27, 2004 or 2005,” defendant’s argument that the statute had been triggered in 2004, and had run, would fail. *Id.* Indeed, “[t]he burden of establishing the bar of the statute of limitations rests upon the one interposing it” *Turner v. Milliman*, 671 S.E.2d 636, 641 (S.C. Ct. App. 2009). “The limitations period is intended to run against those who are neglectful of their rights and who fail to exercise reasonable diligence in enforcing their rights. However, it is not the policy of the law to unjustly deprive an injured person of a remedy.” *Moriarty v. Garden Sanctuary Church*, 534 S.E.2d 672, 679 (S.C. 2000).

But, Janssen boldly ignores this Court’s prior order denying defendant’s Motion for Summary Judgment on Statute of Limitations Grounds in *Lilly*:

The information cited by Lilly stating that the Plaintiff should have been on notice that it had a claim or potentially had a claim is *separate and distinct from the wrongs alleged by the State. Knowledge by the State that Zyprexa may have contributed to weight gain, diabetes or related diseases . . . does not place the State on notice* that Lilly is involved in any of the enumerated wrongful acts above[.]

which include

deceptive promotions, misrepresentations and concealment of information about the safety and efficacy of Zyprexa.

Further, *the anecdotal information . . . does not rise to the level of putting the State on notice* that Lilly was involved in any of the above specified wrongs.

* * *

In this case at the very least there is a substantial conflict of evidence as to the date upon which the statute of limitations would have begun to run. In such cases, “*where there is conflicting testimony regarding the time of discovery, it becomes an issue for the jury to decide.*” *Arrant v. Kressler*, 489 S.E.2d 206 (S.C. 1997).

Lilly, slip op. at 10-11 (emphases added).

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Accordingly, Janssen's conclusory assertion that by virtue of the November 2003 "Dear Doctor" letter and well as industry and medical experts' purported notice, the State was on notice, or should have been on notice, at that time, of Janssen's wrongdoing with respect to its labeling of Risperdal, is entirely incommensurate with the Court's prior rulings in this regard and should be rejected. Like defendant's failed argument in *Lilly*, Janssen "reveals *no facts* concerning the . . . *specified incidences of wrongdoing*, of which *the State* was aware or should have been aware," prior to February 2004. *Lilly*, slip op. at 11 (emphases added).

Rather, Janssen claims, without more, that because Drs. Plunkett and Wirshing (allegedly) could have had knowledge of the misrepresentations in Janssen's labeling, the State should also have had such knowledge at the time they were first made. (See Mot. at 25.) In addition, Janssen speculates that "any reader" of the November 2003 "Dear Doctor" letter, including the State, knew or should have known that a cause of action arose from Janssen's willful, deceptive and unfair course of conduct in violation of SCUTPA upon its dissemination, purely because they, allegedly, "had the ability to review the publicly-available published studies to which Janssen pointed them." (Mot. at 24.)

Fundamentally, Janssen fails to show, if and when the State had notice of the November 2003 "Dear Doctor" letter *at all*—e.g., there is no testimony that the letter was ever received or read by any State official that would even approach "notice" for purposes of triggering the limitations period. Moreover, the mere fact that the November 2003 "Dear Doctor" letter references "publicly-available published studies" is wholly insufficient to show what the State and its healthcare providers knew, or should have known, relative to Janssen's misrepresentations *and when they knew it*, so as to trigger the running of the statute. Janssen's reference to these publications—the majority of which are *Janssen-sponsored* and some of which

do not stand for the proposition for which Janssen claims in its letter—has no bearing on the State’s discovery at that time or at any other time thereafter, and, if anything, only advanced the misrepresentations in the November 2003 “Dear Doctor” letter. Drs. Plunkett and Wirshing have testified regarding the same.¹⁷

In order to charge the State with notice of Janssen’s wrongdoings by way of publication, the referenced publications must be of sufficient “widespread publicity and awareness” to place the State on notice of the *particularized harm* that it seeks to redress. *See Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 333-34, 337-38 (S.C. Ct. App. 2001) (holding that plaintiffs’ claims would be barred by the applicable statute of limitations only where “the record is *replete* with *uncontested evidence of widespread publicity and awareness of the alleged [wrongdoing]*,” combined with (1) plaintiffs’ “*affidavits affirm[ing] that [p]laintiffs knew*,” prior to the running of the statute of limitations “of the alleged problems concerning” defendants’ plant emitting environmental pollution, the basis of plaintiffs’ nuisance causes of action, and *affirming that plaintiffs ‘felt that they had claims arising out of [defendant’s] operation of the facility for injuries to their person and property’*”; and, with (2) the “permanency of the claimed property damages”) (emphases added); *see id.* at 333-34 (“widespread publicity” included “widespread . . . community concerns and allegations that the plant was the alleged source of personal injury and property damage in the surrounding areas,” “community forums, town meetings, government involvement, local political debates, door-to-door communications, media coverage, grassroots organization initiated by local citizens groups, and lawsuits brought by hundreds of residents . . . who . . . were friends, neighbors, and, in many instances, relatives of [p]laintiffs,” in the action at bar, *inter alia*). Janssen’s labeling-based publications, like its Motion, are clearly devoid of evidence of “widespread publicity and awareness” of its illegal conduct in South Carolina.

¹⁷ See Trial Tr. (3/8/11), at 746-748 (Plunkett) (Ex. B); Trial Tr. (3/9/11), at 455-465 (Wirshing) (Ex. B).

Further, Janssen's Motion fails to squarely address *misrepresentations and concealed information in the November 2003 "Dear Doctor" letter and product labeling*—the very “specified incidences of wrongdoing” of which the State was allegedly aware. *See id.*

In sum, Janssen wholly fails to tie to the State any alleged notice of such *actionable offenses in South Carolina causing the State injury*, or legitimately explain how with reasonable diligence the State should have known of such allegations through the November 2003 “Dear Doctor” letter, the product labeling, or otherwise, as it must.

For purposes of the limitations period, the State was arguably not aware of the alleged deception by Janssen, through its labeling, until April 2007 upon the filing of its Original Complaint. Janssen has entirely failed to meet its burden to show otherwise in its Motion, and its Motion must be denied.

G. The State Has Offered Sufficient Evidence to Impose Liability on Johnson & Johnson.

Defendants' attempt to immunize Defendant Johnson & Johnson from liability fails because the State has offered sufficient evidence to impose liability on Johnson & Johnson under the alter ego doctrine. Defendants overlook that basis of liability, maintaining instead that, to impose liability on Johnson & Johnson as a holding company, the State must satisfy a two-prong test that entails a consideration of eight factors under the first prong.¹⁸ The alter ego doctrine, however, is another means by which the corporate veil may be pierced in South Carolina. *Jones v. Enter. Leasing Company-Southeast*, 678 S.E.2d 819 (S.C. Ct. App. 2009) (“[T]he alter ego

¹⁸ To create a basis for their argument, Defendants have taken much license with those eight factors, which do not refer to “parent corporations” or “subordinate corporations,” as Defendants suggest. (See Defs.' Mot. at 26-27.) Moreover, the two cases Defendants cite involved actions against individual officers, directors, and shareholders, not actions against a holding company based on the conduct of its operating companies. *See Dillias v. InfoSafe Corp.*, 463 S.E.2d 641, 642-44 (S.C. Ct. App. 1995) (involving action against individual who was president, director, and sole shareholder of the corporate defendant); *Sturkie v. Sifly*, 313 S.E.2d 316, 317-18 (S.C. Ct. App. 1984) (involving action against sole officers and shareholders of company).

doctrine is merely a means of piercing the corporate veil.”) (alteration in original, citation omitted).

In *State ex rel. Daniel v. Broad River Power Co.*, the Supreme Court of South Carolina explained the standard for imposing alter ego liability on a holding company for the conduct of its operating companies:

It is true that mere ownership of the capital stock of one corporation by another does not create an identity of corporate interest between the two companies, or render *the holding company* the owner of the property of the other, or create the relation of principal and agent, or representative, or *alter ego* between the two; but it is equally true that when the facts show not only stock ownership, common officers and the like, but that *the subsidiary company was a mere agency or department of the holding company*, or that it was an instrumentality to subserve some special purpose of the holding company, *particularly where the public interests are involved, the Court will deal with the substance of the transaction as if separate corporate entities did not exist.*

153 S.E. 537, 545 (S.C. 1930) (second and third emphases added). Here, the evidence shows that Johnson & Johnson is the publicly traded company that owns Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. (“Ortho-McNeil-Janssen”). (Deposition of Ivo Caers, Aug. 19, 2009, Volume 1, at 21:02-05 (Pl. Tr. Ex. 871 at 21:02-05 (Ex. A)).) The evidence also shows that Ortho-McNeil-Janssen is, in truth, nothing more than a division of Johnson & Johnson, which is the “umbrella” under which it operates. (Trial Tr. at 1141:23-25 (Ex. A); *see also id.* at 1141:25-1142:4 (“I [Angie Alderman] work for Johnson & Johnson, but we have different divisions with the company. I’m currently with PriCara, which is a different division, but at the time I worked for Janssen in the elder care department.”) (Ex. A).) As sales representative Angie Alderman explained during her testimony:

Q. So Johnson & Johnson is the top of the umbrella; is that correct?

A. Correct.

Q. And then under Johnson & Johnson are other companies like Janssen Pharmaceutica?

A. Yes.

Q. Or Ortho-McNeil, which is now Janssen Pharmaceutica; is that correct?

A. Yes, sir.

Q. So they're all synonymous?

A. Uh-huh.

Q. They're different divisions, but it's the same company?

A. Correct.

(*Id.* at 1142:7-20.)

The "public interests" are unquestionably involved here because the State has brought this action to recover civil penalties for Defendants' violations of SCUTPA in marketing a prescription drug with potentially fatal side effects. (*See* discussion, *supra* at III.D). The Court should therefore reject Defendants' attempt to shield Johnson & Johnson from liability. *See Broad River*, 153 S.E. at 545.

Furthermore, in the similar but distinct parent-subsidary context, alter ego liability is established where the parent exercises control over the subsidiary to the extent that the subsidiary manifests no separate corporate interests and functions solely to achieve the purpose of the parent corporation, and the "retention of separate corporate personalities would promote fraud, wrong, or injustice, or would contravene public policy." *Jones*, 678 S.E.2d at 823-24. Although the State has introduced sufficient evidence to pierce the corporate veil under the standard set

forth by the Supreme Court in *Broad River*, as discussed above, the evidence offered by the State also establishes alter ego liability under the standard applied in the parent-subsidary context, especially as it contravene public policy to immunize Johnson & Johnson for the conduct of one of its division.

**IV.
CONCLUSION**

For all the foregoing reasons, the State respectfully requests that the Court deny Defendants' Motion in its entirety.

Respectfully submitted,

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March 15, 2011
Spartanburg, South Carolina

Attorneys for the State of South Carolina

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STATE OF SOUTH CAROLINA
COUNTY OF SPARTANBURG

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.
Alan Wilson, in his capacity as Attorney
General of the State of South Carolina,

Civil Action No. 2007-CP-42-1438

Plaintiff,

v.

DEFENDANTS' REPLY IN SUPPORT OF
MOTION FOR A DIRECTED VERDICT

JANSSEN PHARMACEUTICA, INC.,
JANSSEN, L.P. and JOHNSON &
JOHNSON, INC.,

Defendants.

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Contrary to the State's suggestion, *State ex rel. Daniel v. Broad River Power Co.* 157 S.C. 1, 153 S.E. 537 (1929) ("*Broad River*"), does not support the proposition that this Court can ignore the factors set forth in *Dumas v. InfoSafe Corp.*, 320 S.C. 188, 192, 463 S.E.2d 641, 643-44 (Ct. App. 1995) (citation omitted). The *Broad River* court, in fact, specifically weighed a number of these same factors, reasoning:

[W]hen the facts show not only stock ownership, common officers and the like, but that the subsidiary company was a mere agency or department of the holding company, or that it was an instrumentality to subserve some special purpose of the holding company, particularly where the public interests are involved, the Court will deal with the substance of the transaction as if separate corporate entities did not exist.

Broad River, 157 S.C. at 26, 153 S.E. at 545. The State did not introduce in its case in chief any evidence that Johnson & Johnson and Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") have common officers, that Janssen is a mere agency or department of Johnson & Johnson, that Janssen exists to subserve some special purpose of Johnson & Johnson, or any of the other relevant factors.

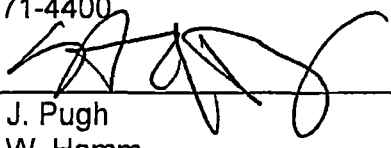
And, even if the involvement of the public interest was the sole factor to be considered, the conduct challenged by the State here is not at all the type of public interest the *Broad River* court considered. There, the court was asked to issue "a writ of mandamus requiring and compelling [corporations] to resume and continue the operation of the electric street railway system in the city of Columbia and other places near said city." *Broad River*, 157 S.C. at 15, 64, 153 S.E. at 541, 559 ("In this connection attention is called to the fact that the corporation before the court is not an 'ordinary private money-making corporation,' but is a corporation of a public service character.").

Finally, the State's alter ego-veil piercing theory also fails. Even if the standard for alter ego liability is as the State suggests, the State utterly failed to introduce any evidence that Johnson & Johnson "exercises control over the subsidiary [Janssen] to the extent that the subsidiary [Janssen] manifests no separate corporate interests and functions solely to achieve the purpose of the parent corporation [Johnson & Johnson], and the retention of separate corporate personalities would promote fraud, wrong, or injustice, or would contravene public policy.'" Pl.'s Response in Opp'n to Defs.' Mot. for a Directed Verdict at 30 (citation omitted).

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WHEREFORE, for the reasons stated herein and in Defendants' Motion for a Directed Verdict and accompanying memorandum of law, the Court should grant Defendants' Motion in its entirety.

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) IN THE COURT OF COMMON PLEAS

) FOR THE SEVENTH JUDICIAL CIRCUIT

)
) Civil Action No.: 2007-CP-42-1438

PLAINTIFF THE STATE OF SOUTH
CAROLINA'S MOTION FOR A
DIRECTED VERDICT AS TO
DEFENDANTS' EIGHTH
AFFIRMATIVE DEFENSE ON
STATUTE OF LIMITATIONS

PLAINTIFF THE STATE OF SOUTH
CAROLINA'S MOTION FOR A
DIRECTED VERDICT AS TO
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**DIRECTED VERDICT AS TO
DEFENDANTS' EIGHTH
AFFIRMATIVE DEFENSE ON
STATUTE OF LIMITATIONS**

M. JOSE BLANCKLEY
 ty as Attorney
 e undersigned
 native Defense
 acaceutics, Inc.,

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson,¹ in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Motion for a Directed Verdict as to the Eighth Affirmative Defense of Defendants Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc. (collectively, "Janssen" or "Defendants"), and would respectfully show the Court as follows:

¹ Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

I.
SUMMARY OF THE MOTION

In order to prove by a preponderance of the evidence that the State's Unfair Trade Practices ("SCUTPA") claim is time-barred, Defendants must prove that the Attorney General's Office discovered Defendants' unlawful conduct in violation of SCUTPA before January 24, 2004.² Defendants failed to offer *any* evidence, however, to justify sending that issue to the jury. Unable to demonstrate the Attorney General's actual or constructive knowledge of Janssen's unlawful conduct in South Carolina, Defendants instead presented evidence that the State, certain employees, and (by inference) other South Carolina prescribers already had knowledge of the general risks of antipsychotic use, without more.³

Defendants apparently overlooked this Court's repeated and consistent rulings on the requisite notice due the State relative to Janssen's limitations defense. Denying Defendants' motions for summary judgment and concluding that the State is not barred by limitations from proceeding to trial, the Court carefully distinguished the *Attorney General's* knowledge of "[u]nfair methods of competition and unfair or deceptive acts or practices . . . in the Defendants' marketing and labeling relative to the sale of Risperdal" from "medical professionals'" generalized "concern[s] about the side effects of" atypical antipsychotics during the relevant time period.⁴ Consistent with all relevant South Carolina law, the Court emphasized that "the essential question . . . is *when the State Attorney General's Office would have become aware of* 'unfair or deceptive acts or practices' in the Defendants' marketing and labeling [of

² See S.C. Code Ann. § 39-5-150 (2010) (three-year limitations statute on SCUTPA claims). This lawsuit was filed April 23, 2007. The State and Janssen entered a "tolling agreement" that tolled the statute of limitations for three months commencing January 24, 2007. See discussion, *infra* at § II.A.

³ See discussion, *infra* at § III.C.

⁴ Order, Feb. 25, 2011, at 6.

Risperdal]”—not when “the medical community nationally and in this State [would have become] aware” of Risperdal’s side effects.⁵ Additionally, the Court considered that “Janssen may have actually taken affirmative action to confuse the issue, so as to hide the disparity between what was being told to the prescribing public and what its own professionals and experts knew” about Risperdal’s true safety profile, finding that “[t]his could in some situations even justify an equitable tolling of the Statute of Limitations.”⁶ The Court reached similar conclusions in the companion *Lilly* case in 2009.⁷

Thus, Janssen’s defense that by virtue of the November 2003 “Dear Doctor” letter or its subsequent Correction Letter, Risperdal’s labeling, or the purported knowledge of certain State employees of Risperdal’s safety profile, the State either had or should have had notice of its

⁵ *Id.* (emphasis added).

⁶ *Id.* As this Court acknowledged, even it could find that the State tardily filed its Complaint in this lawsuit—which for clear reasons amply described herein it did not—the doctrines of equitable estoppel and/or equitable tolling nevertheless permit the State to bring its claims. Because Janssen’s intentionally deceptive conduct was designed to avoid detection, Janssen is equitably stopped from asserting a limitations defense and/or the applicable limitations period is equitably tolled. See *Hooper v. Ebenezer Senior Servs. & Rehab. Ctr.*, 659 S.E.2d 213, 225 (S.C. Ct. App. 2008) (“A defendant will be estopped to assert the statute of limitations in bar of a plaintiff’s claim when the delay that otherwise would give operation to the statute has been induced by the defendant’s conduct.”). Moreover, “[s]ilence, when it is intended, or when it has the effect of misleading a party, may operate as equitable estoppel.” *Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 339 (S.C. Ct. App. 2001).

With respect to equitable tolling, the Court of Appeals of South Carolina observed that “[i]t has been held that equitable tolling applies principally if the plaintiff is actively misled by the defendant about the cause of action or is prevented in some extraordinary way from asserting his or her rights.” *Hooper*, 659 S.E.2d at 221. “[T]he equitable tolling doctrine does not require wrongful conduct on the part of the defendant, such as fraud or misrepresentation.” *Id.*

Janssen’s false representations, concealment of material facts, and knowledge of the true facts, intending to mislead the State about any cause of action it may have had against Janssen, demands the application of the equitable estoppel or equitable tolling doctrines here. Given the scope of deceptive activities in which Janssen engaged as described herein, the Court should necessarily find that any applicable statute of limitations period is equitably tolled and/or that Janssen is equitably estopped from asserting its statute of limitations defense.

⁷ *South Carolina v. Eli Lilly & Co.*, No. 2007-CP-42-1855, slip op. at *10 (S.C. Cir. Ct. Sept. 22, 2009) (denying pharmaceutical manufacturer’s statute of limitations summary judgment motion) (attached as Exhibit A). In *Lilly*, the Court decided that “[k]nowledge by the State that” a prescription drug “may have contributed to weight gain, diabetes, or related diseases . . . does not place the State on notice that [the defendant] is involved in any of the enumerated wrongful acts.” *Id.* The Court emphasized that the State’s acquisition of bits and pieces of anecdotal information about Zyprexa prior to the filing of its Original Complaint is insufficient to trigger the running of the statute. *Id.* at *11. Without “facts concerning the . . . specified incidences of wrongdoing, of which the State was aware or should have been aware . . .,” defendant’s argument that the statute had been triggered in 2004, and had expired prior to filing the lawsuit, failed. *Id.* (emphasis added).

SCUTPA claim is entirely contrary to the Court's prior rulings on limitations. Janssen offered no evidence consistent with those rulings—i.e., actual or constructive knowledge by the Attorney General's Office of Defendants' unlawful conduct in violation of SCUTPA. For the reasons discussed herein, the Court should enter an order granting a directed verdict in favor of the State and against Defendants on their Eighth Affirmative Defense.

II.

PROCEDURAL HISTORY & FACTUAL BACKGROUND

A. Statement of the Case

On February 16, 2007, the State and Janssen, manufacturer of the atypical antipsychotic drug Risperdal, entered a three-month tolling agreement effective January 24, 2007 and expiring April 24, 2007 (attached as Exhibit B). On April 23, 2007, the State initiated this action against Janssen to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for Janssen's willful, deceptive, and unfair course of conduct in its product labeling. In light of the tolling agreement, the Attorney General's Office must not have discovered its SCUTPA claim against Defendants before January 24, 2004.

On March 19, 2010, the State filed its Second Amended Civil Action Complaint (hereinafter, "Amended Complaint"), petitioning the Court to assess against Janssen such penalties in an amount up to five thousand dollars for each "method, act or practice declared unlawful by § 39-5-20" and the willful use thereof. S.C. Code Ann. § 39-5-110(a). At trial, the State has offered in support of that claim sufficient evidence to reach the jury that Janssen's November 2003 "Dear Doctor" letter and Risperdal labeling from 1994 through 2007 were unfair and deceptive, and that Janssen's dissemination of those materials willfully violated SCUTPA.

B. Defendants' Eighth Affirmative Defense

On April 12, 2010, Defendants answered the State's Second Amended Civil Action Complaint and by their Eight Defense contended that the State's claims are barred, in whole or in part, by the applicable statute of limitations. (See Defs.' Answer to Pl.'s 2d Am. Compl. at 19.) Defendants recently clarified their defense that the "State's entire SCUTPA claim is barred by the statute of limitations" in their Motion for Directed Verdict, which this Court denied on March 16, 2011 after the presentation of the State's case. (Defs.' Mem. at 24.) In addition and prior to that, Defendants moved for summary judgment on statute of limitations grounds against the State's SCUTPA claim based on Defendants' November 2003 "Dear Doctor" letter as well as the Risperdal package insert—motions this Court denied on February 25, 2011. (See Defs.' Mem. in Supp. of Mot. Summ. J. on Nov. 10, 2003 Mailing at 8-10; Defs.' Mem. in Supp. of Mot. Summ. J. on Package Insert at 15-21; *see also* Order, Feb. 25, 2011, at 5-7.) For the reasons that follow, the Court should reject this defense for lack of sufficient evidence.

III. ARGUMENT AND AUTHORITIES

A. Standard

"In deciding whether to grant or deny a directed verdict motion, the trial court is concerned only with the existence or nonexistence of evidence." *Wright v. Craft*, 640 S.E.2d 486, 498 (S.C. Ct. App. 2006) (citing *Pond Place Partners, Inc. v. Poole*, 567 S.E.2d 881, 888 (S.C. Ct. App. 2002)). Specifically, the court should determine the elements of the claim or defense alleged and whether evidence existed on each element. *See First State Sav. & Loan v. Phelps*, 385 S.E.2d 821, 824 (S.C. 1989); *accord Long v. Norris & Assocs. Ltd.*, 538 S.E.2d 5, 9 (S.C. Ct. App. 2000). Where there is no evidence on any one element, a directed verdict is warranted. *See Guffey v. Columbia/Colleton Regional Hosp.*, 612 S.E.2d 695, 697 (S.C. 2005)

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(citing *First State Sav. & Loan*, 385 S.E.2d at 824)). Moreover, when such evidence is speculative, theoretical, or hypothetical, a directed verdict in favor of the moving party is proper, because the “rule[s] [do] not authorize submission of speculative, theoretical, and hypothetical views to the jury.” *Hanahan v. Simpson*, 485 S.E.2d 903, 908 (S.C. 1997); *Wright*, 640 S.E.2d at 498; *Long*, 538 S.E.2d at 9.

The statute of limitations defense is an affirmative one on which the burden of proof shifts to Defendants. Accordingly, Defendants bear the burden of proving the defense by the greater weight or preponderance of the evidence. See *McClain v. Anderson Free Press*, 102 S.E.2d 750, 759 (1958) (finding that, in action for libel, where answer pleads affirmative defense of qualified privilege, burden of proof is upon defendant to establish such defense by a preponderance of the evidence); *Lorick & Lowrance, Inc. v. Julius H. Walker & Co.*, 150 S.E. 789, 792 (1929) (“When a defendant interposes an affirmative defense, he becomes as to that matter the actor in the suit, and the burden of proof rests upon him to establish his affirmative defense by preponderance of the evidence.”).

B. Defendants Have Not Offered Sufficient Evidence That the Attorney General Had Actual or Constructive Knowledge of Defendants’ Unlawful Conduct Before January 24, 2004.

1. Unlawful Conduct Must Be Discovered in Order to Trigger the Statute of Limitations.

The applicable statute of limitations for the State’s SCUTPA action is found in S.C. Code Ann. § 39-5-150. Under that section, “[n]o action may be brought under [SCUTPA] more than three years after discovery of the unlawful conduct which is the subject of the suit.” *Id.*

South Carolina’s “discovery rule” applies to SCUTPA claims, which tolls the statute of limitations until a cause of action reasonably ought to have been discovered. See *id.*; *Hedgepath v. AT&T, Co.*, 559 S.E.2d 327, 336 (citing *Dean v. Ruscon Corp.*, 468 S.E.2d 645, 647 (1996)).

More specifically, South Carolina law instructs that limitations begin to run “from the date that the injured party either knows or should have known by the exercise of reasonable diligence that a cause of action arises from the wrongful conduct.” *Hedgepath*, 559 S.E.2d at 355-56; see *Anonymous Taxpayer v. S.C. Dep’t of Revenue*, 661 S.E.2d 73, 80 (S.C. 2008) (quoting *Epstein v. Brown*, 610 S.E.2d 816, 818 (S.C. 2005) (“Under the discovery rule, the statute of limitations begins to run from the date the injured party either knows or should know, by the exercise of reasonable diligence, that a cause of action exists for the wrongful conduct.”)); *Grillo v. Speedrite Prods., Inc.*, 532 S.E.2d 1, 3 (S.C. Ct. App. 2000) (“[T]he statute of limitations is triggered not merely by knowledge of an injury, but by knowledge of facts, diligently acquired, sufficient to put a person on notice of the existence of a cause of action against another.”); *Lilly*, slip op. at *9 (detailing the applicable statute of limitations, attendant to the “discovery rule,” which runs from the date the injured party either knows or should have known by the exercise of reasonable diligence that *a cause of action arises from the wrongful conduct* of the defendant (citing S.C. Code Ann. § 15-3-535 (Supp. 2007); *Burgess v. Am. Cancer Soc’y, South Carolina Div., Inc.*, 386 S.E.2d 798, 800 (S.C. Ct. App. 1989); *Epstein*, 610 S.E.2d at 818) (emphasis added). (See also Order, Feb. 25, 2011, at 5.) “The date on which discovery should have been made is an objective, not subjective, question[.]” and there exists no duty to discover such information or to otherwise undertake a fishing expedition in an effort to find evidence of the wrongful conduct at issue. *Arant v. Kressler*, 489 S.E.2d 206, 208 (S.C. 1997); see *State v. Von Dohlen*, 471 S.E.2d 689, 693 (S.C. 1996) (government “has no duty to undertake a fishing expedition . . . to find . . . evidence” of unlawful activity). While “[t]he limitations period is intended to run against those who are neglectful of their rights and who fail to exercise reasonable diligence in enforcing their rights[.] . . . it is not the policy of the law to unjustly

deprive an injured person of a remedy.” *Moriarty v. Garden Sanctuary Church*, 534 S.E.2d 672, 679 (S.C. 2000). Accordingly, the three-year limitations period is triggered from the *discovery* of facts underlying the State’s SCUTPA claim arising from Defendants’ unlawful conduct.

2. The Attorney General’s Office Must Have Had Actual or Constructive Knowledge.

Under the applicable statute of limitations, the State’s lawsuit must have been filed within three years after the Attorney General discovered the unlawful conduct that is subject of the State’s Complaint. S.C. Code Ann. § 39-5-150. As described herein, the “discovery rule” as applied to the statute of limitations relates to the point in time when the Attorney General knew or should have known that some legal right had been invaded. *See Hedgepath*, 559 S.E.2d at 336; *Epstein*, 610 S.E.2d at 818; *see also Arant*, 489 S.E.2d at 208.

The Attorney General is the only South Carolina government official who may bring a claim for civil penalties pursuant to S.C. Code Ann. § 39-5-110(a), and, therefore, the requisite actual or constructive knowledge relative to the “discovery rule” must be that of the Attorney General’s Office. The knowledge of another state agency or employee cannot be imputed to the Attorney General’s office for purposes of triggering the limitations period. *See Von Doherty*, 471 S.E.2d at 693 (“Although information known to . . . agencies may, under certain circumstances, be imputable to the State, the government has no ‘affirmative duty to take action to discover information which it does not possess’”); *see also Midtrust Bank, SSB v. C.W. Haynes & Co.*, 893 F. Supp. 1304, 1316 (D.S.C. 1994) (holding that although two governmental agencies were divisions of the same department, “the entities operate[d] independently of each other” and it was “unrealistic to charge” one agency with the other agency’s “employee’s knowledge” (citing *Wylar v. Korean Air Lines Co.*, 928 F.2d 1167, 1171 (D.C. Cir. 1991) (“One . . . agency ‘should not be charged with knowledge of what another is doing simply because both

are components of the same . . . government.”) (citation omitted))). “Therefore, the essential question before this Court is when the State Attorney General’s Office would have become aware of ‘unfair or deceptive acts or practices’ in the Defendants’ marketing and labeling actions relative to the sale of Risperal”—clearly “a separate and distinct issue from the question of when [State] medical professionals became concerned about the side effects of the drugs in question.” (Order, Feb. 25, 2011, at 6.)

C. The Only Evidence Defendants Have Presented is General Knowledge About the Side Effects of Their Drug by Certain State Employees.

Defendants have entirely failed to meet their burden of proving by the greater weight of the evidence that the statute of limitations bars the State’s SCUTPA claim. Rather, Defendants have elicited testimony and other evidence implicating certain State employees’ general knowledge of the side effects and relative safety profile of Risperdal and other atypical antipsychotics, including the following:

- one Department of Mental Health prescriber’s professed knowledge of atypical antipsychotics’ metabolic risk profiles as well as his receipt of an “Alert Letter” in 2002 similar to one sent to another physician concerning a patient to whom that physician had prescribed Seroquel,^{8, 9} despite that he purportedly knew prior to 2002, of the relationship between atypicals and the risk of developing diabetes based on his own anecdotal information relative to Risperdal’s safety profile acquired through his prescribing experiences, conversations with other physicians in the community, and review of related publications;¹⁰ and,

⁸ See Trial Tr. at 2113-2118 (attached as Exhibit C.).

⁹ Defs.’ Ex. 7336.

¹⁰ See, e.g., *id.* at 2111-2112 (“Q. My question, Doctor was: Are you aware of an association between atypical antipsychotics and metabolic conditions? A. Yes. Q. Would you explain to the member of the jury what is meant by metabolic conditions? A. When we treat patients, um, particularly psychiatric patients, . . . we noticed that some patients did gain weight and that some patients would be more disposed to having problems with their glucose levels. Q. Now, when you mentioned in the course of your response that you noticed that with these atypicals some patients did gain weight, when did you first notice that or become aware of that phenomena? A. Well, the first medication that became available was a medication called Clozaril, and we noticed that with that medication, there was some weight gain. As more of the medications came on the market, we observed, usually within the first year or two of prescribing the medicine, the weight gain could be a problem.”) (Ex. C.); *id.* at 2118 (“Q. And how is it, Dr. Bank, that you came to know and understand before you received this letter of that relationship between atypicals and the risk of developing Type II diabetes? A. Well, there are several issues. One

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- another Department of Mental Health prescriber's professed knowledge of atypical antipsychotics' various side effects as well as her review of the Consensus Statement¹¹ when it was published in February 2004, despite that she purportedly knew prior to February 2004 of certain aspects of Risperdal's safety profile based on her own prescribing experiences.¹²

However, these "numerous indications that the medical community . . . in this State was becoming aware of an association between the use of atypical antipsychotics and weight gain . . . continuing through its 'Dear Doctor' letters in 2003 and 2004," demonstrate, at most, "an increasing concern with the side effects of these drugs." (Order, Feb. 25, 2011, at 6.) In addition, the "anecdotal information" proffered by Defendants as evidence of actual or constructive knowledge "does not rise to the level of putting the State on notice that [Defendants] [were] involved in any of the above specified wrongs." *Lilly*, slip op. at *10-11 (emphasis added). Thus, Defendants completely failed to connect any of the above-outlined evidence to the Attorney General's actual or constructive knowledge prior to January 24, 2007 that Janssen was committing actionable SCUTPA offenses in South Carolina, as they must.

Likewise, Defendants failed to present any evidence to satisfy their burden of proving that the State knew or should have known of its claim against Janssen based specifically on Defendants' November 2003 "Dear Doctor" letter¹³—which it did not correct until July 21,

is that some of my patients gained weight and had elevated glucose levels. Additionally, conversations between physicians in the community.") (Ex. C.); *id.* at 2119 ("Q. Okay. Had you read any articles that discussed the association between atypical antipsychotics and Type II diabetes before you received your Alert Letter? A. There had been articles in the psychiatric literature previous to this on that subject, yes.") (Ex. C.).

¹¹ See *id.* at 2161-2163 (Ex. C.).

¹² See, e.g., *id.* at 2160 ("Q. Did you have an appreciation for the risks and side effects associated with atypical antipsychotics? A. Yes, I did. Q. And, what did you recognize and understand them to be? A. Um - - um, the newer drugs . . . we looked at blood sugar, weight gain, those were the main things.") (Ex. C.); *id.* at 2161-2163 ("Q. Dr. Ratliff, when you saw this table, sort of ranking atypical antipsychotics with respect to certain side effects, was that something that was news to you or had you known that already? A. I couldn't have put it in a table like this, but I was aware of the various side effects.") (Ex. C.); *id.* at 2166 ("Q. My question to you is, with respect to that last statement, considerable variability in weight gain among the SGAs, was that something you had observed with your patients? A. Yes, I couldn't predict who would have what side effect.") (Ex. C.).

¹³ PL's Exhibit 1736.

2004.¹⁴ Again, Defendants failed to connect to the Attorney General's Office any actual or constructive knowledge of the November 2003 "Dear Doctor" letter, the related April 2004 Warning Letter from the FDA, or the July 2004 Correction Letter. Indeed, assuming the Attorney General's Office had been aware of the 2003 "Dear Doctor" letter (which it was not), it could not reasonably have had reason to investigate the violative nature of that letter under South Carolina law until the FDA issued its April 2004 Warning Letter, regarding which (1) there is no evidence the Attorney General's Office received or was otherwise aware of the FDA's Warning Letter or should have been aware of it (as it was addressed to Defendants only), and (2) by its issue in April 2004, the FDA Warning Letter was *after* January 24, 2004 and, therefore, *not* notice to the State that fell outside the limitations period.

IV. CONCLUSION

For all the foregoing reasons, the State respectfully requests that the Court grant the State's Motion for Directed Verdict as to Defendants' Eighth Affirmative Defense on Statute of Limitations.

Respectfully submitted,

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¹⁴ See Pl.'s Exhibit 438.

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Attorneys for the State of South Carolina

EXHIBIT C

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1 for South Carolina residents; is that correct?

2 A. Yes.

3 Q. Among the medicines that you prescribe,
4 do you prescribe atypical antipsychotics?

5 A. Yes.

6 Q. Now, are you aware, Dr. Bank, of an
7 association between atypical antipsychotics and
8 metabolic conditions?

9 MR. WHITE: Objection, Your Honor,
10 foundation.

11 THE COURT: Overruled.

12 THE WITNESS: Could you repeat the
13 question?

14 BY MR. MURPHY:

15 Q. My question, Doctor, was: Are you
16 aware of an association between atypical
17 antipsychotics and metabolic conditions?

18 A. Yes.

19 Q. Would you explain to the members of the
20 jury what is meant by metabolic conditions?

21 A. When we treat patients, um,
22 particularly psychiatric patients, many of them
23 have a predisposition to gaining weight and a
24 predisposition to diabetes. And that's been known
25 for many years, even before medications were

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1 available.

2 And so, as we've treated our patients
3 over the years, we've always -- it's always been
4 noted that they have these kinds of
5 predispositions, and so, when we prescribe
6 medications, we keep that in mind.

7 And in particular, with these atypical
8 antipsychotics, we noticed that some patients did
9 gain weight and that some patients would be more
10 disposed to having problems with their glucose
11 levels.

12 Q. Now, when you mentioned in the course
13 of your response that you noticed that with these
14 atypicals some patients did gain weight, when did
15 you first notice that or become aware of that
16 phenomena?

17 A. Well, the first medication that became
18 available was a medicine called Clozaril, and we
19 noticed that with that medication, there was some
20 weight gain. As more of the medications came on
21 the market, we observed, usually within the first
22 year or two of prescribing the medicine, the weight
23 gain could be a problem.

24 MR. MURPHY: May I approach the
25 witness, Your Honor?

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1 THE COURT: You may.

2 BY MR. MURPHY:

3 Q. Dr. Bank, in here there are a couple of
4 exhibits that I'm going to ask you about.

5 If you would, I would ask you to turn
6 your attention to what's tabbed there, 7336.

7 MR. MURPHY: Do you have that, John?

8 THE WITNESS: 7336?

9 MR. MURPHY: Yes, sir, it should be
10 toward the back.

11 THE WITNESS: I see it here, okay.

12 MR. WHITE: Is that this letter here?

13 MR. MURPHY: Yes.

14 MR. WHITE: Mine doesn't say 7336, but
15 is this the one?

16 MR. MURPHY: That's it. Do you need
17 another copy?

18 BY MR. MURPHY:

19 Q. Dr. Bank, looking at what's marked as
20 7336, is this the sort of document you've seen
21 before?

22 A. Yes.

23 MR. MURPHY: Okay. Your Honor,
24 Defendants move 7336 into evidence.

25 MR. WHITE: Without objection.

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1 THE COURT: Without objection it will
2 be received. Please have a copy marked.

3 (DEF. EXH. 7336, 2002 Alert Letter From
4 the Department of Health and Human Services to
5 Dr. Todd Engles, was admitted into evidence.)

6 BY MR. MURPHY:

7 Q. Now Dr. Bank, we're now looking at what
8 is in evidence as 7336. During the course of your
9 career, from time to time have you received what
10 are known as Alert Letters from the Department of
11 Health and Human Services?

12 A. Yes.

13 Q. Okay. Does this document appear to be
14 one of the -- like the Alert Letters that you have
15 received from time to time?

16 A. Yes.

17 Q. Now, this particular letter is directed
18 to a Dr. Todd Engles.

19 Do you see that?

20 A. Yes.

21 Q. And the date of the letter is 2002.
22 And if you look at the middle aspect of the letter,
23 that is the second paragraph, it states: During
24 recent review of the enclosed drug history profile,
25 it was noted your patient, name obliterated, is

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1 receiving Seroquel.

2 And you recognize Seroquel to be an
3 atypical, correct?

4 A. Yes, sir, that's right.

5 Q. My question to you, Dr. Bank, is: Do
6 you recall receiving an Alert Letter like this one
7 regarding atypical antipsychotics?

8 A. Yes.

9 Q. Now, the letter goes on to say: The
10 use of clozapine, olanzapine, risperidone or
11 quetiapine may increase the risk of developing Type
12 II diabetes mellitus or impaired glucose
13 intolerance. Patients with a family history of
14 diabetes or with preexisting diabetes may need to
15 have blood sugar monitored closely or changed to an
16 alternative medication.

17 Do you see that?

18 A. Yes.

19 Q. Now, when you received an Alert Letter
20 of this sort regarding atypical antipsychotics, did
21 you have an understanding of why Health and Human
22 Services was sending this letter out?

23 MR. WHITE: Objection, Your Honor.

24 THE COURT: Objection is?

25 MR. WHITE: He can't testify to why

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1 they were sending it out. It would be hearsay.

2 THE COURT: I will sustain that
3 objection.

4 MR. MURPHY: The question was, Your
5 Honor, my question to the witness was does he have
6 an understanding of why he was receiving it.

7 THE COURT: That's -- what you said is
8 -- what you asked about, that indicates to me that
9 you're asking him about the intention for the
10 sending. So for that reason, I have sustained the
11 objection. You can rephrase the question.

12 MR. MURPHY: Understood, Your Honor.

13 BY MR. MURPHY:

14 Q. When you received this letter,
15 Dr. Bank, the information --

16 MR. WHITE: Your Honor, we admitted
17 7336, and it's a similar letter, but we all know
18 this is not the letter that Dr. Bank received nor
19 when he received it. It's just a similar-type
20 letter.

21 THE COURT: All right. Well, who is
22 the addressee on the letter?

23 MR. MURPHY: Dr. Todd Engles.

24 THE COURT: So this is not addressed to
25 this witness?

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MURPHY EXHIBIT

1 MR. MURPHY: That's correct.

2 THE COURT: Okay.

3 MR. WHITE: And it's on a drug
4 Seroquel, not Risperdal.

5 THE COURT: I understand what it is.
6 I'm going to let him ask the question.

7 You may proceed, Mr. Murphy.

8 MR. MURPHY: Thank you, Your Honor.

9 BY MR. MURPHY:

10 Q. Just so you're clear, Dr. Bank, you do
11 have a recollection of having received an Alert
12 Letter of this sort regarding atypical
13 antipsychotics?

14 A. Yes.

15 Q. And when you received the letter that
16 you did, in fact, receive and read the information
17 regarding the use of atypicals may increase the
18 risk of developing Type II diabetes mellitus, was
19 that news to you?

20 A. No, it was not something new as far as
21 my practice.

22 Q. So, fair to say that you were aware
23 that these atypical antipsychotics may increase the
24 risk of developing Type II diabetes mellitus,
25 correct?

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1 MR. WHITE: Object, leading.

2 THE COURT: Overruled. Try not to lead
3 the witness.

4 MR. MURPHY: Understood, Your Honor.

5 BY MR. MURPHY:

6 Q. Did you understand, before you received
7 the letter, that, in fact, use of atypical
8 antipsychotics may increase the risk of developing
9 Type II diabetes?

10 A. Yes.

11 Q. And how is it, Dr. Bank, that you came
12 to know and understand before you received this
13 letter of that relationship between atypicals and
14 the risk of developing Type II diabetes?

15 A. Well, there are several issues. One is
16 that some of my patients gained weight and had
17 elevated glucose levels. Additionally,
18 conversations between physicians in the community

19 MR. WHITE: Conversations with other
20 community, that's not responsive to the question.
21 That's hearsay. Object. Move to strike.

22 THE COURT: Well, I will ask the
23 witness not to quote anyone outside of the -- other
24 people who are not in the courtroom, either as a
25 party or otherwise.

1 Continue with your answer, but don't
2 quote anyone.

3 THE WITNESS: Okay, Your Honor.

4 Uh, I'm trying to think of how to say
5 this. It was my experience that other physicians
6 had similar experiences.

7 BY MR. MURPHY:

8 Q. Okay. Had you read any articles that
9 discussed the association between atypical
10 antipsychotics and Type II diabetes before you
11 received your Alert Letter?

12 A. There had been articles in the
13 psychiatric literature previous to this on that
14 subject, yes.

15 Q. Dr. Bank, do you recall that -- when
16 was that you received your Alert Letter? We see
17 here this one was sent in September of 2002.

18 What is your recollection as to when
19 you received yours?

20 A. It would have been in that time frame,
21 but I couldn't say exactly when.

22 Q. And when you say "that time frame," is
23 that -- are you confining it to calendar year 2002,
24 or what do you mean by "that time frame," sir?

25 A. Well, I would say, give or take, three

1 select one that I think is the best match.

2 And a balance between, you know, risk
3 factors and side effects and symptoms to try to
4 bring some relief to patients who may be suffering.

5 Q. Did you have an appreciation for the
6 risks and side effects associated with atypical
7 antipsychotic?

8 A. Yes, I did.

9 Q. And what did you recognize and
10 understand them to be?

11 A. Um -- um, the newer drugs, initially we
12 thought, caused tardive dyskinesia. There's some
13 question about that now. And that's a symptom we
14 see with a lot of the older drugs.

15 Newer drugs, we looked at blood sugar,
16 weight gain, those were the main things, and the
17 complications that came with that; when you gain
18 weight, your blood pressure goes up; and if your
19 blood pressure goes up, you get renal failure.

20 Q. Dr. Ratliff, I would like to direct
21 your attention to an exhibit that you have in the
22 binder, it's 7185.

23 MR. MURPHY: Your Honor, this document
24 already has been admitted.

25 THE COURT: All right, it is.

1 BY MR. MURPHY:

2 Q. Dr. Ratliff, you're looking at what is
3 commonly called the consensus statement. Do you
4 recognize it?

5 A. Yes.

6 Q. Was that something that you read when
7 it came out?

8 A. Yes.

9 Q. Is it your recollection that in or
10 about 2004 you read the consensus statement?

11 A. I can't tell you exactly when I read
12 it, but I read it about the time it came out.

13 Q. About the time it came out?

14 A. Uh-huh.

15 Q. Fair enough.

16 Now, during your tenure as medical
17 director, did you from time to time share articles
18 in publications of interest with your colleagues at
19 DMH.

20 A. I did.

21 Q. Do you know whether this consensus
22 statement was one of the things that you shared
23 with your colleagues?

24 A. It was.

25 Q. Okay. And why did you share this

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1 consensus statement with your colleagues?

2 A. Because of documented information we
3 have now that the drug had been on the market long
4 enough to have more people, not just a small test
5 group. And we began to see a different array of
6 side effects then than we might have been aware of
7 in the beginning. And it helps to decide how to
8 monitor patients that still need that medicine.

9 Q. And if we could page in to Table 2 in
10 the consensus statement, the bottom right aspect,
11 do you see that, Table 2?

12 A. Yes.

13 Q. It's on your monitor, it ought to be
14 blown up.

15 Dr. Ratliff, when you saw this table,
16 sort of ranking atypical antipsychotics with
17 respect to certain side effects, was that something
18 that was news to you or had you known that already?

19 A. I couldn't have put it in a table like
20 this, but I was aware of the various side effects.

21 Q. And just so I understand your testimony
22 and the jury does, prior to seeing this table,
23 prior to reading the consensus statement, was it
24 your understanding or observation that there were
25 differences among the atypical antipsychotics with

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1 regard to these side effects we see here?

2 MR. WHITE: Your Honor, object,
3 leading.

4 THE COURT: Sustain the objection.
5 Please rephrase.

6 BY MR. MURPHY:

7 Q. What you see here reflected in this
8 table, Dr. Ratliff, was that consistent with the
9 observations that you had made prior to the time
10 you had seen this table?

11 A. Pretty much. Like I said, I couldn't
12 have ranked them and put a nice little table out
13 there, but it's consistent with what I was seeing.

14 Q. Thank you.

15 Doctor, let me now direct your
16 attention to the exhibit you have in your binder
17 7186.

18 MR. MURPHY: Do you have that,
19 Mr. White?

20 MR. WHITE: Yes, I do.

21 MR. MURPHY: Your Honor, Defendants
22 would move 7186.

23 THE COURT: Any objection?

24 MR. WHITE: Without objection.

25 THE COURT: It will be received as

1 marked. If you will pass a copy in to be marked.

2 (DEF. EXH. 7186 was admitted into
3 evidence.)

4 THE COURT: You may proceed.

5 BY MR. MURPHY:

6 Q. Dr. Ratliff, looking at 7186, do you
7 recognize this document?

8 A. Yes.

9 Q. If I look at the bottom left aspect of
10 the document, I see something in the margin.

11 A. Yes.

12 Q. Is that your handwriting?

13 A. That is.

14 Q. Okay. Now, explain to the jury exactly
15 what are we looking at in 7186, what is this?

16 A. Um, this table tells you how the drug
17 works, and it's listed as a generic name. And I
18 wrote the brand name out beside it. So that's why
19 you get varying side effects, because of how the
20 drugs act in these various systems in the brain.

21 Q. Now, at the top of the document, it
22 says SCDMH Laboratory Monitoring Guidelines For
23 Antipsychotic Medication.

24 Do you see that?

25 A. Yes.

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K. ROBERTS, JR.

1 Q. Okay. And do you know when or about
2 this document was generated?

3 A. No.

4 Q. Okay. Was it generated after the
5 consensus statement came out?

6 A. Probably, but I can't -- I can't say.

7 Q. Now, you didn't write these, or did you
8 write these guidelines?

9 A. Um, I think that most of that is lifted
10 out of the consensus and without so much discussion
11 to try to have an outline of how we can monitor
12 patients in the community. And one of the things I
13 was promoting and we implemented was finger sticks
14 for blood sugar, getting weights every time, to
15 make sure we were doing as much as we could.

16 Q. Now, if you could turn to Page 2 of the
17 document. Above the -- the heading at the top
18 says, Second-Generation Antipsychotics and Obesity.

19 Do you see that?

20 A. Yes.

21 Q. And thereunder, it reads:

22 "Second-generation antipsychotic, SGA,
23 can cause a rapid increase in body weight in the
24 first few days of therapy that may not reach a
25 plateau even after one year of treatment. There is

1 considerable variability in weight gain among the
2 SGAs."

3 My question to you is, with respect to
4 that last statement, considerable variability in
5 weight gain among the SGAs, was that something you
6 had observed with your patients?

7 A. Yes, I couldn't predict who would have
8 what side effect.

9 Q. So those who were taking SGAs
10 had -- there was some variability in their weight
11 gain?

12 A. Yes.

13 Q. And was that variability tied to the
14 individual SGA?

15 A. No. You know, I would see a patient
16 and they would gain zero weight on the drug; and
17 another patient on the same drug with similar kinds
18 of health factors might gain a lot of weight. I
19 couldn't predict that ahead of time.

20 Q. Now, this monitoring guideline, was
21 this something that doctors at DMH used?

22 MR. WHITE: Your Honor, object to what
23 doctors at DMH used.

24 THE COURT: You have to lay a
25 foundation as to whether or not she was aware that

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STATE OF SOUTH CAROLINA)
)
COUNTY OF SPARTANBURG)

IN THE COURT OF COMMON PLEAS
FOR THE SEVENTH JUDICIAL CIRCUIT

STATE OF SOUTH CAROLINA ex rel.)
Alan Wilson, in his capacity as Attorney)
General of the State of South Carolina,)
)
Plaintiff,)

Civil Action No. 2007-CP-42-1438

v.)

DEFENDANTS' OFFER OF PROOF
FOR THE EXPERT TESTIMONY OF
DR. WILLIAM E. WECKER

ORTHO-McNEIL-JANSSEN)
PHARMACEUTICALS, INC., f/k/a)
JANSSEN PHARMACEUTICA INC.,)
and/or JANSSEN, L.P. and)
JOHNSON & JOHNSON, INC.,)
)
Defendants.)

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby submit this Offer of Proof in response to the Court's order of February 25, 2011 and pursuant to South Carolina Rule of Evidence 103. The Court's order excluded the testimony of Defendants' expert Dr. William E. Wecker, a statistician. If permitted to testify at trial, Dr. Wecker would testify as follows:

Testimony of William E. Wecker, Ph.D.

My name is William E. Wecker. My testimony is supported by a slide presentation, attached here at Exhibit A, that summarizes my qualifications, provides information about the data sources I have reviewed and the methodology used for that review, and presents the results of my data analysis. Where relevant and helpful to explain my testimony, I refer here to slides by number.

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M. HOPE E. ACHILLE

A. Background and Experience

I am a statistician from Novato, California, which is located approximately 20 miles north of San Francisco. As summarized on Slide 2, I received my Bachelor of Science degree in 1963 from the United States Air Force Academy. (Ex. A, Slide 2.) After serving as a fighter pilot in the U.S. Air Force, I received a Master of Science degree (Operations Research, 1970) and Doctor of Philosophy degree (Statistics and Management Science, 1972) from the University of Michigan. My graduate studies included courses in mathematics, statistical theory, statistical methods, and computer science. I conducted original research in statistics, culminating in a published Ph.D. thesis on statistical prediction theory. I served on the faculties of the University of Chicago, the University of California Davis, and Stanford University where I taught statistics and applied mathematics, including the theory and methods of statistics such as the collection and analysis of data, at the graduate level for almost 20 years. I performed research on statistical theory and methods and published articles in statistical journals. My research focused primarily on statistical theory, including time series analysis, which has to do with data that evolve over time. My research is applicable broadly to statistical issues in a wide variety of industries.

I am currently President of William E. Wecker Associates, Inc., a statistics and applied mathematics consulting firm that I founded in 1990. As shown on Slide 3, Wecker Associates employs twenty statisticians and mathematicians and uses more than 50 different computer systems for analyzing more than 65 billion records of data – just for currently active projects. (Ex. A, Slide 3.) Most of our work involves analysis of large databases for companies of all kinds, including medical, pharmaceutical, computer, and automobile companies, as well as local, state, federal, and foreign government entities. We have analyzed databases of every fatal traffic accident occurring on a public roadway in the United States since 1974, American Cancer Society data on health risks, databases from

airline reservation systems, and databases from large banks, such as Bank of America. We also do statistical sampling and survey design and analysis, as well as a wide variety of other statistical and mathematical consulting work. I am personally involved with nearly every project we undertake.

I am a member of the American Statistical Association, the Institute of Mathematical Statistics, and the Society for Risk Analysis. I have served as associate editor of the *Journal of the American Statistical Association* for four years and the *Journal of Business and Economic Statistics* for eighteen years.

I have testified as an expert on behalf of both plaintiffs and defendants in a number of cases, including patent disputes and cases involving automobile and airline safety and computer designs. I have also been a court appointed expert in a matter involving the State of California and Bank of America. My work in that case involved extensive statistical analysis of checking and savings accounts from all bank branches over a period of several decades.

B. Overview of Statistical Analysis

I have analyzed three primary data sources during my work related to this case. First, I reviewed and analyzed the statistical conclusions contained in the eight then-existing published peer reviewed epidemiological studies cited in Janssen's November 10, 2003 mailing to health care providers. Second, I reviewed claims data from the State of South Carolina Medicaid and State Health Plan programs. Third, I reviewed deposition answers provided by 20 South Carolina doctors identified at random to participate in a survey concerning their experience with Risperdal and other antipsychotic medications and their exposure to Janssen promotion.

C. Statistical Conclusions From the Studies Cited in Janssen's November 10, 2003 Mailing to Health Care Providers

The mailing that Janssen sent on November 10, 2003 cited the eight then-existing epidemiological studies comparing the risk of diabetes in patients treated with Risperdal to the risk in patients treated with other antipsychotics and untreated schizophrenia patients. Plaintiff alleges that this mailing from Janssen to doctors in South Carolina contained misleading information about the risk of diabetes in patients taking Risperdal. I reviewed and analyzed the statistical conclusions presented in the eight studies and then compared them to the opinions Janssen expressed in the November mailing. The eight studies provide results that support the statements in the November 10, 2003 mailing.

The concept of statistical significance is an important one in statistics. When results are statistically significant, it means that we have been able to rule out, to a specific degree of certainty, the possibility that the results were caused by chance rather than representing true differences, for example, between two groups. Consequently, one may conclude that a statistically significant difference between two groups is "real" and that it arises from the different treatment of the two groups and not from mere chance fluctuations. Statistical significance is often expressed by the probability that the observed difference could have arisen merely by chance, known as a p-value. A commonly accepted criterion for statistical significance of primary endpoints of a study is a p-value of 0.05 or less, which means there is a five percent or lower probability that the observed result could have arisen from chance alone. There is a correspondence between statistical significance and confidence intervals. If a 95 percent confidence interval for the difference of a measurement between two groups does not include 0, the associated p-value for that result will be less than 0.05, and the difference would commonly be considered to be statistically significant. Similarly, if a 95 percent confidence interval for the relative risk of a particular disease

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between two treatment groups does not cover 1.00, the associated p-value for that result will be less than 0.05, and the relative risk would commonly be considered to be statistically significant.

By way of example, consider the Caro Study on *"The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis,"* which is marked as trial exhibit P1155. Caro and his colleagues reported results comparing the relative risk of developing diabetes in olanzapine versus risperidone users. The article states, "Conclusion: Compared with risperidone, olanzapine was associated with an increased risk of developing diabetes." The results of the Caro study are reproduced at Slide 4. (Ex. A, Slide 4.) The center column shows the relative risk and the 95% confidence interval. For the first three comparisons (shown in red on Slide 4), the results are statistically significant at the 95% confidence level. For the final three (shown in blue on Slide 4), while the adjusted relative risk still shows the risk of developing diabetes in olanzapine to be greater than the risk in risperidone users, the results are not statistically significant at the 95% confidence level because the confidence interval includes values less than 1.00. The third column contains p-values and shows, for example, that the results for all patients are statistically significant with a p-value of .005 and the results for women are statistically significant with a p-value of 0.02. In contrast, the results for patients with more than 12 months exposure time are not statistically significant because the p-values exceed the commonly accepted criterion of 0.05 for statistical significance.

Turning specifically to findings in the eight studies on statements in Janssen's November 10, 2003 mailing that are challenged by plaintiff in this case, four of the eight studies contained results comparing patients treated with Risperdal to untreated patients: Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3, and Koro. (Ex. A, Slide 5.) All four of those studies found "that RISPERDAL is not associated with an increased risk of diabetes

when compared to untreated patients” Six of the eight studies contained results comparing patients treated with Risperdal to patients treated with conventional antipsychotics: Buse, Gianfrancesco 1, Gianfrancesco 2, Gianfrancesco 3, Koro and Sernyak. All six of those studies found “that RISPERDAL is not associated with an increased risk of diabetes when compared to . . . patients treated with conventional antipsychotics.”

The Buse study found overall that the incidence of diabetes mellitus for patients treated with Risperdal was lower than for patients treated with conventional antipsychotics. Buse separately reported results for a subgroup analysis that compared each of the four atypical antipsychotics, including Risperdal, to the Haloperidol cohort. As a part of this subgroup analysis, Buse calculated that Risperdal's hazard ratio compared to haloperidol was 1.23, with a p-value of 0.04. A p-value of 0.04 would indicate a statistically significant result for a primary endpoint of a study, but it does not indicate a statistically significant result for a secondary, subgroup analysis. Subgroup p-values need to be interpreted based on the number of comparisons made in subgroups that are analyzed—at least four in this case. There are several formulaic ways to assess statistical significance for subgroup analyses. The most common and easiest method to apply is the method of Bonferroni. Properly interpreted, the p-value of 0.04 does not indicate a statistically significant result for this subgroup analysis.

All eight studies contain results comparing patients treated with Risperdal to patients treated with another atypical antipsychotic, and four of those eight found statistically significant results: Caro, Fuller, Gianfrancesco 2, and Gianfrancesco 3. All four of those studies reported results showing “that RISPERDAL is associated with a [statistically significant] lower risk of diabetes than some other studied atypical antipsychotics.”

In all, more than 6 million patients were analyzed for the statistical conclusions reported in these eight studies. Janssen's statement in the mailing was an accurate reflection of the risks posed by Risperdal, whether judged by the then-existing body of published peer-reviewed epidemiological literature or the data from South Carolina doctors and patients, addressed below.

D. South Carolina Medicaid and State Health Plan Claims Data

The State of South Carolina maintains a database of information about all claims that are submitted for payment for prescriptions and medical care (including doctor visits, hospital stays, and procedures) provided to Medicaid patients and patients participating in the State Health Plan ("SHP"). (Ex. A, Slides 6 and 7.) The claims data provided complete claims histories for all South Carolina Medicaid and SHP patients who took Risperdal and other antipsychotics from 1994 through 2007 for Medicaid Fee-for-Service ("FFS") patients from 1999 through 2007 for Medicaid HMO patients, and from 1995 through 2007 for SHP patients. I was able to utilize claims data produced by the State to compare the incidence of side effects alleged by plaintiff to be risks from Risperdal use to the incidence of the same side effects in untreated patients suffering from psychotic disorders; patients treated with first generation (conventional) antipsychotics ("FGAs"); and patients treated with other second generation (atypical) antipsychotics ("SGAs").

Before I further explain my analysis of the data, it is important to understand the data that I analyzed. The South Carolina Medicaid and SHP databases consist of computer data recorded and maintained by the State of South Carolina containing a list of the medical treatments and medications that were paid for by the Medicaid and SHP programs. (Ex. A, Slide 7.) There is one line of information (data) for each claim paid by the Medicaid and SHP programs. Each claim line contains information such as the doctor's name, the procedure performed by the doctor, the medicine prescribed, the amount paid, and in some

cases, a medical diagnosis. The claims databases are not the same as doctor medical files.

I reviewed the entries for all Medicaid and SHP treatment provided to a patient who received a prescription for an antipsychotic, whether for Risperdal or any other antipsychotic. (Ex. A, Slide 8.) That would include doctor visits, community centers, and other types of medical treatment, no matter what the treatment was for, so long as a claim was submitted for payment to Medicaid or the SHP. If a patient got a prescription for Risperdal, I was able to review the patient's entire Medicaid and SHP claims history going back as far as 1994 and extending all the way up to the time that the State produced data in 2007. The databases contain different types of information, such as which drug was prescribed, whether there was a hospital stay, and how much it cost; in some cases there also a diagnosis listed for the treatment. I analyzed data for 136,694 Medicaid and SHP patients. (Ex. A, Slide 9.) This consisted of 90,397,060 medical claims records. The 136,694 patients included those who received any antipsychotic medication, whether Risperdal, another atypical, or one of the conventional antipsychotics.

To conduct my analysis, I compared the experience of Medicaid and SHP patients who received Risperdal to those who received other antipsychotics. My overall conclusions are shown on Slides 10 and 11, and my methodology is illustrated on Slides 12 and 13.

To summarize how I performed my analysis, I first identified the claims history for all South Carolina Medicaid and SHP patients who ever received an antipsychotic. I then examined all claims in the 36 months after their first antipsychotic drug prescription for diagnoses indicating an alleged side effect. The alleged side effects I analyzed were diabetes, metabolic adverse events (e.g., diabetes, abnormal weight gain, abnormal glucose, obesity), and increased prolactin secretion. I also examined the patient's claims history before the first prescription for an antipsychotic. To attempt to ensure that the first

antipsychotic drug prescription recorded in the State claims data was a patient's first use of the drug, I required a minimum of 12 months of uninterrupted program eligibility prior to the first antipsychotic drug prescription. I also examined the claims data prior to the first antipsychotic drug prescription to ensure that patients had no treatment for the alleged side effects before they began receiving antipsychotics. I was able to compare patients who got only Risperdal to patients who got only a first generation antipsychotic and patients who got only a second generation antipsychotic other than Risperdal. I could then learn whether there were differences between those patients in terms of the frequency that they developed certain side effects.

I also compared patients who received Risperdal to untreated patients who only later received an antipsychotic, as shown on a slide that I prepared. (Ex. A, Slide 13) To analyze untreated patients, I separately identified patients with uninterrupted eligibility for a period of at least 48 months prior to their first antipsychotic drug prescription and no diagnosis indicating the side effect prior to the 36 month period immediately preceding their first antipsychotic drug prescription. I then examined all claims in that 36 month period for diagnoses indicating an alleged side effect.

I analyzed the data for two time periods—first, for all the data as of November 10, 2003, and, second, for all of the patients who ever received an antipsychotic medication through Medicaid or the SHP from the time Risperdal came on the market through the time that the FDA sent its Warning Letter in April 2004. That included Risperdal, all conventional antipsychotics, and all of the atypicals.

Based on my analysis, Risperdal patients were diagnosed with diabetes, metabolic adverse events, and increased prolactin secretion less frequently than untreated patients, patients who took FGAs, and patients who took other SGAs. I prepared tables that set forth the results of my analysis showing excess side effect risks relative to Risperdal.

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For diabetes, I learned that Risperdal patients were diagnosed with diabetes less frequently than untreated patients, patients who took FGAs, and patients who took other SGAs. (Ex. A, Slide 14.) Compared to patients treated with Risperdal, untreated patients have a 1.29% greater risk of diabetes, patients treated with FGAs have a 1.62% greater risk of diabetes, and patients treated with other SGAs have a 2.33% greater risk of diabetes. Each of these results is statistically significant.

For my analysis of the comparative incidence of metabolic adverse events, I looked at diagnoses of diabetes mellitus, secondary diabetes mellitus, excessive weight and diabetes, abnormal weight gain, and abnormal glucose. (Ex. A, Slide 15.) Through my analysis of the data, I learned that Risperdal patients were diagnosed with metabolic adverse events less frequently than untreated patients, patients who took FGAs, and patients who took other SGAs. Compared to patients treated with Risperdal, untreated patients have a 0.99% greater risk of metabolic adverse events, patients treated with FGAs have a 1.46% greater risk of metabolic adverse events, and patients treated with other SGAs have a 4.47% greater risk of metabolic adverse events. Each of these results is statistically significant.

Regarding increased prolactin secretion, I learned that Risperdal patients were diagnosed with increased prolactin secretion less frequently than untreated patients, patients who took FGAs, and patients who took other SGAs. (Ex. A, Slide 16.) Compared to patients treated with Risperdal, untreated patients have a 2.22% greater risk of increased prolactin secretion, patients treated with FGAs have a 3.64% greater risk of increased prolactin secretion, and patients treated with other SGAs have a 1.82% greater risk of increased prolactin secretion. Each of these results is statistically significant.

Returning to diabetes, I also analyzed the excess risk of diabetes relative to Risperdal using data through the date of the November 10, 2003 mailing. (Ex. A, Slide 17.)

I learned that Risperdal patients were diagnosed with diabetes less frequently than untreated patients, patients who took FGAs or other SGAs. Each of the results is statistically significant. Compared to patients treated with Risperdal, untreated patients have a 1.32% greater risk of diabetes, patients treated with FGAs have a 1.17% greater risk of diabetes, and patients treated with other SGAs have a 1.84% greater risk of diabetes.

One of the challenged sentences in the November 10, 2003 mailing refers to the body of then-existing peer reviewed epidemiological evidence and goes on to state that it suggests that Risperdal is "not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics." (Ex. A, Slide 18.) Through my analysis of the claims data, I learned that in the South Carolina Medicaid and SHP population, this was true: Risperdal use was not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. As already noted, compared to patients treated with Risperdal, untreated patients have a 1.32% excess risk of diabetes and patients treated with FGAs have a 1.17% excess risk. Thus, the data support Janssen's statement.

Similarly, the data support Janssen's next scientific opinion in the mailing: "Evidence also suggests that RISPERDAL is also associated with a lower risk of diabetes than some other studied atypical antipsychotics." (Ex. A, Slide 19.) In the South Carolina Medicaid and SHP population, Risperdal in fact was associated with a lower risk of diabetes than patients treated with other SGAs. As noted, patients treated with other SGAs have a 1.84% excess diabetes risk over patients treated with Risperdal.

E. Survey of South Carolina Prescribers

A primary data source with information related to plaintiff's allegations is documented South Carolina physician experience, which may be learned from South Carolina doctors who treat patients with Risperdal. Relevant information includes the doctors' experience

with Risperdal's efficacy and with the potential side effects of antipsychotic medications, the circumstances in which off-label use is regarded by the doctor as appropriate, and Janssen's promotional practices. I gathered information from South Carolina doctors because they are in a good position to have firsthand knowledge about questions relating to efficacy and safety of antipsychotic drugs. (Ex. A, Slide 20.)

Given the size of the relevant prescriber population, it would be prohibitively time consuming and expensive to interview each prescriber of Risperdal in South Carolina about his or her experience with Risperdal and other antipsychotic medications. Therefore, I obtained information about the experience of South Carolina doctors from depositions of randomly identified doctors who treated Medicaid FFS or SHP beneficiaries in the State. (Ex. A, Slide 21.) This random sample allows us to learn what the experience of South Carolina doctors has been with Risperdal and other antipsychotics, without speaking to every doctor in the State who prescribes Risperdal.

Random sampling allows one to make statements that are reliable and scientifically defensible about the entire population, having only looked at a sample. (Ex. A, Slide 22.) Professional statisticians as well as scientists and scholars in related fields widely accept that random sampling is the only generally applicable, scientifically valid method for creating a representative sample from a universe that is too large to process exhaustively. Random sampling is commonly used; for instance, nearly every night on television news programs there are reports of a sample survey describing what Americans have to say about a certain issue or how they might vote in an upcoming election. For these polls to be scientifically valid, they must be based on a proper random sample.

The theory and practice of statistical sampling, including random sampling using surveys of human subjects, has been a fundamental topic within the science of statistics since the early twentieth century and is addressed in authoritative statistical textbooks such

as *Statistics Principles and Methods* by Richard Johnson and Gouri Bhattacharyya and *Sampling Techniques* by leading statistician William Cochran, as shown by the passages from those leading texts that have been identified as exhibits for trial. (Ex. D3624 (Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd edition, 1996); Ex. D6339 (William Cochran, *Sampling Techniques*, John Wiley & Sons, New York, 1977).) For instance, Johnson and Bhattacharya explain that: "The subject of statistics provides the methodology to make inferences about the population from the collection and analysis of sample data. These methods enable one to derive plausible generalizations and then assess the extent of uncertainty underlying these generalizations." They emphasize that "[s]tatistical concepts are also essential during the planning stage of an investigation when decisions must be made as to the mode and extent of the sampling process," so the "design of the sampling process is an important step" and "[a] good design for the process of data collection permits efficient inferences, often with a straightforward analysis."

Random sampling is the only reliable, scientific way to look at some elements from a large population, study the few that are selected, and make scientifically defensible statements about the entirety of the population without looking at the entirety. During the decades of my education and career as a professional statistician in academia and consulting, I have acquired extensive experience with numerous aspects of sampling theory, sample and survey design, sample and survey implementation, and the analysis of sample and survey data.

The Court allowed Janssen to survey 20 doctors through deposition. Because doctors who prescribe antipsychotic drugs to greater numbers of patients generally can be expected to have more experience regarding the efficacy of Risperdal and more experience regarding marketing and promotional activities of Janssen than doctors with fewer such

patients, the population to be sampled was the top 100 prescribers who prescribed antipsychotics most frequently for South Carolina patients in the FFS or SHP claims databases. Two doctors tied for the 100th place, so the sample was drawn from the top 101 prescribers. Those 101 doctors wrote 33 percent of the antipsychotic prescriptions paid for through the FFS and SHP programs. Ex. D7049 (Wecker electronic file "ffs_top_101.apd_pct.lst").

From the 101 most frequent prescribers, I selected at random, with equal probability of selection, a sample of 20. I used a standard random process—a sequence of random numbers generated by a computer—to identify the sample of 20 doctors at random from a list of all doctors eligible for selection. This random selection procedure guarantees a statistically representative sample because it rules out any purposive or inadvertent selection bias that could skew the composition of the sample towards any favored subgroup of doctors. Random sampling of this kind is a standard procedure in scientific survey research. (Ex. A, Slide 23.)

Defendants' counsel worked to contact the selected doctors in the deposition sample to arrange for and conduct their depositions. If a selected doctor was not available for deposition, which sometimes happened if a doctor was deceased or had moved from the State of South Carolina, the next member in the random selection sequence was designated as a replacement. To show the geographic location of the doctor-deponents in South Carolina, I prepared a map of the state with symbols identifying the doctors' locations. (Ex. A, Slide 24.) The doctors are spread all over the state, which makes sense because it is a random sample from the entire state.

For the depositions, I prepared a script with a set of 72 questions that addressed four issues—safety, tolerability, marketing, and the November 10, 2003 mailing. (Ex. A, Slide 25.) Exhibit 4 of my report shows the questions asked and the responses given. (Ex.

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D7008 (Wecker Report Exhibit 4).) Each of the 20 doctors was deposed under oath by an attorney, and each deposition was recorded by a court reporter. (Ex. A, Slide 23.) The attorneys taking the depositions followed the script and read the questions as I had written them and in the order in which I had written them. Doctors were asked about their experience with Risperdal and other antipsychotic medications and their specific exposure to Janssen promotional activity and communications. I designed the questions to elicit fact-based answers from doctors in response to questions about whether Janssen had marketed Risperdal to them for off-label uses, whether they had received specific correspondence from Janssen, and how their patients fared while taking Risperdal and other antipsychotics.

The attorneys representing the Attorney General were present at these depositions and they were allowed to ask questions. Based on my review, they did not take the opportunity to ask the same questions of every doctor so that the answers the doctor gave to the questions put to them by counsel for the Attorney General could be generalized to the entire survey population.

The deposition transcripts, which were prepared by the court reporters, were sent to me in electronic form. I coded the answers, which is a straightforward process because I designed the questions so that they were not open-ended. The questions were formulated so that doctors could respond "yes," "no," or that they did not have a basis to answer the question. Most answers were "yes" or "no," so I could code the responses "yes" or "no." In instances where a doctor responded that he or she had no basis to answer, I coded those answers accordingly.

Applying well-established statistical methodology to this sample, I was able to calculate, with a known degree of potential error, the responses that would be provided by the larger South Carolina population of frequent antipsychotic prescribers based on the answers provided in the survey. Exhibit 5 of my report shows the conclusions that can be

derived from the responses of 20 doctor-deponents about the entire population of the 101 most frequent prescribers. Ex. D7008 (Wecker Report Exhibit 5). The deposition transcripts show that the actual experience of South Carolina doctors prescribing Risperdal and other antipsychotics contradicts plaintiff's allegations.

As already noted, there were four categories of questions—safety, tolerability, marketing, and the November 10, 2003 mailing—and the results of the survey do not support plaintiff's allegations on these issues. (Ex. A, Slide 25.) To begin, the results concerning safety refute plaintiff's allegations. (Ex. A, Slides 26-28.) When doctors were asked "In your experience, are patients who take first generation antipsychotics such as Haldol and thorazine more likely to experience tardive dyskinesia than patients who take second generation antipsychotics?", ninety percent responded "yes" or "probably yes." Doctors were also asked "In your experience, does Risperdal typically have a more moderate side effect profile than first generation antipsychotics?" Seventy percent said "yes" or "probably yes." Finally, doctors were asked, "Overall, in your experience, is Risperdal a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?" Ninety-five percent answered "yes" or "probably yes."

The results on the issue of tolerability also fail to support plaintiff's contentions. (Ex. A, Slides 29-30.) First, when asked "In your experience, is Risperdal typically better tolerated than first generation antipsychotics?", 85 percent responded "yes" or "probably yes." Second, 95 percent of doctors answered "yes" or "probably yes" when asked "In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?" Finally, doctors were asked "In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?" Again, 95 percent said "yes" or "probably yes."

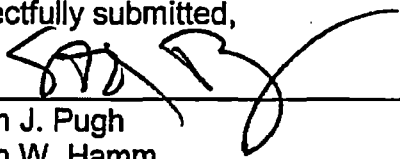
As to marketing, plaintiff's allegations are again contradicted by the results. (Ex. A, Slides 31-32.) Specifically, every doctor affirmed that no Janssen sales representative had "ever represented to you anything inconsistent with the warnings about Risperdal that are provided on the package insert." Likewise, every doctor affirmed that no Janssen sales representative had "ever misrepresented to you information about the potential side effects associated with Risperdal use."

Only a small number of doctors recall seeing Janssen's November 10, 2003 mailing to health care professionals. (Ex. A, Slides 33-35:) When asked "Have you ever seen this letter before?", referencing the November 10, 2003 mailing, only 20 percent said "yes" or "probably yes." Of those, almost none changed their choice of antipsychotic medication based on the mailing. Only 5 percent responded "yes" or "probably yes" to the questions

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"Did this letter cause you to change the circumstances in which you prescribed antipsychotics to your patients?" and "Did it cause you to change your choice of which antipsychotic to prescribe?"

Respectfully submitted,



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March 21, 2011.

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EXHIBIT A

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William E. Wecker, Ph.D.

Statistical Analysis

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WILLIAM E. WECKER
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■ **EDUCATION**

B.S. (Basic Science) (1963), USAF Academy

M.S. (Operations Research) (1970), University of Michigan

Ph.D. (Statistics and Management Science) (1972), University of Michigan

■ **EMPLOYMENT**

1963-1967 Fighter pilot, USAF

1968-1969 Chief of Protocol, USAF, Berlin, Germany

1970-1972 Graduate Student, University of Michigan

1973-1976 Assistant Professor, Graduate School of Business, University of Chicago

1977-1983 Associate Professor, Graduate School of Business, University of Chicago

1984-1985 Associate Professor, Graduate School of Management,

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1985-1989 Professor, Graduate School of Management, University of California, Davis

1994-1998 Consulting Professor of Law, School of Law, Stanford University

1990-present President, William E. Wecker Associates, Inc.

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William E. Wecker Associates, Inc.

- **20 Statisticians and Mathematicians**
- **More than 50 different computer systems**
- **Analyzing more than 65 billion records of data for currently active projects alone (many times the amount of information in the entire United States Library of Congress)**

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Caro Study: Statistical Significance

Relative Risk of Developing Diabetes in Olanzapine Versus Risperidone Users (adjusted for age, gender, and haloperidol use)		
Model	Adjusted Relative Risk (95% CI)	p Value
All Patients	1.20 (1.00 to 1.43)	.05
Women	1.30 (1.05 to 1.65)	.02
Drug exposure time		
< 3 months	1.90 (1.40 to 2.57)	.0001
3 < 6 months	1.16 (0.75 to 1.78)	.50
6 < 12 months	1.11 (0.81 to 1.51)	.51
≥ 12 months	1.06 (0.86 to 1.31)	.58

Statistically significant results shown in red.
Non-statistically significant results shown in blue.

Source: Caro JJ, Ward A, Levinton C and Robinson K. *The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis.* Journal of Clinical Psychiatry 2000;63:1135-1139.

Statistical Evidence: November 10, 2003

<i>Peer-Reviewed Studies</i>	Risperdal is not associated with an increased risk of diabetes when compared to ...		Risperdal is associated with a lower risk of diabetes than some other studied atypical antipsychotics
	... untreated patients	... patients treated with conventional antipsychotics	
<i>Buse</i>		✓	
<i>Caro</i>			✓
<i>Fuller</i>			✓
<i>Gianfrancesco No. 1</i>	✓	✓	
<i>Gianfrancesco No. 2</i>	✓	✓	✓
<i>Gianfrancesco No. 3</i>	✓	✓	✓
<i>Koro</i>	✓	✓	
<i>Sernyak</i>		✓	

✓: article supports the statement.

Blank: article does not address the statement or results are not statistically significant.

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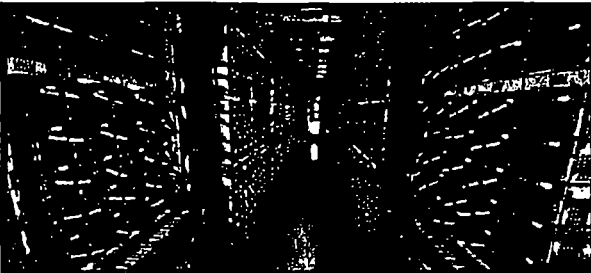
What else did you analyze for this case?



- I reviewed the South Carolina Medicaid and State Health Plan claims data to learn what happened to **South Carolina patients** who took Risperdal or other antipsychotics.

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South Carolina Patients: How did you get information about them?



The Medicaid and State Health Plan Claims Databases

R. 8721 The State's claims databases are computerized databases for Medicaid and the State Health Plan that contain an entry for every time a patient received a prescription or medical treatment that was submitted for payment to one of the programs.

The databases are not like getting a patient's medical records or "chart."

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South Carolina Patients: How did you analyze the patient data?

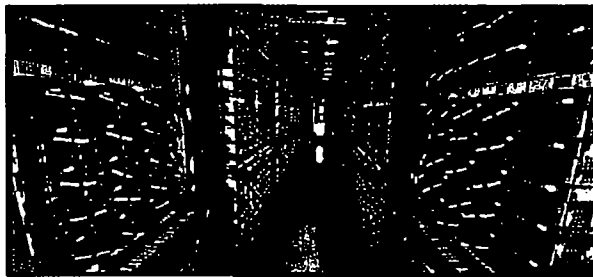


The Medicaid and State Health Plan Claims Databases (cont.)

I reviewed the entries in the databases for all patients who received an antipsychotic prescription, whether for Risperdal or any other antipsychotic, for all of the treatment those patients received when they were eligible for Medicaid or the State Health Plan.

The databases contain different types of information, such as what drug was prescribed, whether there was a hospital stay, and how much it cost; in some cases there is also a diagnosis listed for the patient.

South Carolina Patients: How many patients and records did you analyze?



The Medicaid and State Health
Plan Claims Databases

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Total Patients: 136,694

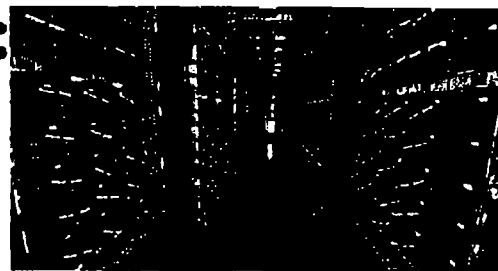
Total Records: 90,397,060

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Source: South Carolina Medicaid and State Health Plan Claims Databases.



South Carolina Patients: What did you learn about side effects?



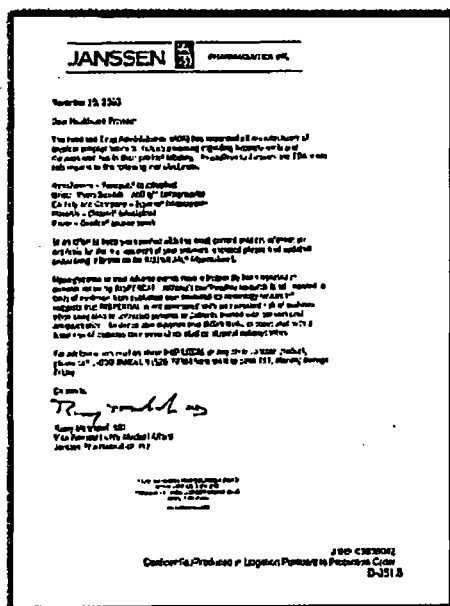
South Carolina Medicaid and State Health Plan patients who took Risperdal experienced fewer side effects than:

- ✓ Untreated patients.
- ✓ Patients who took conventional antipsychotics.
- ✓ Patients who took other atypical antipsychotics.

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South Carolina Patients: What did you learn about side effects?



South Carolina patients' experience is consistent with:



The statements Janssen made in the November 10, 2003 mailing.

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South Carolina Patients: How did you compare Risperdal patients to patients receiving other antipsychotics?

Date of First
Antipsychotic Drug
Prescription

Side Effect Diagnosis?

1	2	3	4	5	6	7	8	9	10	11	12	Year One	Year Two	Year Three

←
At least 12 Months of Uninterrupted
Eligibility with No Side Effect Diagnosis

Review Each Patient's Medicaid Claims

South Carolina Patients: How did you compare Risperdal patients to untreated patients?

Date of First
Antipsychotic Drug
Prescription

Side Effect Diagnosis?

1	2	3	4	5	6	7	8	9	10	11	12	Year One	Year Two	Year Three

←
At least 12 Months of Uninterrupted
Eligibility with No Side Effect Diagnosis

Review Each Patient's Medicaid Claims

South Carolina Patients: Excess Side Effect Risk Relative to Risperdal

Antipsychotic Drug Prescribed	Excess Diabetes Risk (Compared to Risperdal)
1 st Generation	1.62% (*)
Other 2 nd Generation	2.33% (*)
Untreated	1.29% (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

Source: South Carolina Medicaid and State Health Plan Claims Databases.

South Carolina Patients: Excess Side Effect Risk Relative to Risperdal

Antipsychotic Drug Prescribed	Excess Risk of Metabolic Adverse Events (Compared to Risperdal)
1 st Generation	1.46% (*)
Other 2 nd Generation	4.47% (*)
Untreated	0.99% (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

Metabolic Adverse Events include:	
☒	Diabetes mellitus
☒	Secondary diabetes mellitus
☒	Overweight and obesity
☒	Abnormal weight gain
☒	Abnormal glucose

Source: South Carolina Medicaid and State Health Plan Claims Databases.

South Carolina Patients: Excess Side Effect Risk Relative to Risperdal

Antipsychotic Drug Prescribed	Excess Risk of Increased Prolactin Secretion (Compared to Risperdal)
1 st Generation	3.64% (*)
Other 2 nd Generation	1.82% (*)
Untreated	2.22% (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

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Source: South Carolina Medicaid and State Health Plan Claims Databases.

South Carolina Patients: Excess Diabetes Risk Relative to Risperdal As of November 10, 2003

Antipsychotic Drug Prescribed	Alleged Side Effect: Diabetes
1 st Generation	1.17% (*)
Other 2 nd Generation	1.84% (*)
Untreated	1.32% (*)

(*) Value is statistically significantly different from Risperdal value at 95% confidence level.

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Source: South Carolina Medicaid and State Health Plan Claims Databases.

South Carolina Patients: Patient Experience Supports Janssen's Statements

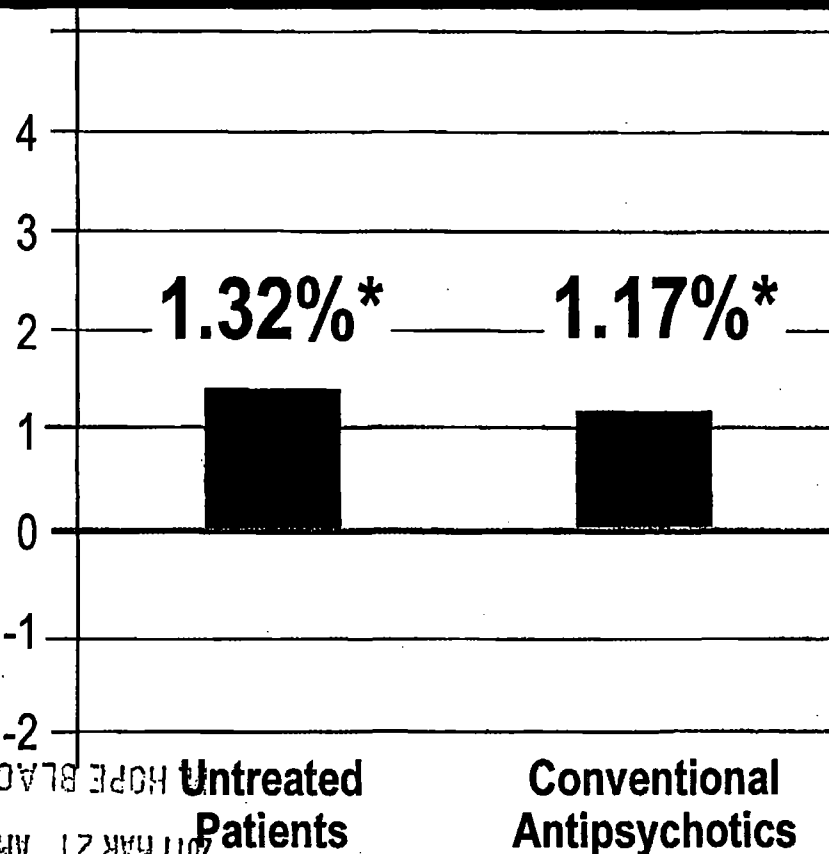
November 10, 2003 Mailing

JANSSEN  PHARMACEUTICALS, INC.

"Although confirmatory evidence is still needed, a body of evidence from published peer-reviewed epidemiology research suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics."

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**Excess Diabetes Risk Relative to Risperdal
(all age groups)**



Source: South Carolina Medicaid and State Health Plan Claims Databases.

* Statistically significant result.

South Carolina Patients: Patient Experience Supports Janssen's Statements

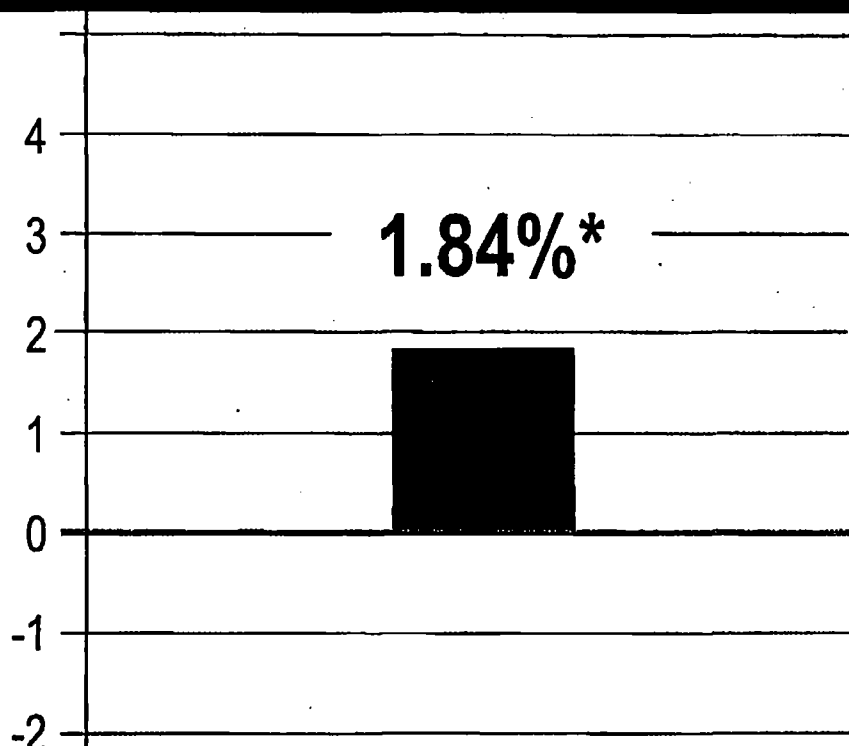
November 10, 2003 Mailing

JANSSEN  PHARMACEUTICALS, INC.

"Although confirmatory evidence is still needed, a body of evidence from published peer-reviewed epidemiology research suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics."

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D-351.5

**Excess Diabetes Risk Relative to Risperdal
(all age groups)**



**Other Atypical
Antipsychotics**

* Statistically significant result.

Source: South Carolina Medicaid and State Health Plan Claims Databases.

What else did you do to analyze plaintiff's claims?



- I learned what the experience of **South Carolina doctors** says about the plaintiff's claims.

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South Carolina Doctors: How did you get information from them?



- I identified at random 20 South Carolina doctors who prescribed Risperdal and other antipsychotics to Medicaid and State Health Plan patients.
- The doctors were questioned under oath.
- The answers the doctors gave were recorded.

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South Carolina Doctors:

Why did you choose the 20 doctors at random?



- Random sampling is the only valid method for creating a properly representative sample from a group when the group is too big to question every member.
- *Statistics Principles and Methods* (statistics textbook):
 - "The subject of statistics provides the methodology to make inferences about the population from the collection and analysis of sample data."

Source: Richard Johnson and Gouri Bhattacharyya, *Statistics Principles and Methods*, John Wiley & Sons, 3rd ed., 1996, 14, Exhibit D3624.

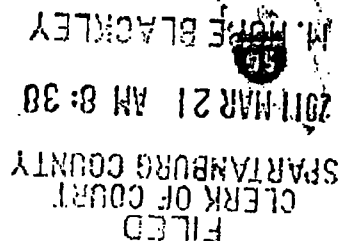
South Carolina Doctors: How did you learn about their experience?



- Each doctor was asked the same questions, in the same order.
- The doctors gave their answers under oath.
- The answers were recorded in writing by a court reporter.
- All of the answers were reviewed and counted.

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South Carolina Doctors: What did you learn?

In the experience of South Carolina doctors:

- ✓ **Safety**: Risperdal is safer than first generation antipsychotics.
- ✓ **Tolerability**: Risperdal is better tolerated than first generation antipsychotics.
- ✓ **Marketing**: Janssen did not make false statements to doctors about Risperdal's side effects.
- ✓ **The November 2003 Mailing**: The mailing had no impact on doctors' prescribing habits.

Source: Depositions of 20 South Carolina Doctors.

South Carolina Doctors: What did you learn about Risperdal's safety?

DR. SALLIE A. CARTER, after having been first duly sworn by the above-mentioned Court Reporter, did testify as follows:

Q. In your experience, are patients who take **first-generation antipsychotics** such as Haldol and Thorazine **more likely to experience tardive dyskinesia** than patients who take second-generation antipsychotics?

A. Yes.

Q. In your experience, does **Risperdal** typically have a **more moderate side effect profile** than first generation antipsychotics?

A. Yes.

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South Carolina Doctors: What did you learn about Risperdal's safety?

Question	South Carolina Doctors
In your experience, are patients who take first generation antipsychotics such as Haldol and thorazine more likely to experience tardive dyskinesia than patients who take second generation antipsychotics?	90% "Yes" or "Probably Yes"
In your experience, does Risperdal typically have a more moderate side effect profile than first generation antipsychotics?	70% "Yes" or "Probably Yes"

Source: Depositions of 20 South Carolina Doctors.

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South Carolina Doctors: What did you learn about Risperdal's safety?

Question	South Carolina Doctors
Overall, in your experience, is Risperdal a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	95% "Yes" or "Probably Yes"

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Source: Depositions of 20 South Carolina Doctors.

South Carolina Doctors: What did you learn about Risperdal's tolerability?

DR. KATHY MARIE WAGGETT, having been first duly sworn, was examined and testified as follows:

Q. In your experience, is Risperdal typically better tolerated than first generation antipsychotics?

A. Yes.

Q. In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?

A. Yes.

Q. ... are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?

A. Yes.

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South Carolina Doctors: What did you learn about Risperdal's tolerability?

Question	South Carolina Doctors
In your experience, is Risperdal typically better tolerated than first generation antipsychotics?	85% "Yes" or "Probably Yes"
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	95% "Yes" or "Probably Yes"
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?	95% "Yes" or "Probably Yes"

Source: Depositions of 20 South Carolina Doctors.

South Carolina Doctors: What did you learn about Janssen's marketing?

EUGENE F. SMITH, M.D., 250 DEWEY AVE, SPARTANBURG, SOUTH CAROLINA
being duly sworn and cautioned to speak the truth, testified as follows:

Q. Dr. Smith, has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal that are provided on the package insert?

A. No.

Q. Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal use?

A. No.

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South Carolina Doctors: What did you learn about Janssen's marketing?

Question	South Carolina Doctors
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal that are provided on the package insert?	0% "Yes" or "Probably Yes"
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal use?	0% "Yes" or "Probably Yes"

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Source: Depositions of 20 South Carolina Doctors.

South Carolina Doctors:

Did the November 2003 mailing cause a change in doctors' choice of antipsychotics for patients?

DR. ROSEN J. LAWSIN, testified under oath as follows:

Q. Dr. Lawsin, have you seen this letter before?

A. Yes, sir.

Q. You have.

A. I received it and I read it.

Q. When you received this letter, did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?

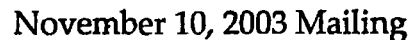
A. No, sir.

Q. Did it cause you to change your choice of which antipsychotic to prescribe?

A. Not really. No, sir.

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R. 8748



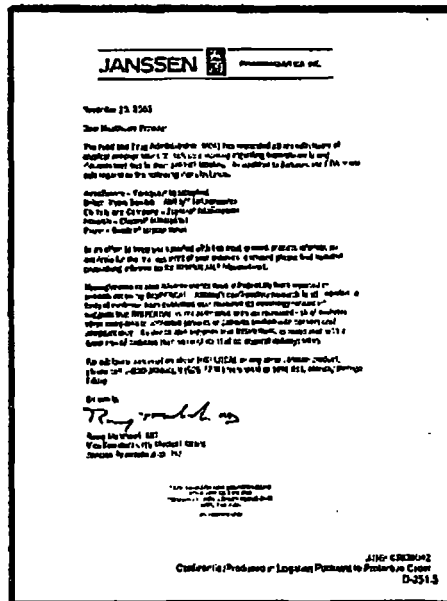
Question	South Carolina Doctors
Have you ever seen this letter before?	20% “Yes” or “Probably Yes”

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South Carolina Doctors: Did the November 2003 mailing cause a change in doctors' choice of antipsychotics for patients?

R. 8749



November 10, 2003 Mailing

Question	South Carolina Doctors
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	5% "Yes" or "Probably Yes"
Did it cause you to change your choice of which antipsychotic to prescribe?	5% "Yes" or "Probably Yes"

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Statistics

Principles and Methods

THIRD EDITION

Richard A. Johnson

Gouri K. Bhattacharyya

University of Wisconsin at Madison

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Library of Congress Cataloging-in-Publication Data:
Johnson, Richard Arnold.

Statistics : principles and methods / Richard A. Johnson, Gouri K.
Bhattacharyya.—3rd ed.

p. cm.

Includes index.

ISBN 0-471-04194-7 (cloth : alk. paper)

I. Statistics. I. Bhattacharyya, Gouri K., 1940–

QA276.12J63 1996

519.5—dc20

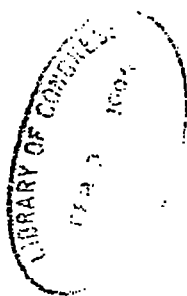
II. Title.

95-39204

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Introduction

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1. What Is Statistics?
2. Statistics in Our Everyday Life
3. Statistics in Aid of Scientific Inquiry
4. Two Basic Concepts—Population and Sample
5. The Purposeful Collection of Data
6. Objectives of Statistics
7. Review Exercises

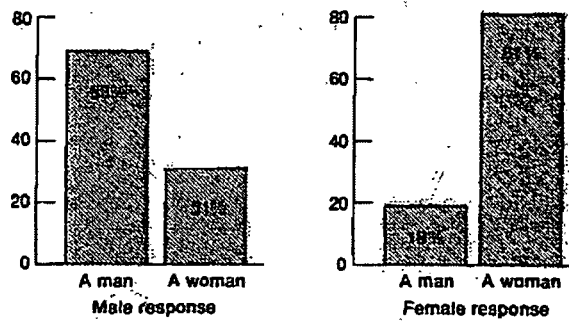
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Gallup Opinion Index

Trend in the popularity of the big three sports. Football is the favorite spectator sport in the United States. What is your favorite spectator sport?

	1990	1981	1972	1960	1948
Football	35%	38%	36%	21%	17%
Baseball	16%	16%	21%	34%	39%
Basketball	15%	9%	8%	9%	10%
Other	33%	37%	35%	36%	34%

Opposites Often Attract
Is your best friend a man or a woman?



Hometown fans attending today's game are but a sample of the population of all local baseball fans. A self-selected sample may not be entirely representative of the population on issues such as ticket price increases.

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1. WHAT IS STATISTICS?

The word statistics originated from the Latin word "status" meaning "state." For a long time, it was identified solely with the displays of data and charts pertaining to the economic, demographic, and political situations prevailing in a country. Even today, a major segment of the general public thinks of statistics as synonymous with forbidding arrays of numbers and myriads of graphs. This image is enhanced by numerous government reports that contain massive compilation of numbers and carry the word statistics in their titles: "Statistics of Farm Production," "Statistics of Trade and Shipping," "Labor Statistics," to name a few. However, gigantic advances during the twentieth century have enabled statistics to grow and assume its present importance as a discipline of data-based reasoning. Passive display of numbers and charts is now a minor aspect of statistics, and few, if any, of today's statisticians are engaged in the routine activities of tabulation and charting.

What, then, are the role and principal objectives of statistics as a scientific discipline? Stretching well beyond the confines of data display, statistics deals with collecting informative data, interpreting these data, and drawing conclusions about a phenomenon under study. The scope of this subject naturally extends to all processes of acquiring knowledge that involve fact finding through collection and examination of data. Opinion polls (surveys of households to study sociological, economic, or health-related issues), agricultural field experiments (with new seeds, pesticides, or farming equipment), clinical studies of vaccines, and cloud seeding for artificial rain production are just a few examples. The principles and methodology of statistics are useful in answering questions such as, What kind and how much data need to be collected? How should we organize and interpret the data? How can we analyze the data and draw conclusions? How do we assess the strength of the conclusions and gauge their uncertainty?

Statistics as a subject provides a body of principles and methodology for designing the process of data collection, summarizing and interpreting the data, and drawing conclusions or generalities.

2. STATISTICS IN OUR EVERYDAY LIFE

Fact finding through the collection and interpretation of data is not confined to professional researchers. In our attempts to understand issues of environmental protection, the state of unemployment, or the performance of competing football teams, numerical facts and figures need to be reviewed and interpreted. In our day-to-day life, learning takes place through an often implicit analysis of factual information.

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We are all familiar to some extent with reports in the news media on important statistics.

Employment. Monthly, as part of the Current Population Survey, the Bureau of Census collects information about employment status from a sample of about 65,000 households. Households are contacted on a rotating basis with three-fourths of the sample remaining the same for any two consecutive months.

The survey data are analyzed by the Bureau of Labor Statistics which reports monthly unemployment rates. □

Cost of living. The consumer price index (CPI) measures the cost of a fixed market basket of over 400 goods and services. Each month, prices are obtained from a sample of over 18,000 retail stores that are distributed over 85 metropolitan areas. These prices are then combined taking into account the relative quantity of goods and services required, in 1967, by a hypothetical "urban wage earner." Let us not be concerned with the details of the sampling method and calculations as these are quite intricate. They are, however, under close scrutiny because of the importance to the hundreds of thousands of Americans whose earnings or retirement benefits are tied to the CPI. □

Election time brings the pollsters into the limelight.

Gallup Poll. This, the best known of the national polls, produces estimates of the percentage of popular vote for each candidate based on interviews with a minimum of 1500 adults. Beginning several months before the presidential election, results are regularly published. These reports help predict winners and track changes in voter preferences.

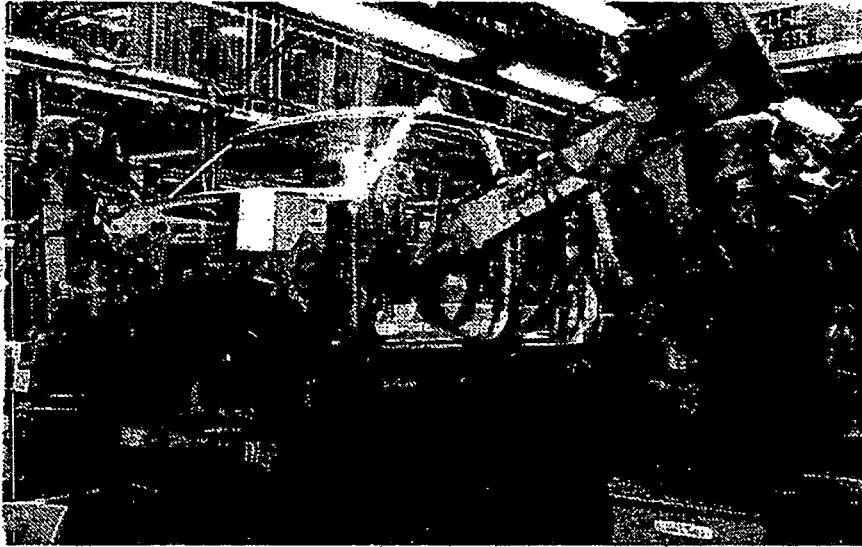
Our sources of factual information range from individual experience to reports in news media, government records, and articles in professional journals. As consumers of these reports, citizens need some idea of statistical reasoning to properly interpret the data and evaluate the conclusions. Statistical reasoning provides criteria for determining which conclusions are supported by the data and which are not. The credibility of conclusions also depends greatly on the use of statistical methods at the data collection stage. Statistics provides a key ingredient for any systematic approach to improve any type of process from manufacturing to service.

Quality and productivity improvement. In the past 30 years, the United States has faced increasing competition in the world marketplace. An international revolution in quality and productivity improvement has heightened the pressure on the U. S. economy. The ideas and teaching of W. Edwards Deming helped rejuvenate Japan's industry in the late 1940s and 1950s. In the 1980s and 1990s, Deming stressed to American executives that, in order to survive, they must mobilize their work force to make a continuing commitment to quality improvement. His ideas have also been applied to government. The city of

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Statistical reasoning can guide the purposeful collection and analysis of data toward the continuous improvement of any process.

Madison, WI, has implemented quality improvement projects in the police department and in bus repair and scheduling. In each case, the project goal was better service at less cost. Treating citizens as the customers of government services, the first step was to collect information from them in order to identify situations that needed improvement. One end result was the strategic placement of a new police substation and a subsequent increase in the number of foot patrol persons to interact with the community.

Once a candidate project is selected for improvement, data must be collected to assess the current status and then more data collected on the effects of possible changes. At this stage, statistical skills in the collection and presentation of summaries are not only valuable but necessary for all participants.

In an industrial setting, statistical training for all employees—production line and office workers, supervisors, and managers—is vital to the quality transformation of American industry.

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3. STATISTICS IN AID OF SCIENTIFIC INQUIRY

The phrase scientific inquiry refers to a systematic process of learning. A scientist sets the goal of an investigation, collects relevant factual information (or data), analyzes the data, draws conclusions, and decides further courses of action. We briefly outline a few illustrative scenarios.

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Training programs. Training or teaching programs in many fields designed for a specific type of clientele (college students, industrial workers, minority groups, physically handicapped people, retarded children, etc.) are continually monitored, evaluated, and modified to improve their usefulness to society. To learn about the comparative effectiveness of different programs, it is essential to collect data on the achievement or growth of skill of the trainees at the completion of each program. □

Monitoring advertising claims. The public is constantly bombarded with commercials that claim the superiority of one product brand in comparison to others. When such comparisons are founded on sound experimental evidence, they serve to educate the consumer. Not infrequently however, misleading advertising claims are made due to insufficient experimentation, faulty analysis of data, or even blatant manipulation of experimental results. Government agencies and consumer groups must be prepared to verify the comparative quality of products by using adequate data collection procedures and proper methods of statistical analysis. □

Plant breeding. To increase food production, agricultural scientists develop new hybrids by cross-fertilizing different plant species. Promising new strains need to be compared with the current best ones. Their relative productivity is assessed by planting some of each variety at a number of sites. Yields are re-



Statistically designed experiments are needed to document the advantages of the new breed versus the old breed.

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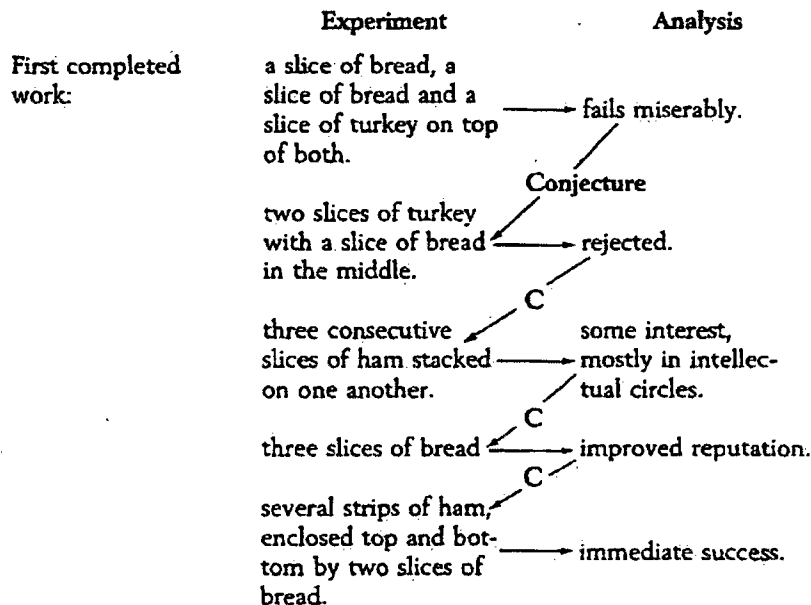
corded and then analyzed for apparent differences. The strains may also be compared on the basis of disease resistance or fertilizer requirements.

Building beams. Wooden beams that support roofs on houses and public buildings must be strong. Most beams are constructed by laminating together several boards. Wood scientists have collected data that show stiffer boards are generally stronger. This relation can be used to predict the strength of candidate boards for laminating on the basis of their stiffness measurements.

Factual information is crucial to any investigation. The branch of statistics called experimental design can guide the investigator in planning the manner and extent of data collection.

After the data are collected, statistical methods are available that summarize and describe the prominent features of data. These are commonly known as descriptive statistics. Today, a major thrust of the subject is the evaluation of information present in data and the assessment of the new learning gained from this information. This is the area of inferential statistics and its associated methods are known as the methods of statistical inference.

The Conjecture-Experiment-Analysis Learning Cycle
Invention of the Sandwich by the Earl of Sandwich
 (According to Woody Allen, Humorist)*



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It must be realized that a scientific investigation is typically a process of trial and error. Rarely, if ever, can a phenomenon be completely understood or a theory perfected by means of a single, definitive experiment. It is too much to expect to get it all right in one shot. Even after his first success with the electric light bulb, Thomas Edison had to continue to experiment with numerous materials for the filament before it was perfected. Data obtained from an experiment provide new knowledge. This knowledge often suggests a revision of an existing theory, and this itself may require further investigation through more experiments and analysis of data. Humorous as it may appear, the excerpt boxed above from a Woody Allen writing captures the vital point that a scientific process of learning is essentially iterative in nature.

4. TWO BASIC CONCEPTS—POPULATION AND SAMPLE

In the preceding sections, we cited a few examples of situations where evaluation of factual information is essential for acquiring new knowledge. Although these examples are drawn from widely differing fields and only sketchy descriptions of the scope and objectives of the studies are provided, a few common characteristics are readily discernible.

First, in order to acquire new knowledge, relevant data must be collected. Second, some amount of variability in the data is unavoidable even though observations are made under the same or closely similar conditions. For instance, the treatment for an allergy may provide long-lasting relief for some individuals whereas it may bring only transient relief or even none at all to others. Likewise, it is unrealistic to expect that college freshmen whose high school records were alike would perform equally well in college. Nature does not follow such a rigid law.

A third notable feature is that access to a complete set of data is either physically impossible or from a practical standpoint not feasible. When data are obtained from laboratory experiments or field trials, no matter how much experimentation has been performed, more can always be done. In public opinion or consumer expenditure studies, a complete body of information would emerge only if data were gathered from every individual in the nation—undoubtedly a monumental if not an impossible task. To collect an exhaustive set of data related to the damage sustained by all cars of a particular model under collision at a specified speed, every car of that model coming off the production lines would have to be subjected to a collision! Thus, the limitations of time, resources, and facilities, and sometimes the destructive nature of the testing, mean that we must work with incomplete information—the data that are actually collected in the course of an experimental study.

The preceding discussions highlight a distinction between the data set that is actually acquired through the process of observation and the vast collection of all potential observations that can be conceived in a given context. The statistical name for the former is sample; for the latter, it is population, or statistical population. To further elucidate these concepts, we observe that each measure-

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ment in a data set originates from a distinct source which may be a patient, tree, farm, household, or some other entity depending on the object of a study. The source of each measurement is called a sampling unit, or simply, a unit. A sample or sample data set then consists of measurements recorded for those units that are actually observed. The observed units constitute a part of a far larger collection about which we wish to make inferences. The set of measurements that would result if all the units in the larger collection could be observed is defined as the population.

A statistical population is the set of measurements (or record of some qualitative trait) corresponding to the entire collection of units about which information is sought.

The population represents the target of an investigation. We learn about the population by taking a sample from the population.

A sample from a statistical population is the set of measurements that are actually collected in the course of an investigation.

Example 1

A newspaper headline reads, **CAFFEINE CONSUMPTION CAN LEAD TO DEPENDENCE**, and the article¹ describes a medical study in which ninety-nine subjects volunteered as having a problem, physically or psychologically, with caffeine dependence. Among these subjects, 11 were confirmed to have a dependence and agreed to take part in a trial. They alternated two weeks of taking pills containing caffeine with two weeks of taking look-alike pills without caffeine. The trial was called a double blind trial because neither the subjects nor those administering the pills knew which set of pills had the active ingredient. Nine of the patients showed objective evidence of withdrawal.

Identify the population and sample.

SOLUTION

As the article implies, the information should apply to you and me. The population here could well be the withdrawal responses of all who consume caffeine in the United States or even in the world, although the cultural customs may vary the type of caffeine consumption from coffee breaks, to

¹E. C. Strain, et al. "Caffeine Dependence Syndrome," *Journal of the American Medical Association* 272, (1994), pp. 1043–1048.

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tea time, to kola nut chewing. The sample would consist of the withdrawal responses of the 11 persons who agreed to participate in the double blind trial.

Example 2 A host of a radio music show announced that she wants to know what singer is the favorite among city residents. Listeners were then asked to call in and name their favorite singer.

Identify the population and sample. Comment on how to get a sample that is more representative of the city's population.

SOLUTION The population is the collection of singer preferences of all city residents and the purported goal was to learn who was the favorite singer. Because it would be nearly impossible to question all the residents in a large city, one must necessarily settle for taking a sample.

Having residents make a local call is certainly a low-cost method of getting a sample. The sample would then consist of the singers named by each person who calls the radio station. Unfortunately, with this selection procedure, the sample is not very representative of the responses from all city residents. Those that listen to the particular radio station are already a special subgroup with similar listening tastes. Furthermore, those listeners who take the time and effort to call are usually those who feel strongest about their opinions. The resulting responses could well be much stronger in favor of a particular country western or rock singer than is the case for preference among the total population of city residents or even those who listen to the station.

If the purpose of asking the question is really to determine the favorite singer of the city's residents, we have to proceed otherwise. One procedure commonly employed is a phone survey where the phone numbers are chosen at random. For instance, one can imagine that the numbers 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 are written on separate pieces of paper and placed in a hat. Slips are then drawn one at a time without replacement. Later, we will see that computers can mimic this selection quickly and easily. Four draws will produce a random telephone number within a three-digit exchange. Telephone numbers chosen in this manner will certainly produce a much more representative sample than the self-selected sample of persons who call the station.

Self-selected samples consisting of responses to call-in or write-in requests will, in general, not be representative of the population. They arise primarily from subjects who feel strongly about the issue in question. To their credit, many TV news and entertainment programs now state that their call-in polls are non-scientific and merely reflect the opinions of those persons who responded.

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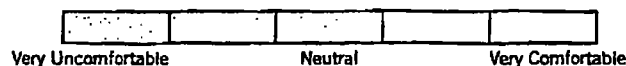
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Data collected with a clear-cut purpose in mind are very different from anecdotal data. Most of us have heard people say they won money at a casino, but certainly most people cannot win most of the time as casinos are not in the business of giving away money. People tend to tell good things about themselves. In a similar vein, some drivers' lives are saved when they are thrown free of car wrecks because they were not wearing seat belts. Although such stories are told and retold, you must remember that there is really no opportunity to hear from those who would have lived if they had worn their seat belts. Anecdotal information is usually repeated because it has some striking feature that may not be representative of the mass of cases in the population. Consequently, it is not apt to provide reliable answers to questions.

5. THE PURPOSEFUL COLLECTION OF DATA

Many poor decisions are made, in both business and everyday activities, because of the failure to understand and account for variability. Certainly, the purchasing habits of one person may not represent those of the population, or the reaction of one mouse, on exposure to a potentially toxic chemical compound, may not represent that of a large population of mice. However, despite diversity among the purchasing habits of individuals, we can obtain accurate information about the purchasing habits of the population by collecting data on a large number of persons. By the same token, much can be learned about the toxicity of a chemical if many mice are exposed.

Just making the decision to collect data to answer a question, to provide the basis for taking action, or to improve a process is a key step. Once that decision has been made, an important next step is to develop a statement of purpose that is both specific and unambiguous. If the subject of the study is public transportation being behind schedule, you must carefully specify what is meant by late. Is it 1 minute, 5 minutes, or more than 10 minutes behind scheduled times that should result in calling a bus or commuter train late? Words like soft or uncomfortable in a statement are even harder to quantify. One common approach, for a quality like comfort, is to ask passengers to rate the ride on public transportation on the five-point scale



where the numbers 1 through 5 are attached to the scale, with 1 for very uncomfortable and so on through 5 for very comfortable.

A clearly specified statement of purpose will guide the choice of what data to collect and help ensure that it will be relevant to the purpose. Without a clearly specified purpose, or terms unambiguously defined, much effort can be wasted in collecting data that will not answer the question of interest.

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The overall goal for a study can be quite general, but at each step a specific statement of purpose is needed. For instance, a primary health facility became aware that sometimes it was taking too long to return patients' phone calls. That is, patients would phone in with requests for information. These requests, in turn, had to be turned over to doctors or nurses who would collect the information and return the call. The overall objective was to understand the current procedure and then improve on it. As a good first step, it was decided to find how long it was taking to return calls under the current procedure. Variation in times from call to call is expected, so the purpose of the initial investigation is to benchmark the variability with the current procedure by collecting a sample of times.

PURPOSE: Obtain a reference or benchmark for the current procedure by collecting a sample of times to return a patient's call under the current procedure.

For a sample of incoming calls collected during the week, the time received was noted along with the request. When the return call was completed, the elapsed time, in minutes, was recorded. Each of these times is represented as a dot in Figure 1. Notice that over one-third of the calls took over 120 minutes, or over two hours, to return. This could be a long time to wait for information if it concerns a child with a high fever or an adult with acute symptoms. If the purpose was to determine what proportion of calls took too long to return, we would need to agree on a more precise definition of "too long" in terms of number of minutes. Instead, these data clearly indicate that the process needs improvement and the next step is to proceed in that direction.

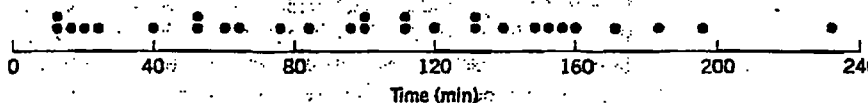


Figure 1 Time in minutes to return call.

In any context, to pursue potential improvements of a process, one needs to focus more closely on particulars. Three questions

When Where Who

should always be asked before gathering further data. More specifically, data should be sought that will answer the following questions.

When do the difficulties arise? Is it during certain hours, certain days of the week or month, or in coincidence with some other activities?

Where do the difficulties arise? Try to identify the locations of bottlenecks and unnecessary delays.

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Who was performing the activity and who was supervising? The idea is not to pin blame, but to understand the roles of participants with the goal of making improvements.

It is often helpful to construct a cause-and-effect diagram or fishbone diagram. The main centerline represents the problem or the effect. A somewhat simplified fishbone chart is shown in Figure 2 for the *where* question regarding the location of delays when returning patients' phone calls. The main centerline represents the problem: Where are delays occurring? Calls come to the reception desk, but when these lines are busy, the calls go directly to nurses on the third or fourth floor. The main diagonal arms in Figure 2 represent the floors and the smaller horizontal lines more specific locations on the floor where the delay could occur. For instance, the horizontal line representing a delay in retrieving a patient's medical record connects to the second floor diagonal line. The resulting figure resembles the skeleton of a fish. Consideration of the diagram can help guide the choice of what new data to collect.

Fortunately, the quality team conducting this study had already given preliminary consideration to the *When*, *Where*, and *Who* questions and recorded not only the time of day, but day and person receiving the call. That is, their current data gave them a start on determining if the time to return calls depends on when or where the call is received.

Although we go no further with this application here, the quality team next developed more detailed diagrams to study the flow of paper between the time the call is received and when it is returned. They then identified bottlenecks in the flow of information that were removed and the process was improved. In later chapters, you will learn how to compare and display data from two locations or old and new processes, but the key idea emphasized here is the purposeful collection of relevant data.

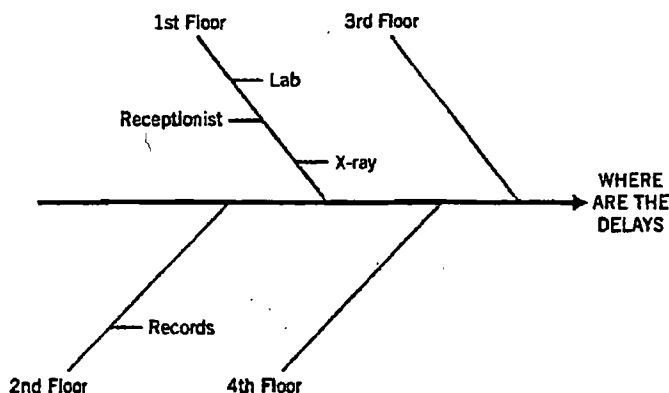


Figure 2 A cause-and-effect diagram for the location of delays.

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6. OBJECTIVES OF STATISTICS

The subject of statistics provides the methodology to make inferences about the population from the collection and analysis of sample data. These methods enable one to derive plausible generalizations and then assess the extent of uncertainty underlying these generalizations. Statistical concepts are also essential during the planning stage of an investigation when decisions must be made as to the mode and extent of the sampling process.

The major objectives of statistics are:

1. To make inferences about a population from an analysis of information contained in sample data. This includes assessments of the extent of uncertainty involved in these inferences.
2. To design the process and the extent of sampling so that the observations form a basis for drawing valid inferences.

The design of the sampling process is an important step. A good design for the process of data collection permits efficient inferences to be made; often with a straightforward analysis. Unfortunately, even the most sophisticated methods of data analysis cannot, in themselves, salvage much information from data that are produced by a poorly planned experiment or survey.

The early use of statistics in the compilation and passive presentation of data has been largely superseded by the modern role of providing analytical tools with which data can be efficiently gathered, understood, and interpreted. Statistical concepts and methods make it possible to draw valid conclusions about the population, on the basis of a sample. Given its extended goal, the subject of statistics has penetrated all fields of human endeavor in which the evaluation of information must be grounded in data-based evidence.

The basic statistical concepts and methods, described in this book, form the core in all areas of application. We present examples drawn from a wide range of applications to help develop an appreciation of various statistical methods, their potential uses, and their vulnerabilities to misuse.

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KEY IDEAS

A population is the complete set of measurements, or record of a qualitative trait, corresponding to the collection of all units about which information is desired.

A sample from the population is the set of measurements that are actually collected.

Statistics is a body of principles for designing the process of data collection and making inferences about the population from the information in the sample.

A statement of purpose is a key step in designing the data collection process.

7. REVIEW EXERCISES

- 7.1 A newspaper headline reads,

U.S. TEENS TRUST, FEAR THEIR PEERS

and the article explains that a telephone poll was conducted of 1055 persons 13 to 17 years old. Identify a population and the sample.

- 7.2 A consumer magazine article asks,

HOW SAFE IS THE AIR IN AIRPLANES?

and then says that its study of air quality is based on measurements taken on 158 different flights of U.S. based airlines. Identify a population and the sample.

- 7.3 A scientist² testifying before a congressional hearing on the effects of estrogenic pesticides told every man in the room that he "is half the man his grandfather was." The scientist was dramatizing a report on worldwide studies involving 14,847 men, over many different years and in many countries, that showed male semen concentrations have dropped approximately 50% over the past 50 years.

Identify a population and the sample.

- 7.4 A magazine that features the latest electronics and computer software for homes enclosed a short questionnaire on a postcard. Readers were asked to answer questions concerning their use and ownership of various software and hardware products, and to then send the card to the publisher. A summary of the results appeared in a later issue of the magazine that

²Louis Guillelte. Hearing before the Subcommittee on Health and the Environment. Serial No. 103-87, Oct. 21, 1993.

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- used the data to make statements such as 40% of readers have purchased program X. Identify a population and sample and comment on the representativeness of the sample. Are readers who have not purchased any new products mentioned in the questionnaire as likely to respond as those who have purchased?
- 7.5 Each year a local weekly newspaper gives out "Best of the City" awards in categories such as restaurant, deli, pastry shop, and so on. Readers are asked to fill in their favorites on a form enclosed in this free weekly paper and then send it to the publisher. The establishment receiving the most votes is declared the winner in its category. Identify the population and sample and comment on the representativeness of the sample.
- 7.6 Which of the following are anecdotal and which are based on a sample?
- (a) Erik says that check-out is faster at the grocery store on Tuesday than any other night of the week.
 - (b) Out of 58 cars clocked on a busy road, 22 were exceeding the speed limit.
 - (c) During a tornado, a man wrapped himself in a mattress in his bedroom. He was sucked out of his home along with the mattress, but was unhurt.
- 7.7 Which of the following are anecdotal and which are based on a sample?
- (a) Joan says that adding a few drops of almond flavoring makes her cookies taste better.
 - (b) Out of 102 customers at a quick-stop market, 31 made their purchases with a credit card.
 - (c) Out of 80 persons who purchased catsup at the supermarket one night, 71 purchased the same brand as their previous purchase.
- 7.8 What is wrong with this statement of purpose?
- Purpose: Determine if a newly designed recliner chair is comfortable.*
Give an improved statement of purpose.
- 7.9 What is wrong with this statement of purpose?
- Purpose: Determine if a paper tissue product is soft.*
Give an improved statement of purpose.
- 7.10 Give a statement of purpose for determining how long it takes to wait in line and get cash from an automated teller machine during the lunch hour.
- 7.11 A consumer magazine article asks readers to respond to the question, "How do you like to spend your free time?" and from the responses of 100 persons it concluded that 74% consider shopping at least a hobby. Identify a population and the sample and comment on the representativeness of the sample.

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- 7.12 According to the cause-and-effect diagram on page 13, where are the possible delays on the first floor?
- 7.13 Refer to the cause-and-effect diagram on page 13. The workers have now noticed that a delay could occur
- (a) On the fourth floor at the pharmacy
 - (b) On the third floor at the practitioners station
- Redraw the diagram and include this added information.

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Sampling Techniques

third edition

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JOHN WILEY & SONS

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Tab2.1

Preface

As did the previous editions, this textbook presents a comprehensive account of sampling theory as it has been developed for use in sample surveys. It contains illustrations to show how the theory is applied in practice, and exercises to be worked by the student. The book will be useful both as a text for a course on sample surveys in which the major emphasis is on theory and for individual reading by the student.

The minimum mathematical equipment necessary to follow the great bulk of the material is a familiarity with algebra, especially relatively complicated algebraic expressions; plus a knowledge of probability for finite sample spaces, including combinatorial probabilities. The book presupposes an introductory statistics course that covers means and standard deviations, the normal, binomial, hypergeometric, and multinomial distributions, the central limit theorem, linear regression, and the simpler types of analyses of variance. Since much of classical sample survey theory deals with the distributions of estimators over the set of randomizations provided by the sampling plan, some knowledge of nonparametric methods is helpful.

The topics in this edition are presented in essentially the same order as in earlier editions. New sections have been included, or sections rewritten, primarily for one of three reasons: (1) to present introductions to topics (sampling plans or methods of estimation) relatively new in the field; (2) to cover further work done during the last 15 years on older methods, intended either to improve them or to learn more about the performance of rival methods; and (3) to shorten, clarify, or simplify proofs given in previous editions.

New topics in this edition include the approximate methods developed for the difficult problem of attaching standard errors or confidence limits to nonlinear estimates made from the results of surveys with complex plans. These methods will be more and more needed as statistical analyses (e.g., regressions) are performed on the results. For surveys containing sensitive questions that some respondents are unlikely to be willing to answer truthfully, a new device is to present the respondent with either the sensitive question or an innocuous question; the specific choice, made by randomization, is unknown to the interviewer. In some sampling problems it may seem economically attractive, or essential in countries without full sampling resources, to use two overlapping lists (or frames, as they are called) to cover the complete population. The method of double sampling has been extended to cases where the objective is to compare the means

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of a number of subgroups within the population. There has been interesting work on the attractive properties that the ratio and regression estimators have if it can be assumed that the finite population is itself a random sample from an infinite superpopulation in which a mathematical model appropriate to the ratio or regression estimator holds. This kind of assumption is not new—I noticed recently that Laplace used it around 1800 in a sampling problem—but it clarifies the relation between sample survey theory and standard statistical theory.

An example of further work on topics included in previous editions is Chapter 9A, which has been written partly from material previously in Chapter 9; this was done mainly to give a more adequate account of what seem to me the principal methods produced for sampling with unequal probabilities without replacement. These include the similar methods given independently by Brewer, J. N. K. Rao, and Durbin, Murthy's method, the Rao, Hartley, Cochran method, and Madow's method related to systematic sampling, with comparisons of the performances of the methods on natural populations. New studies have been done of the sizes of components of errors of measurement in surveys by repeat measurements by different interviewers, by interpenetrating subsamples, and by a combination of the two approaches. For the ratio estimator, data from natural populations have been used to appraise the small-sample biases in the standard large-sample formulas for the variance and the estimated variance. Attempts have also been made to create less biased variants of the ratio estimator itself and of the formula for estimating its sampling variance. In stratified sampling there has been additional work on allocating sample sizes to strata when more than one item is of importance and on estimating sample errors when only one unit is to be selected per stratum. Some new systematic sampling methods for handling populations having linear trends are also of interest.

Alva L. Finkner and Emil H. Jebe prepared a large part of the lecture notes from which the first edition of this book was written. Some investigations that provided background material were supported by the Office of Naval Research, Navy Department. From discussions of recent developments in sampling or suggestions about this edition, I have been greatly helped by Tore Dalenius, David J. Finney, Daniel G. Horvitz, Leslie Kish, P. S. R. Sambasiva Rao, Martin Sandelius, Joseph Sedransk, Amode R. Sen, and especially Jon N. K. Rao, whose painstaking reading of the new and revised sections of this edition resulted in many constructive suggestions about gaps, weaknesses, obscurities, and selection of topics. For typing and other work involved in production of a typescript I am indebted to Rowena Foss, Holly Grano, and Edith Klotz. My thanks to all.

William G. Cochran

South Orleans, Massachusetts
February, 1977

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CHAPTER 1

Introduction

1.1 ADVANTAGES OF THE SAMPLING METHOD

Our knowledge, our attitudes, and our actions are based to a very large extent on samples. This is equally true in everyday life and in scientific research. A person's opinion of an institution that conducts thousands of transactions every day is often determined by the one or two encounters he has had with the institution in the course of several years. Travelers who spend 10 days in a foreign country and then proceed to write a book telling the inhabitants how to revive their industries, reform their political system, balance their budget, and improve the food in their hotels are a familiar figure of fun. But in a real sense they differ from the political scientist who devotes 20 years to living and studying in the country only in that they base their conclusions on a much smaller sample of experience and are less likely to be aware of the extent of their ignorance. In science and human affairs alike we lack the resources to study more than a fragment of the phenomena that might advance our knowledge.

This book contains an account of the body of theory that has been built up to provide a background for good sampling methods. In most of the applications for which this theory was constructed, the aggregate about which information is desired is finite and delimited—the inhabitants of a town, the machines in a factory, the fish in a lake. In some cases it may seem feasible to obtain the information by taking a complete enumeration or census of the aggregate. Administrators accustomed to dealing with censuses were at first inclined to be suspicious of samples and reluctant to use them in place of censuses. Although this attitude no longer persists, it may be well to list the principal advantages of sampling as compared with complete enumeration.

Reduced Cost

If data are secured from only a small fraction of the aggregate, expenditures are smaller than if a complete census is attempted. With large populations, results accurate enough to be useful can be obtained from samples that represent only a small fraction of the population. In the United States the most important recurrent surveys taken by the government use samples of around 105,000

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persons, or about one person in 1240. Surveys used to provide facts bearing on sales and advertising policy in market research may employ samples of only a few thousand.

Greater Speed

For the same reason, the data can be collected and summarized more quickly with a sample than with a complete count. This is a vital consideration when the information is urgently needed.

Greater Scope

In certain types of inquiry highly trained personnel or specialized equipment, limited in availability, must be used to obtain the data. A complete census is impracticable: the choice lies between obtaining the information by sampling or not at all. Thus surveys that rely on sampling have more scope and flexibility regarding the types of information that can be obtained. On the other hand, if accurate information is wanted for many subdivisions of the population, the size of sample needed to do the job is sometimes so large that a complete enumeration offers the best solution.

Greater Accuracy

Because personnel of higher quality can be employed and given intensive training and because more careful supervision of the field work and processing of results becomes feasible when the volume of work is reduced, a sample may produce more accurate results than the kind of complete enumeration that can be taken.

1.2 SOME USES OF SAMPLE SURVEYS

To an observer of developments in sampling over the last 25 years the most striking feature is the rapid increase in the number and types of surveys taken by sampling. The Statistical Office of the United Nations publishes reports from time to time on "Sample Surveys of Current Interest" conducted by member countries. The 1968 report lists surveys from 46 countries. Many of these surveys seek information of obvious importance to national planning on topics such as agricultural production and land use, unemployment and the size of the labor force, industrial production, wholesale and retail prices, health status of the people, and family incomes and expenditures. But more specialized inquiries can also be found: for example, annual leave arrangements (Australia), causes of divorce (Hungary), rural debt and investment (India), household water consumption (Israel), radio listening (Malaysia), holiday spending (Netherlands), age structure of cows (Czechoslovakia), and job vacancies (United States).

Sampling has come to play a prominent part in national decennial censuses. In the United States a 5% sample was introduced into the 1940 Census by asking

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extra questions about occupation, parentage, fertility, and the like, of those persons whose names fell on two of the 40 lines on each page of the schedule. The use of sampling was greatly extended in 1950. From a 20% sample (every fifth line) information was obtained on items such as income, years in school, migration, and service in armed forces. By taking every sixth person in the 20% sample, a further sample of $3\frac{1}{3}\%$ was created to give information on marriage and fertility. A series of questions dealing with the condition and age of housing was split into five sets, each set being filled in at every fifth house. Sampling was also employed to speed up publication of the results. Preliminary tabulations for many important items, made on a sample basis, appeared more than a year and half before the final reports.

This process continued in the 1960 and 1970 Censuses. Except for certain basic information required from every person for constitutional or legal reasons, the whole census was shifted to a sample basis. This change, accompanied by greatly increased mechanization, resulted in much earlier publication and substantial savings.

In addition to their use in censuses, continuing samples are employed by government bureaus to obtain current information. In the United States, examples are the Current Population Survey, which provides monthly data on the size and composition of the labor force and on the number of unemployed, the National Health Survey, and the series of samples needed for the calculation of the monthly Consumer Price Index.

On a smaller scale, local governments—city, state, and county—are making increased use of sample surveys to obtain information needed for future planning and for meeting pressing problems. In the United States most large cities have commercial agencies that make a business of planning and conducting sample surveys for clients.

Market research is heavily dependent on the sampling approach. Estimates of the sizes of television and radio audiences for different programs and of newspaper and magazine readership (including the advertisements) are kept continually under scrutiny. Manufacturers and retailers want to know the reactions of people to new products or new methods of packaging, their complaints about old products, and their reasons for preferring one product to another.

Business and industry have many uses for sampling in attempting to increase the efficiency of their internal operations. The important areas of quality control and acceptance sampling are outside the scope of this book. But, obviously, decisions taken with respect to level or change of quality or to acceptance or rejection of batches are well grounded only if results obtained from the sample data are valid (within a reasonable tolerance) for the whole batch. The sampling of records of business transactions (accounts, payrolls, stock, personnel)—usually much easier than the sampling of people—can provide serviceable information quickly and economically. Savings can also be made through sampling in the estimation of inventories, in studies of the condition and length of the life of equipment, in the

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inspection of the accuracy and rate of output of clerical work, in investigating how key personnel distribute their working time among different tasks, and, more generally, in the field known as operations research. The books by Deming (1960) and Slonim (1960) contain many interesting examples showing the range of applications of the sampling method in business.

Opinion, attitude, and election polls, which did much to bring the technique of sampling before the public eye, continue to be a popular feature of newspapers. In the field of accounting and auditing, which has employed sampling for many years, a new interest has arisen in adapting modern developments to the particular problems of this field. Thus, Neter (1972) describes how airlines and railways save money by using samples of records to apportion income from freight and passenger service. The status of sample surveys as evidence in lawsuits has also been subject to lively discussion. Gallup (1972) has noted the major contribution that sample surveys can make to the process of informed government by determining quickly people's opinions on proposed or new government programs and has stressed their role as sources of information in social science.

Sample surveys can be classified broadly into two types—*descriptive* and *analytical*. In a descriptive survey the objective is simply to obtain certain information about large groups: for example, the numbers of men, women, and children who view a television program. In an analytical survey, comparisons are made between different subgroups of the population, in order to discover whether differences exist among them and to form or to verify hypotheses about the reasons for these differences. The Indianapolis fertility survey, for instance, was an attempt to determine the extent to which married couples plan the number and spacing of children, the husband's and wife's attitudes toward this planning, the reasons for these attitudes, and the degree of success attained (Kiser and Whelpton, 1953).

The distinction between descriptive and analytical surveys is not, of course, clear-cut. Many surveys provide data that serve both purposes. Along with the rise in the number of descriptive surveys, there has, however, been a noticeable increase in surveys taken primarily for analytical purposes, particularly in the study of human behavior and health. Surveys of the teeth of school children before and after fluoridation of water, of the death rates and causes of death of people who smoke different amounts, and the huge study of the effectiveness of the Salk polio vaccine may be cited. The study by Coleman (1966) on equality of educational opportunity, conducted on a national sample of schools, contained many regression analyses that estimated the relative contributions of school characteristics, home background, and the child's outlook to variations in exam results.

1.3 THE PRINCIPAL STEPS IN A SAMPLE SURVEY

As a preliminary to a discussion of the role that theory plays in a sample survey, it is useful to describe briefly the steps involved in the planning and execution of a

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survey. Surveys vary greatly in their complexity. To take a sample from 5000 cards, neatly arranged and numbered in a file, is an easy task. It is another matter to sample the inhabitants of a region where transport is by water through the forests, where there are no maps, where 15 different dialects are spoken, and where the inhabitants are very suspicious of an inquisitive stranger. Problems that are baffling in one survey may be trivial or nonexistent in another.

The principal steps in a survey are grouped somewhat arbitrarily under 11 headings.

Objectives of the Survey

A lucid statement of the objectives is most helpful. Without this, it is easy in a complex survey to forget the objectives when engrossed in the details of planning, and to make decisions that are at variance with the objectives.

Population to be Sampled

The word *population* is used to denote the aggregate from which the sample is chosen. The definition of the population may present no problem, as when sampling a batch of electric light bulbs in order to estimate the average length of life of a bulb. In sampling a population of farms, on the other hand, rules must be set up to define a farm, and borderline cases arise. These rules must be usable in practice: the enumerator must be able to decide in the field, without much hesitation, whether or not a doubtful case belongs to the population.

The population to be sampled (the *sampled* population) should coincide with the population about which information is wanted (the *target* population). Sometimes, for reasons of practicability or convenience, the sampled population is more restricted than the target population. If so, it should be remembered that *conclusions drawn from the sample apply to the sampled population. Judgment about the extent to which these conclusions will also apply to the target population must depend on other sources of information.* Any supplementary information that can be gathered about the nature of the differences between sampled and target population may be helpful.

Data to be Collected

It is well to verify that all the data are relevant to the purposes of the survey and that no essential data are omitted. There is frequently a tendency, particularly with human populations, to ask too many questions, some of which are never subsequently analyzed. An overlong questionnaire lowers the quality of the answers to important as well as unimportant questions.

Degree of Precision Desired

The results of sample surveys are always subject to some uncertainty because only part of the population has been measured and because of errors of measurement. This uncertainty can be reduced by taking larger samples and by using

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superior instruments of measurement. But this usually costs time and money. Consequently, the specification of the degree of precision wanted in the results is an important step. This step is the responsibility of the person who is going to use the data. It may present difficulties, since many administrators are unaccustomed to thinking in terms of the amount of error that can be tolerated in estimates, consistent with making good decisions. The statistician can often help at this stage.

Methods of Measurement

There may be a choice of measuring instrument and of method of approach to the population. Data about a person's state of health may be obtained from statements that he or she makes or from a medical examination. The survey may employ a self-administered questionnaire, an interviewer who reads a standard set of questions with no discretion, or an interviewing process that allows much latitude in the form and ordering of the questions. The approach may be by mail, by telephone, by personal visit, or by a combination of the three. Much study has been made of interviewing methods and problems (see, e.g., Hyman, 1954 and Payne, 1951).

A major part of the preliminary work is the construction of record forms on which the questions and answers are to be entered. With simple questionnaires, the answers can sometimes be precoded—that is, entered in a manner in which they can be routinely transferred to mechanical equipment. In fact, for the construction of good record forms, it is necessary to visualize the structure of the final summary tables that will be used for drawing conclusions.

The Frame

Before selecting the sample, the population must be divided into parts that are called *sampling units*, or *units*. These units must cover the whole of the population and they must not overlap, in the sense that every element in the population belongs to one and only one unit. Sometimes the appropriate unit is obvious, as in a population of light bulbs, in which the unit is the single bulb. Sometimes there is a choice of unit. In sampling the people in a town, the unit might be an individual person, the members of a family, or all persons living in the same city block. In sampling an agricultural crop, the unit might be a field, a farm, or an area of land whose shape and dimensions are at our disposal.

The construction of this list of sampling units, called a *frame*, is often one of the major practical problems. From bitter experience, samplers have acquired a critical attitude toward lists that have been routinely collected for some purpose. Despite assurances to the contrary, such lists are often found to be incomplete, or partly illegible, or to contain an unknown amount of duplication. A good frame may be hard to come by when the population is specialized, as in populations of bookmakers or of people who keep turkeys. Jessen (1955) presents an interesting method of constructing a frame from the branches of a fruit tree.

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Selection of the Sample

There is now a variety of plans by which the sample may be selected. For each plan that is considered, rough estimates of the size of sample can be made from a knowledge of the degree of precision desired. The relative costs and time involved for each plan are also compared before making a decision.

The Pretest

It has been found useful to try out the questionnaire and the field methods on a small scale. This nearly always results in improvements in the questionnaire and may reveal other troubles that will be serious on a large scale, for example, that the cost will be much greater than expected.

Organization of the Field Work

In extensive surveys many problems of business administration are met. The personnel must receive training in the purpose of the survey and in the methods of measurement to be employed and must be adequately supervised in their work. A procedure for *early* checking of the quality of the returns is invaluable. Plans must be made for handling nonresponse, that is, the failure of the enumerator to obtain information from certain of the units in the sample.

Summary and Analysis of the Data

The first step is to edit the completed questionnaires, in the hope of amending recording errors, or at least of deleting data that are obviously erroneous. Decisions about computing procedure are needed in cases in which answers to certain questions were omitted by some respondents or were deleted in the editing process. Thereafter, the computations that lead to the estimates are performed. Different methods of estimation may be available for the same data.

In the presentation of results it is good practice to report the amount of error to be expected in the most important estimates. One of the advantages of probability sampling is that such statements can be made, although they have to be severely qualified if the amount of nonresponse is substantial.

Information Gained for Future Surveys

The more information we have initially about a population, the easier it is to devise a sample that will give accurate estimates. Any completed sample is potentially a guide to improved future sampling, in the data that it supplies about the means, standard deviations, and nature of the variability of the principal measurements and about the costs involved in getting the data. Sampling practice advances more rapidly when provisions are made to assemble and record information of this type.

There is another important respect in which any completed sample facilitates future samples. Things never go exactly as planned in a complex survey. The alert

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sampler learns to recognize mistakes in execution and to see that they do not occur in future surveys.

14 THE ROLE OF SAMPLING THEORY

This list of the steps in a sample survey has been given in order to emphasize that sampling is a practical business, which calls for several different types of skill. In some of the steps—the definition of the population, the determination of the data to be collected and of the methods of measurement, and the organization of the field work—sampling theory plays at most a minor role. Although these topics are not discussed further in this book, their importance should be realized. Sampling demands attention to all phases of the activity: poor work in one phase may ruin a survey in which everything else is done well.

The purpose of sampling theory is to make sampling more efficient. It attempts to develop methods of sample selection and of estimation that provide, at the lowest possible cost, estimates that are precise enough for our purpose. This principle of specified precision at minimum cost recurs repeatedly in the presentation of theory.

In order to apply this principle, we must be able to predict, for any sampling procedure that is under consideration, the precision and the cost to be expected. So far as precision is concerned, we cannot foretell exactly how large an error will be present in an estimate in any specific situation, for this would require a knowledge of the true value for the population. Instead, the precision of a sampling procedure is judged by examining the frequency distribution generated for the estimate if the procedure is applied again and again to the same population. This is, of course, the standard technique by which precision is judged in statistical theory.

A further simplification is introduced. With samples of the sizes that are common in practice, there is often good reason to suppose that the sample estimates are approximately normally distributed. With a normally distributed estimate, the whole shape of the frequency distribution is known if we know the mean and the standard deviation (or the variance). A considerable part of sample survey theory is concerned with finding formulas for these means and variances.

There are two differences between standard sample survey theory and the classical sampling theory as taught in books on mathematical statistics. In classical theory the measurements that are made on the sampling units in the population are usually assumed to follow a frequency distribution, for example, the normal distribution, of known mathematical form apart from certain population parameters such as the mean and variance whose values have to be estimated from the sample data. In sample survey theory, on the other hand, the attitude has been to assume only very limited information about this frequency distribution. In particular, its mathematical form is not assumed known, so that the approach might be described as model-free or distribution-free. This attitude is natural for

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large surveys in which many different measurements with differing frequency distributions are made on the units. In surveys in which only a few measurements per unit are made, studies of their frequency distributions may justify the assumption of known mathematical forms, permitting the results from classical theory to be applied.

A second difference is that the populations in survey work contain a *finite* number of units. Results are slightly more complicated when sampling is from a finite instead of an infinite population. For practical purposes these differences in results for finite and infinite populations can often be ignored. Cases in which this is not so will be pointed out.

1.5 PROBABILITY SAMPLING

The sampling procedures considered in this book have the following mathematical properties in common.

1. We are able to define the set of distinct samples, $S_1, S_2, \dots, S_n$, which the procedure is capable of selecting if applied to a specific population. This means that we can say precisely what sampling units belong to S_1 , to S_2 , and so on. For example, suppose that the population contains six units, numbered 1 to 6. A common procedure for choosing a sample of size 2 gives three possible candidates— $S_1 \sim (1, 4)$; $S_2 \sim (2, 5)$; $S_3 \sim (3, 6)$. Note that not all possible samples of size 2 need be included.

2. Each possible sample S_i has assigned to it a known probability of selection π_i .

3. We select one of the S_i by a random process in which each S_i receives its appropriate probability π_i of being selected. In the example we might assign equal probabilities to the three samples. Then the draw itself can be made by choosing a random number between 1 and 3. If this number is j , S_j is the sample that is taken.

4. The method for computing the estimate from the sample must be stated and must lead to a unique estimate for any specific sample. We may declare, for example, that the estimate is to be the average of the measurements on the individual units in the sample.

For any sampling procedure that satisfies these properties, we are in a position to calculate the frequency distribution of the estimates it generates if repeatedly applied to the same population. We know how frequently any particular sample S_i will be selected, and we know how to calculate the estimate from the data in S_i . It is clear, therefore, that a sampling theory can be developed for any procedure of this type, although the details of the development may be intricate. The term *probability sampling* refers to a method of this type.

In practice we seldom draw a probability sample by writing down the S_i and π_i as outlined above. This is intolerably laborious with a large population, where a sampling procedure may produce billions of possible samples. The draw is most

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Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Have you ever treated pediatric patients, meaning patients 0 through 12 years old?	95.0%	(77.2% , 99.0%)
Have you ever treated adolescent patients, meaning patients 13 through 17 years old?	100.0%	(85.1% , 100.0%)
Have you ever treated non-geriatric adult patients, meaning patients 18 through 64 years old.	100.0%	(85.1% , 100.0%)
Have you ever treated geriatric patients, meaning patients 65 or older?	95.0%	(77.2% , 99.0%)
Have you ever prescribed Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed Risperdal® for a pediatric patient?	70.0%	(48.5% , 86.1%)
For an adolescent patient?	70.0%	(48.5% , 86.1%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	85.0%	(64.4% , 95.0%)
For a South Carolina Medicaid patient?	100.0%	(85.1% , 100.0%)
For a South Carolina State Health Plan patient?	55.0%	(33.7% , 74.3%)
Have you ever prescribed antipsychotic medications other than Risperdal® for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed antipsychotic medications other than Risperdal® for a pediatric patient?	80.0%	(59.4% , 93.1%)
For an adolescent patient?	90.0%	(71.3% , 98.0%)
For a non-geriatric adult patient?	100.0%	(85.1% , 100.0%)
For a geriatric patient?	95.0%	(77.2% , 99.0%)
Have you ever prescribed first generation antipsychotics for any of your patients?	100.0%	(85.1% , 100.0%)
Have you ever prescribed second generation antipsychotics other than Risperdal® for any of your patients?	95.0%	(77.2% , 99.0%)

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Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, is Risperdal® generally effective for treating the positive symptoms of schizophrenia?	100.0%	(85.1% , 100.0%)
In your experience, is Risperdal® generally effective for treating the negative symptoms of schizophrenia?	70.0%	(48.5% , 86.1%)
In your experience, do patients who take Risperdal® have better overall outcomes more frequently than patients who take a first generation antipsychotic?	65.0%	(43.6% , 82.2%)
In your practice, for patients requiring antipsychotic medications, do you generally prefer to use first generation antipsychotics, or, second generation antipsychotics? [Percent shown is for "second generation".]	70.0%	(48.5% , 86.1%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience extrapyramidal and anticholinergic side effects than patients who take second generation antipsychotics?	100.0%	(85.1% , 100.0%)
In your experience, are patients who take first generation antipsychotics, such as Haldol and Thorazine, more likely to experience Tardive Dyskinesia than patients who take second generation antipsychotics?	90.0%	(71.3% , 98.0%)
In your experience, does Risperdal® typically have a more moderate side effect profile than first generation antipsychotics?	70.0%	(48.5% , 86.1%)
In your experience, is Risperdal® typically better tolerated than first generation antipsychotics?	85.0%	(64.4% , 95.0%)
In your experience with antipsychotic medications, are both efficacy and tolerability important considerations in the choice of which antipsychotic to prescribe?	95.0%	(77.2% , 99.0%)
In your experience, do both efficacy and tolerability increase the likelihood that a patient will take an antipsychotic medication consistently?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely to require costly follow-up treatment, such as in-patient psychiatric care, than patients who do not consistently take their medications?	95.0%	(77.2% , 99.0%)
In your experience, are patients who consistently take their antipsychotic medications less likely, to require costly follow-up treatment, such as emergency room care, than patients who do not consistently take their medications?	85.0%	(64.4% , 95.0%)
In your experience, does increased patient compliance with antipsychotic prescriptions result in overall conservation, as opposed to consumption, of healthcare resources?	85.0%	(64.4% , 95.0%)
In your experience, does the use of Risperdal® typically conserve healthcare resources as compared to first generation antipsychotics?	45.0%	(25.7% , 66.3%)

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Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
In your experience, does increased patient compliance with antipsychotic prescriptions typically decrease the human consequences of psychiatric illnesses?	100.0%	(85.1% , 100.0%)
In your experience, does compliance taking antipsychotic medications typically make patients less likely to experience recurrence of psychosis?	100.0%	(85.1% , 100.0%)
Less likely to be violent?	90.0%	(71.3% , 98.0%)
Less likely to be an extreme burden on family members?	100.0%	(85.1% , 100.0%)
Less likely to experience worsening of their conditions?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a reasonably safe and effective medication for treating schizophrenia and other psychotic disorders?	95.0%	(77.2% , 99.0%)
Overall, in your experience, is Risperdal® a safer and more effective medication for treating schizophrenia and other psychotic disorders than the first generation medications?	55.0%	(33.7% , 74.3%)
In your experience, are there circumstances when the off-label use of medications is appropriate?	100.0%	(85.1% , 100.0%)
In your experience, is it fair to say that off-label use of medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
In your experience, are there circumstances when the off-label use of antipsychotic medications is appropriate?	90.0%	(71.3% , 98.0%)
In your experience, is it fair to say that off-label use of antipsychotic medications is not an uncommon practice?	90.0%	(71.3% , 98.0%)
Have you ever prescribed a medication for off-label use?	95.0%	(77.2% , 99.0%)
In those circumstances, did you expect your patients to benefit from the off-label use of the medication?	95.0%	(77.2% , 99.0%)
Have you ever prescribed an antipsychotic medication for off-label use?	90.0%	(71.3% , 98.0%)
Have you ever prescribed Risperdal® for off-label use?	90.0%	(71.3% , 98.0%)
Did you expect your patients to benefit from the off-label use of Risperdal®?	90.0%	(71.3% , 98.0%)

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Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in children?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® in geriatric patients?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever promoted to you any off-label use of Risperdal® at all?	0.0%	(0.0% , 11.9%)
Have you ever received or seen any communication from Janssen promoting the off-label use of Risperdal®?	0.0%	(0.0% , 11.9%)
Based on your training and experience, is it common for medications to have both benefits and risks?	100.0%	(85.1% , 100.0%)
Based on your training and experience, is it your understanding that all antipsychotic medications — both first generation and second generation — have potential side effects?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and weight gain?	100.0%	(85.1% , 100.0%)
Are you aware of an association between antipsychotic medications and risk of diabetes?	95.0%	(77.2% , 99.0%)
When you prescribe antipsychotic medications, including Risperdal®, do you monitor your patients for weight gain?	100.0%	(85.1% , 100.0%)
If you see or learn of rapid weight gain in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
If you see or learn of a change in blood glucose level in a patient after the patient begins taking antipsychotics, do you typically consider changing the dosage and medication?	60.0%	(38.6% , 78.2%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and weight gain?	100.0%	(85.1% , 100.0%)
Would you agree that the 1993 package insert for Risperdal® advised of an association between Risperdal® and diabetes?	100.0%	(85.1% , 100.0%)
Would you agree that the 2004 package insert for Risperdal® incorporated a class warning of hyperglycemia and diabetes?	100.0%	(85.1% , 100.0%)
Were you aware of an association between second generation antipsychotics, and weight gain or a risk of diabetes, prior to the 2004 revision to the package insert for Risperdal®?	80.0%	(59.4% , 93.1%)
Did the change to the package insert for Risperdal® in 2004 cause you to change the circumstances in which you prescribe Risperdal® for patients?	15.0%	(5.0% , 35.6%)

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Exhibit 5

Population Estimates from Responses to Deposition Questions

Question	Estimated Percent Responding "Yes" or "Probably Yes"	95% Confidence Limits
Has any Janssen sales representative ever represented to you anything inconsistent with the warnings about Risperdal® that are provided on the package insert?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever represented to you that there is no association between Risperdal® and increased mortality in the elderly?	0.0%	(0.0% , 11.9%)
Has any Janssen sales representative ever misrepresented to you information about the potential side effects associated with Risperdal® use?	0.0%	(0.0% , 11.9%)
Have you ever seen this letter before? [November 10, 2003]	20.0%	(6.9% , 40.6%)
Did this letter cause you to change the circumstances in which you prescribe antipsychotics to your patients?	5.0%	(1.0% , 22.8%)
Did it cause you to change your choice of which antipsychotic to prescribe?	5.0%	(1.0% , 22.8%)
Did it cause you to change your methods for monitoring for side effects in your patients on antipsychotic medications?	5.0%	(1.0% , 22.8%)
Prior to the deposition today, have you had any communications with any of the attorneys for the Plaintiff in this case?	15.0%	(5.0% , 35.6%)

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Percent of Antipsychotic Prescriptions Written by 101 Most Frequent FFS APD Prescribers Under SHP and FFS Programs

The FREQ Procedure

Prescriber in 101 Most Frequent FFS Prescribers

ffs_101	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	913028	67.36	913028	67.36
1	442163	32.64	1355191	100.00

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Percent of 101 Most Frequent FFS APD Prescribers Who Also Prescribed Under SHP Program

The FREQ Procedure

Prescribed Under SHP

shp_prescriber	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	8	7.92	8	7.92
1	93	92.08	101	100.00

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2011 MAR 21 AM 8:37

M. HOPE BLACKLEY

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ffs_top_101.apd_pctsas
libname data ".../sasdata";
libname data12 ".../sasdata";
libname data15 ".../sasdata";

options nodate nonumber ls=125 ps=84;

data ffs_sample_101; data.ffc_top_101_sample;
run;

proc sort data=ffc_sample_101; by lname fname prescriber12;
run;

data shp; set data.shp_prescribers;
run;

data ffs; set data.ffc_prescribers;
run;

proc summary data=shp(where=(totchg_apd_a > 0)) nway missing;
  class PRSCRBR_ID;
  output out=apd_ids;
run;

data prasc; set data12.prescriber_12_1 data12.prescriber_12_2 data15.prescriber_15;
  l_name = left(compbl(upcase(l_name)));
  f_name = left(compbl(upcase(f_name)));
  PRSCRBR_ID = left(upcase(PRSCRBR_ID));

  length lname $9 fname $14;
  lname = l_name;
  fname = f_name;

  if lname = "BLOCH" and fname = "SILVIA" then fname = "SILVIA MARGIT";
  if lname = "HILL" and fname = "VERNETTA" then lname = "HILL JACO";
  if lname = "KITHIANIS" and fname = "CARRIE S" then fname = "CARRIE";
  if lname = "VALITE" and fname = "DELFIN" then fname = "DELFIN FERDINAND";
  if lname = "SCHNACKENB" and fname = "BOB" then fname = "ROBERT";
  if lname = "SCHNACKENB" and fname = "BOB" then fname = "ROBERT";
  if lname = "SCHNACKENB" and fname = "ROBERT" then lname = "SCHNACKENBERG";
  if lname = "SCHNACKENB" and fname = "ROBERT" then lname = "SCHNACKENBERG";

run;

proc summary data=prasc nway missing;
  class PRSCRBR_ID lname fname l_name f_name;
  output out=names;
run;

proc summary data=names nway missing;
  class PRSCRBR_ID;
  output out=names2(rename=(freq=name_mult));
run;

data result;
  merge names(in=p) names2(in=n);
  by prscrbr_id;

  multiple = 0;
  if name_mult > 1 then multiple = 1;
run;

proc summary data=result nway missing;
  class prscrbr_id lname fname l_name f_name name_mult multiple;
  output out=result2(rename=(freq=multiplicity));
run;

proc sort data=result2; by lname fname; run;
proc sort data=ffc_sample_101; by lname fname; run;

data test;
  merge result2(in=s) ffs_sample_101(in=f);
  by lname fname;
  if s then src = "SRP ";
  if f then src = "SMPL";
  if s and f then src = "BOTH";

  shp_prescriber = 0;
  if s then shp_prescriber = 1;
run;

proc sort data=test; by prscrbr_id; run;
data test2;
  merge test(in=t) apd_ids(in=s);
  by prscrbr_id;

  apddoc = 0;
  if s then apddoc = 1;
run;

proc summary data=test2(where=(src ne "SRP")) nway missing;

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ffs_top_101.apd_pctsas
class lname fname;
var shp_prescriber apddoc;
output out=result max=;
run;

data result_a; set result;
if apddoc = 0 then shp_prescriber = 0;
run;

proc summary data=test(where=(src ne "SHP")) nway missing;
class prscrbr_id;
output out=ids_shp;
run;
proc summary data=test(where=(src ne "SHP")) nway missing;
class prescribenp12;
output out=ids_ffs;
run;

proc sort data=shp; by prscrbr_id; run;
proc sort data=ffs; by prescribenp12; run;

data freq_shp; merge shp ids_shp(in=1);
by prscrbr_id;
ffs_101 = 0;
if 1 then ffs_101 = 1;
label ffs_101 = "Prescriber in 101 Most Frequent PFS Prescribers";
run;
data freq_ffs; merge ffs ids_ffs(in=1);
by prescribenp12;
ffs_101 = 0;
if 1 then ffs_101 = 1;
label ffs_101 = "Prescriber in 101 Most Frequent PFS Prescribers";
run;

proc summary data=freq_shp(where=(totchg_apd_n > 0)) nway missing;
class prscrbr_id;
var ffs_101;
output out=shp_count max=;
run;

data freq_shp; set freq_shp;
rename totchg_apd_n = charge_apd_n;
run;

data total; set freq_shp(keep=ffs_101 charge_apd_n) freq_ffs(keep=ffs_101 charge_apd_n);
run;

proc freq data=total;
title "Percent of Antipsychotic Prescriptions Written by 101 Most Frequent PFS APD Prescribers Under SHP and PFS Programs";
tables ffs_101;
weight charge_apd_n;
run;

proc freq data=result_a(where=(shp_prescriber ne .));
title "Percent of 101 Most Frequent PFS APD Prescribers Who Also Prescribed Under SHP Program";
tables shp_prescriber / list missing;
label shp_prescriber = "Prescribed Under SHP";
run;

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