UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION This document relates to: *Linda Guinn*, No. 6:07-CV-10291 *Janice Burns*, No. 6:07-CV-15959 *Richard Unger*, No. 6:07-CV-15812 *Connie Curley*, No. 6:07-CV-15701 *Linda Whittington*, No. 6:07-CV-10475 *Eileen McAlexander*, No. 6:07-CV-10360 *David Haller*, No. 6:07-CV-15733	**MDL DOCKET NO:** **6:06-MDL-1769-ACC-DAB**

PLAINTIFFS' OMNIBUS LEGAL MEMORANDUM RESPONDING IN OPPOSITION TO ASTRAZENECA'S SUMMARY JUDGMENT MOTIONS IN THE FLORIDA TRIAL POOL "GROUP ONE" CASES

The above-listed Plaintiffs submit their Omnibus Legal Memorandum ("Brief") pursuant to the Court's order of August 1, 2008 (Doc. 1059), responding in opposition to the summary judgment motions ("Motions") and omnibus legal memorandum (Doc. 1113, the "Memorandum") filed by Defendants AstraZeneca Pharmaceuticals LP and AstraZeneca LP (collectively, "AstraZeneca" or the "Company"), and would respectfully show the Court as follows:

1. Plaintiffs have adduced more than sufficient **causation evidence** to present to a jury (*see* Br. at 38-42);
2. **Implied conflict preemption** cannot bar Plaintiffs' claims primarily because Plaintiffs' state law tort claims complement, not conflict with, FDA rules and regulations governing prescription drug labeling, and because AstraZeneca has not made the requisite showing of congressional intent to preempt Plaintiffs' claims, among other reasons (*see* Br. at 42-58);
3. AstraZeneca's **learned intermediary defense** fails because the warnings at issue are not adequate as a matter of law. Furthermore, AstraZeneca cannot overcome the inadequacy of the warning based on any alleged "independent

knowledge" of the risks by Plaintiffs' prescribers, or by fabricating "breaks" in the causal chain that are unsupported by Florida law and which are based on prescribers' speculative testimony (*see* Br. at 59-80);

4. Plaintiffs have met their burden on their **fraud** and **negligent misrepresentation** claims, as there exists sufficient summary judgment evidence that Plaintiffs' prescribers saw or heard and relied upon AstraZeneca's misrepresentations, and although causation is not an element of misrepresentation claims in Florida, Plaintiffs have proffered sufficient causation evidence as well (*see* Br. at 81-84); and
5. Plaintiffs **design defect** claim survives summary judgment because Plaintiffs' summary judgment evidence satisfies both the consumer expectations test and the risk/benefits test (*see* Br. at 85-90).

For the reasons above and that follow, in addition to the arguments and evidence set forth in Plaintiffs' individual Responses in Opposition to AstraZeneca's Motions and Memorandum (the "Responses"), filed herewith, the Court should deny AstraZeneca's Motions.[1]

I.
FACTUAL BACKGROUND ON DIABETES, SCHIZOPHRENIA, AND SEROQUEL'S DEVELOPMENT AND MARKETING

A. "Whenever ideas fail, men invent words."[2]

Before or soon after Seroquel was first approved by FDA and marketed in 1997, AstraZeneca faced the stark reality that its 'idea' for a safer, more effective schizophrenia drug had 'failed'—clinical trials showed Seroquel was neither safer nor more effective than cheaper, decades-old generic medicines.[3] It was *less effective*, in fact, than its competitors and traditional mental illness drugs, and Company data showed Seroquel was only *more*

---

1 AstraZeneca also argued that Plaintiffs' "conspiracy" and "off-label" claims failed at the summary judgment stage. (Mem. at 51-53, 59.) Plaintiffs have hereby elected to abandon their conspiracy claims, and while Plaintiffs do not waive their right to raise AstraZeneca's off-label promotion of Seroquel as a *factual matter* in support of their arguments or proof at summary judgment, at trial, or in any other proceeding, Plaintiffs do not assert claims for the recovery of damages under any unique *legal theory* of "off-label promotion." Therefore, Plaintiffs' Brief and the individual Responses filed herewith do not address either of those claims.

2 Martin H. Fischer, American physician and author, 1879-1962.

3 *See* discussion, *infra* at 12-16.

effective than a sugar pill (at least one study showed that the average low dose of Seroquel worked *no better than* placebo).[4] Worse, Company data showed that patients treated with Seroquel experienced potentially deadly side-effects: rapid, clinically significant weight gain and greatly increased risk for treatment-onset diabetes.[5] Undeterred by the deficient scientific data and desiring to parlay Seroquel's recent, limited FDA approval into a sizeable revenue stream, the Company opted to 'invent words'—embarking on promotional campaigns so successful, AstraZeneca's 'little pill that couldn't' quickly became the most prescribed antipsychotic by 2006 (reportedly largely on off-label use).[6] Plaintiffs' injuries—chiefly, diabetes mellitus—were collateral damage to Seroquel's success.

B. First and Second Generation Antipsychotics

Seroquel is in a family of prescription drugs that, in the 1990s, was "trumpeted" as a "new class of drugs" for the mentally ill, which their makers "billed as a dream solution"—better treatment, fewer side effects.[7] Manufacturers of the new "second generation antipsychotics" ("SGAs")[8] intended for the SGAs to replace traditional, first-line (or "first

---

4 *See* note 76 and accompanying discussion, *infra* at 16.

5 *See* note discussion, *infra* at 16-20.

6 AstraZeneca ("AstraZeneca Website"), AstraZeneca Business Review 2006 Presentation, at 4, http://www.astrazeneca.com/sites/7/imagebank/typearticleparam511665/astrazeneca-2006-business-review-Carolyn-Fitzsimons.pdf (last visited Nov. 22, 2008); Carolyn Fitzsimons Seroquel script, at 1, http://www.astrazeneca.com/sites/7/imagebank/typearticleparam511665/astrazeneca-business-review-2006-CF-script.pdf (last visited Nov. 22, 2008); *see* Shannon Pettypiece & Etain Lavelle, *AstraZeneca, Lilly Drugs Surge On Use By Teens, Aged*, Bloomberg, March 9, 2007, http://www.bloomberg.com/apps/news?pid=20601102&sid=asdaiFP8111I&refer=uk.

7 Robert Farley, *Drug research: To test or to tout?*, St. Petersburg Times, April 13, 2008, http://www.tampabay.com/news/health/article454391.ece.

8 The SGAs, also known as "atypical" antipsychotics, include quetiapine (marketed as "Seroquel" by AstraZeneca), clozapine ("Clozaril," Novartis), olanzapine ("Zyprexa," Eli Lilly & Co.), risperidone ("Risperdal," Ortho-McNeil-Janssen), ziprasidone ("Geodon," Pfizer), aripiprazole ("Abilify," Bristol-Myers Squibb), and paliperidone ("Invega," Ortho-McNeil-Janssen).

generation antipsychotic") treatments for schizophrenia such as Haldol and Thorazine.[9] The FGAs were widely considered effective treatment for schizophrenia and other mental illnesses, but were also known to cause Parkinson's-like movement disorders.[10] By 2005, the SGAs garnered 90 percent of the United States antipsychotic market.[11] From its introduction in 1997, Seroquel's annual sales grew from $0 to $3.4 *billion* dollars in 2006.[12]

The Company's own clinical trials have shown for years that Seroquel causes rapid, clinically significant weight gain.[13] Seroquel is also a cause of hyperglycemia and diabetes in its users;[14] Seroquel users have at least ***double*** the risk of contracting diabetes-level hyperglycemia compared to patients taking placebo in clinical trials according to AstraZeneca's recently revised package insert.[15] While Seroquel sales increased by *billions* of dollars in less than ten years, AstraZeneca deliberately downplayed those serious risks. Indeed, the evidence shows that where SGAs generally "promised enhanced efficacy and safety,"[16] Seroquel delivered neither.[17]

---

9 American Diabetes Association et al., *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes*, 27(2) Diabetes Care 596, 596 (Feb. 2004); *see* Carol A. Tamminga, M.D., *Editorial: Practical Treatment for Schizophrenia*, 164(4) Am. J. Psychiatry 563, 563 (Apr. 2006) ("We are at a point where we can ask which, among the multiple antipsychotic treatments, are best for effectiveness, efficacy, and tolerability. . . . . The hope that other new antipsychotics with fewer metabolic side effects might offer a similar effect was not fulfilled. Some have pointed out that older drugs like perphenazine, with their lower costs, may now once again become rational first-line therapies.").

10 Farley, *supra* note 7; *see also* Jeffrey A. Lieberman et al., *Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia*, 353 New Eng. J. Med. 1209, 1210 (2005). The "first generation antipsychotics" ("FGAs"), also referred to as "typical" or "conventional" antipsychotics, include among them haloperidol ("Haldol"), chlorpromazine ("Thorazine"), and perphenazine ("Trilafon"). They have long been associated with high rates of neurologic side effects, such as extrapyramidal symptoms (Parkinson's disease-like shakes) and tardive dyskinesia, an incurable, physically disfiguring condition. Lieberman et al. at 1210.

11 Lieberman et al., *supra* note 10, at 1210.

12 Pettypiece et al., *supra* note 6.

13 *See* discussion, *infra* at 16-20.

14 *See* discussion, *infra* at 16-29.

15 *See* discussion, *infra* at 31-35.

16 Lieberman et al., *supra* note 10, at 1210.

17 *See* discussion, *infra* at 12-35.

C. Danger of Diabetes

Diabetes is a condition in which the body fails to produce enough insulin action for its needs.[18] Insulin and glucagon help control and fine-tune the level of nutrients derived after meals and during fasting periods.[19] Weight gain and obesity are known causes of insulin resistance.[20] With insufficient insulin and excess glucagon action, the body produces excess amounts of glucose and fatty acids.[21] Excess blood sugar above the renal threshold causes spillage of sugar into the urine, excessive urination and significant energy deficit, resulting in weight loss and dehydration.[22] High levels of fatty acids are broken down in the liver to produce ketone bodies and a metabolic acidosis that can proceed to severe illness and death.[23] In some cases, a non-diabetic subject can contract the disease when increased levels of triglycerides are produced from the liver, which can result in massive accumulations of triglycerides in the blood and acute pancreatitis, contributing to the later development of diabetes.[24]

"Type 2" diabetes, also known as "adult onset diabetes," is a progressive condition in which the pancreas steadily loses insulin secretory function over five to fifteen years despite maximum doses of available oral medicines.[25] The pancreas ultimately loses the ability to produce sufficient insulin for adequate sugar control despite maximum dosing of oral medications, and subjects later in the disease require a source of exogenous insulin to achieve

---

18 *See, e.g.*, Report of Plaintiffs' expert Brian Tulloch, M.D. ("Tulloch Rep.") at 3.
19 *Id.*
20 *Id.*
21 *Id.*
22 *Id.*
23 *Id.*
24 *Id.*
25 *Id.* at 7.

glucose control.[26] Initially a once-a-day program of long-acting insulin is sufficient, but as the pancreatic function continues to deteriorate, many type 2 diabetics require additional, pre-meal, short-acting insulin to control the post-prandial rise in glucose.[27] ***That necessitates daily, pre-meal blood sugar monitoring by the patient and greater vigilance by both physician and patient to stabilize daily variations in glucose values.***[28]

According to the American Diabetes Association, 65% of diabetics die of heart disease or stroke.[29] Diabetics die of heart disease two to four times more frequently than non-diabetics.[30] In subjects who have poorly controlled diabetes, the condition also contributes to accelerated levels of small vessel degeneration, leading to early progression of kidney failure (diabetes is the most common factor for renal dialysis), as well as contributes to blindness (diabetes is the leading cause of blindness in young people), and to limb loss (diabetes is the greatest factor leading to non-traumatic limb loss).[31]

Ninety percent of persons diagnosed with new type 2 diabetes are overweight.[32] Being overweight or obese is a leading risk factor for type 2 diabetes.[33] At least one out of every five overweight people have several metabolic problems at once, which can lead to serious complications like heart disease.[34] "Cardiometabolic risk" means that if a person has

---

26 *Id.*

27 *Id.*

28 *Id.*; *see* American Diabetes Association ("ADA Website"), How to Tell If You Have Pre-Diabetes, http://www.diabetes.org/pre-diabetes/pre-diabetes-symptoms.jsp (last visited Nov. 23, 2008).

29 *See id.* at 5; ADA Website, Complications of Diabetes in the United States, http://www.diabetes.org/diabetes-statistics/complications.jsp (last visited Nov. 12, 2008).

30 *Id.*

31 *Id.* at 5; *see also* ADA Website, *supra* note 29.

32 ADA Website, Weight Loss Matters, http://www.diabetes.org/weightloss-and-exercise/weightloss.jsp (last visited Nov. 21, 2008).

33 ADA Website, Diabetes and Metabolic Health, http://www.diabetes.org/weightloss-and-exercise/diabetes-metabolic-health.jsp (last visited Nov. 21, 2008).

34 *Id.*

one of these problems, s/he is at higher risk for developing the others.[35]

D. Role of FDA in New Drug Approval, Labeling, Marketing, and Monitoring

Under the Food, Drug, and Cosmetics Act ("FDCA"), a new pharmaceutical medication cannot be marketed in the United States unless the drug's sponsor demonstrates to FDA's satisfaction that the drug is safe and effective for each intended use.[36] A drug receives FDA approval only for treatment of specified conditions, referred to as "indications."[37] For each indication sought, a manufacturer must provide condition-specific safety and efficacy information.[38]

To determine whether a drug is "safe and effective," FDA relies on information provided by a drug's manufacturer; it does not conduct any substantial analysis.[39] Applications for FDA approval (known as New Drug Applications or "NDAs") must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."[40] FDA approval of prescription drugs is wholly dependent upon the accuracy of information provided by drug manufacturers.[41]

FDA not only depends upon industry-supplied data, but it also relies upon direct financial support from the industry. "By law, makers of brand-name drugs pay application

---

35 *Id.*

36 21 U.S.C. §§ 355(a), (d).

37 21 U.S.C. §§ 352, 355(d).

38 *Id.*

39 *In re Zyprexa Prods. Liab. Litig.*, ___ F.R.D. ___, 2008 WL 4097408, at *42 (E.D.N.Y. Sept. 5, 2008).

40 21 U.S.C. § 355(b)(1)(A).

41 *In re Zyprexa*, 2008 WL 4097408, at *42; *see* Wayne A. Ray & Michael Stein, *Reform of Drug Regulation—Beyond an Independent Drug-Safety Board*, 354(2) New Eng. J. Med. 194 (Jan. 12, 2006). A manufacturer desiring to market an approved drug for indications other than those already approved must submit a supplemental NDA with clinical trial information similar to that required for the initial NDA. 21 U.S.C. §§ 301 *et seq.*, 360aaa(b), (c); 21 C.F.R. § 314.54. Unless and until an additional indication is approved by FDA, the unapproved use is considered to be "off-label." *In re Zyprexa*, 2008 WL 4097408, at *43. Pharmaceutical sales representatives are prohibited from promoting off-label uses of the drugs they represent. *Id.* at *40.

fees to the F.D.A. in exchange for the agency's commitment to act within 180 days."[42] "[S]ince the enactment of the Prescription Drug User Fee Act of 1992 . . . the pharmaceutical industry provides between twenty to fifty percent of the funding for the FDA's activities. The regulating agency is therefore dependent on those it is supposed to be regulating."[43] As a result, FDA regulatory policy favors the pharmaceutical industry.[44]

FDA approval does not require that a new drug be more effective or safer than other drugs approved to treat the same condition.[45] Nor does it require that the drug be cost effective.[46] A drug must only be shown to be more effective than a placebo in treating a particular condition.[47] Furthermore, because short-term studies are accepted, drug applications often do not contain long-term data on the safety or efficacy of the drug.[48] Approval of a new drug generally requires that the drug maker pursue further long-term

---

[42] Bloomberg News, *F.D.A. Revises Its Letter for Nonapproval of Drugs*, N.Y. Times, July 10, 2008.

[43] Karen Baswell, Note, *Time for a Change: Why the FDA Should Require Greater Disclosure of Differences of Opinion on the Safety and Efficacy of Approved Drugs*, 35 Hofstra L. Rev. 1799, 1828 (2007).

[44]
> [F]ederal drug policy seems to currently favor the commercial pharmaceutical industry. Differences of opinion regarding safety and efficacy in a new drug application seem to be decided in favor of the manufacturer (at least initially). After approval, challenges to a drug's safety or to the adequateness of the drug's label regarding risks become so egregious that the manufacturer or the FDA is forced to address them. This set-aside period allows the manufacturer to maximize profits before removing either an indication for a drug or the drug itself.

Id. at 1829; *see* Gardiner Harris, *Potentially Incompatible Goals at F.D.A.: Critics Say a Push to Approve Drugs Is Compromising Safety*, N.Y. Times, June 11, 2007, at A14 (reporting that "several F.D.A. safety reviewers in recent years have been punished or discouraged after uncovering . . . drug dangers"); *see also In re Zyprexa*, 2008 WL 4097408, at *42; Lisa Richwine, *Pfizer CEO: Independence needed at FDA*, Reuters, Nov. 20, 2008, http://www.reuters.com/article/Health08/idUSTRE4AJ9B320081120 (quoting Pfizer Inc. CEO Jeff Kindler: "We need a strong, independent, well-resourced FDA. The starting point for that is to have a commissioner who has strong scientific credentials and credibility and stature who can bring independence to bear on the agency, to ensure that it is proceeding as far from politics as is possible.").

[45] *In re Zyprexa*, 2008 WL 4097408, at *43. Comparative data showing performance as against that of existing drugs is not required; FDA has no basis for determining whether one drug is more effective than another drug. Ray et al., *supra* note 41, at 194.

[46] *Id.*; *see* Robert Rosenheck, *The Growth of Psychopharmacology in the 1990s: Evidence-Based Practice of Irrational Exuberance*, 28 Int'l J.L. & Psychiatry 467 (2005).

[47] ; *In re Zyprexa*, 2008 WL 4097408, at *43.

[48] *In re Zyprexa*, 2008 WL 4097408, at *43.

studies, but two-thirds of the promised studies never materialize, and FDA lacks authority to compel them.[49]

Critical for conveying a drug's approved uses and known warnings to prescribers, FDA must also approve a drug's labeling as part of the original application.[50] By law, "labels" include all marketing and promotional materials relating to the drug as well as the printed insert included in the packaging.[51] They may not describe intended uses for the drug that have not been approved.[52]

Manufacturers and FDA typically negotiate over the wording and content of the label, especially in regard to adverse information about the drug.[53] Labels are drafted by manufactures and submitted in the NDA.[54]

After a drug is approved, FDA may require a label change to reflect the increased risk of various side effects or interactions, restrict a drug's indications, or, in extreme cases, force

---

[49] *Id.* No systematic provision requires drug manufacturers to conduct—or provide results from—post-marketing studies. *Id.*; *see* United States Government Accountability Office, Drug Safety – Further Actions Needed to Improve FDA's Postmarket Decision-making Process, at 9 (2007) (hereinafter, "GAO Drug Safety Report") ("FDA does not have broad authority to require that a drug sponsor conduct an observational study or clinical trial for the purpose of investigating a specific postmarket safety concern. One senior FDA official and several outside drug safety experts told us that FDA needs greater authority to require such studies."), *available at* http://www.gao.gov/new.items/d07856t.pdf; AP Analysis: *How a Drug's Risks Emerge*, N.Y. Times, May 23, 2007.

[50] 21 U.S.C. § 355(a), (b)(1)(F); *see In re Zyprexa*, 2008 WL 4097408, at *43.

[51] *Id.* Federal law broadly defines "labeling," which includes not only package inserts, but also separate communications concerning the drug, such as "Dear Doctor" letters sent by drug manufacturers to physicians to provide information about a drug. *See* 42 U.S.C. § 262(g); 21 U.S.C. § 321(m) (defining "labeling" under FDCA: "all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article"); *see also Kordel*, 335 U.S. at 349-50 (clarifying that separate literature sent by the manufacturer constituted "labeling" under the FDCA when it supplemented or explained materials sent with the drug); *Walls v. Armour Pharm. Co.*, 832 F. Supp. 1467, 1482-83 (E.D.N.Y. 1993).

[52] 21 U.S.C. §§ 331, 352.

[53] *In re Zyprexa*, 2008 WL 4097408, at *44; *accord* William C. Wirshing, M.D. Decl. ("Wirshing Decl.") ¶ 16 (Exhibit 43).

[54] 21 U.S.C. § 355.

a drug's withdrawal from the market.[55] Negotiation over proposed modifications is common, and compromise often results.[56] ***Importantly, a manufacturer must change its label independently, before receiving FDA approval, upon learning of a reasonable association of the drug with a serious hazard. A causal association need not be proven.*** [57]

FDA's Office of Surveillance and Epidemiology ("OSE") is responsible for overseeing the safety of approved drugs.[58] Like other divisions within the agency, OSC is underfunded and understaffed.[59] For example, "[t]he F.D.A. has 200 inspectors, some of whom audit clinical trials part time, to police an estimated 35,000 testing sites."[60] Furthermore, although drug companies are under a continuing obligation to report serious adverse events, with safety reports required to be filed every quarter during a drug's first few years on the market, FDA's adverse event reporting system is also largely voluntary.[61] Health care professionals are not required to report serious adverse events suspected to be caused by medications, and are not even encouraged to report adverse events other than those

---

55 21 U.S.C. § 355(e); 21 C.F.R. § 314.50; *see In re Zyprexa*, 2008 WL 4097408, at *44; *see also* GAO Drug Safety Report, *supra* note 49, at 5 ("FDA has the authority to withdraw the approval of a drug on the market for safety-related and other reasons, although it rarely does so. In almost all cases of drug withdrawals for safety reasons, the drug's sponsor has voluntarily removed the drug from the market.").

56 *See* 21 U.S.C. § 355(d); Ray et al., *supra* note 41, at 194-95; Raymond L. Woosley, *Drug Labeling Revisions—Guaranteed to Fail?*, 284(23) JAMA 3047 (Dec. 20, 2000); *accord* Wirshing Decl. ¶ 16 (Ex. 43).

57 21 C.F.R. § 201.57(e) (2006) (Ex. 45).

58 *In re Zyprexa*, 2008 WL 4097408, at *46; *see* U.S. Food and Drug Administration, Office of Surveillance and Epidemiology (formerly Office of Drug Safety), http://www.fda.gov/cder/Offices/ODS/default.htm (last visited Nov. 23, 2008).

59 *In re Zyprexa*, 2008 WL 4097408, at *46; *see* GAO Drug Safety Report, *supra* note 49, at 9-10.

60 Gardiner Harris, *Report Assails F.D.A. Oversight of Clinical Trials*, N.Y. Times, Sept. 28, 2007, at A1 (noting a government report's conclusion that "the agency's oversight of clinical trials is disorganized and underfinanced . . . . [F]ederal health officials did not know how many clinical trials were being conducted, audited fewer than 1 percent of all testing sites and, on the rare occasions when inspectors did appear, generally showed up long after the tests had been completed"); *see* Gardiner Harris, *Advisers Say F.D.A.'s Flaws Put Lives at Risk*, N.Y. Times, Dec. 11, 2007, at A12 (reporting on an FDA Advisory Board's conclusion that the "FDA is falling farther and farther behind in carrying out its responsibilities and understanding the science it needs to do its many jobs"); *see also In re Zyprexa*, 2008 WL 4097408, at *46.

61 Phil B. Fontanarosa et al., *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*, 292 JAMA 2647, 2647 (2004), *cited in In re Zyprexa*, 2008 WL 4097408, at *47.

classified as "serious."[62] Doctors may not immediately recognize a connection between a new drug and deleterious side effects.[63] Adverse events are, therefore, significantly underreported; reported events are thought to represent only 1% to 10% of total complications.[64]

E. Development and Marketing of Seroquel

As a preliminary matter, in reviewing the development and marketing of Seroquel the Court should note that, at virtually all times relevant to this litigation, AstraZeneca was subject to the following express FDA regulatory mandate with respect to the information contained on Seroquel's label/package insert:

> (e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. ***The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.***[65]

The evidence clearly demonstrates that AstraZeneca failed to comply with this regulation, much less Florida failure-to-warn law. Indeed, FDA knew little more about Seroquel's dangerous propensities than did the medical community or the public—and all markedly less

---

62 Timothy Brewer, *Postmarketing Surveillance and Adverse Drug Reactions*, 281(9) JAMA 824 (Mar. 3, 1999), *cited in In re Zyprexa*, 2008 WL 4097408, at *47.

63 *In re Zyprexa*, 2008 WL 4097408, at *47.

64 *See* A.S. Rogers et al., *Physician Knowledge, Attitudes, and Behavior Related to Reporting Adverse Drug Events*, 148(7) JAMA (July 1, 1988), *cited in In re Zyprexa*, 2008 WL 4097408, at *47; *see also* GAO Drug Safety Report, *supra* note 49, at 8 ("While decisions about postmarket drug safety have often been based on adverse event reports, FDA cannot establish the true frequency of adverse events in the population with data from adverse event reports. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and comparisons of risks across similar drugs are difficult.").

65 21 C.F.R. § 201.57(e) (2006). That section has very recently been modified to read as follows:

> In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is sufficient evidence of a causal association with a drug; a causal relationship need not have been definitely established.

21 C.F.R. § 201.57(c)(6) (2008).

than AstraZeneca itself.

Also crucial to the Court's review is this fact: measuring drug "safety" requires analysis not only of a drug's risks, but its benefits as well.[66] In reviewing risks and benefits of a drug, the higher the risk associated with a drug, the higher the benefit threshold that must be met; the converse is true as well: the lower the benefit, the lower tolerance for risks of serious side-effects.[67] Likewise, Plaintiffs address both the benefits and risks of Seroquel in setting forth the evidentiary record in this case, as follows:

1. Benefit (efficacy) – "The data don't look good."

Even before its launch, AstraZeneca's studies revealed a troubling truth about the Company's antipsychotic drug: Seroquel was *less effective* (or at least no more effective)

---

[66] As the French government explained in rejecting a marketing authorization for Seroquel in that country in 2005: [redacted]

[67]

> [W]hen . . . the physician . . . prescrib[es] an unavoidably dangerous drug, [s/he] must consider risk/benefit analysis. In considering the risks and benefits, the doctor needs to take into account the benefit of the drugs, the patient's health, and any alternatives such as surgery or therapy that may be available in a particular situation. Clearly, where the plaintiff is only ten to twenty pounds over the recommended weight, and the physician has prescribed Fen-phen as a first line of defense to the weight problem, it is unlikely that this situation will allow the doctor to say there was no better alternative.

Carin A. Crisanti, *Product Liability and Prescription Diet Drug Cocktail, Fen-Phen: A Hard Combination to Swallow*, 15 J. Contemp. Health. L. & Pol'y 207, 234 (1998).

> The physician must consider the risks and benefits of a particular product, the patient's health status, and possible therapeutic alternatives. Under some circumstances, prescribing a drug with very severe side effects might be medically warranted because of the consequences of not employing the treatment. For example, the severe side effects of chemotherapy are medically acceptable when a cancer is otherwise untreatable; these same effects would be intolerable for a patient suffering from the flu.

Jeffrey N. Gibbs and Bruce F. Mackler, *Food and Drug Administration and Products Liability: Strong Sword, Weak Shield*, 22 Tort Trial & Ins. Prac. L.J. 194, 200 (1987).

than comparator drugs, or even placebo at low doses.[68]

AstraZeneca's March 9, 2000 "Technical Document 4," a meta-analysis[69] of the results of ten earlier-conducted trials (but *not* the "cursed" trial 15, discussed *infra* at 16-18) contained the following chart summarizing the Company's efficacy findings for Seroquel:

Comparator	**Category**						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✱	-	✱	-	✱	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✱	✱	✱	✱	-	✱	✱
Other typicals	-	✱	-	✱	-	✱	-

(Exhibit 2 § 3.) According to the accompanying legend, a ✓ was entered on the chart where Seroquel showed a "statistically significant benefit." (*Id.*) That mark only appeared in relation to tests against placebo. (*Id.*) For all other comparators, the comparator drug either "demonstrated significant superiority compared to Seroquel" (marked by an ✱), or showed no statistically significant difference (marked -). (*Id.*) Technical Document 4 concluded:

---

[68] Data generated in Defendant's pre-marketing clinical trials, and submitted to FDA in support of Defendant's New Drug Application (NDA), revealed Seroquel's limitations as treatment for schizophrenia. Of the eight controlled trials submitted, FDA considered four "capable by design of providing meaningful data on the efficacy of" Seroquel. (Studies 0006, 0008, 0013 and 0012). Studies 0007 and 0014 "failed to show a difference between quetiapine and the comparator drug . . . . In fact, the CGI [clinical global impression] results favored haloperidol over quetiapine in study 0014." According to FDA, study 0006 "provides marginal support for antipsychotic efficacy of quetiapine, when titrated to a wide dose range. Strictly speaking, however, the data fall short of meeting the customary level of statistical proof, particularly for the observed cases analyses." Studies 0008 and 0013, designed to assess the efficacy of Seroquel at high and low doses revealed that efficacy of low doses, below 250 mg, "was not supported." Critically, study 0013, which compared various doses of Seroquel to 12 mg of Haldol showed that Haldol "generally performed better in the observed cases analysis than any of the quetiapine groups." Further, other than an observation that lower doses of Seroquel were ineffective, "there appeared to be little evidence for a dose response effect . . . ." *See* FDA, Review and Evaluation of Clinical Data, at 7-8, 12, 15, 18, *available at* http://www.fda.gov/cder/foi/nda/97/020639ap_Seroquel_medrP2.pdf.

[69] Meta-analysis combines the results of several studies that address a set of related research hypotheses and is widely used in health services research.

> In terms of generating positive claims for Seroquel, these analyses seem somewhat disappointing. [T]here was no evidence in these analyses of a significant benefit for using Seroquel over any other of the active agents assessed. There is, however, consistent evidence that Seroquel is better than placebo for a number of the BPRS (Brief Psychiatric Rating Scale) sub-categories assessed.
>
> There was little evidence of improvement with high-doses of Seroquel relative to including 'all doses' of Seroquel . . . . [I]n the comparisons against Risperidone (trial 5077IL/0053), looking at high doses of Seroquel appears to give relatively worse results than looking at all patients together.

(*Id.*)

Near the same time, another meta-analysis was completed against the FGA Haldol alone. (Exhibit 3.) That analysis concluded that "[t]he intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of equivalence is not ruled out." (*Id.* § 4.)

To AstraZeneca decision-makers, the efficacy results were unsettling. In anticipation of a paper that AstraZeneca had apparently arranged for a Dr. S. Charles Schulz to write regarding Seroquel's superior efficacy, John Tumas, AstraZeneca's U.S. Publications Manager for Seroquel, sent the following email to others in the Company:

From: Tumas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

* * *

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo **and** haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own anaylsis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or teleconference) and discuss where to go from here.

* * *

(Exhibit 4; underscored emphasis added.)

Out of those disastrous studies grew a brilliant (and highly effective) promotional campaign founded on clever—or "incredibly careful"[70]—wordsmithing. In particular, the Company coined the phrase "unsurpassed efficacy" to describe the fact that Seroquel trials resulted in a finding of no greater efficacy than its competitors, while not-so-subtly suggesting superiority at the same time. Geoffrey Birkett, former Global Vice President of Central Nervous System Product Marketing, testified that "unsurpassed efficacy" was one of the cornerstones of the Seroquel marketing strategy for the treatment of schizophrenia.[71] He testified that the phrase meant "in the correct patient treated for the correct indication at the correct dose Seroquel is highly effective and there's nothing more effective."[72]

Yet, in reviewing "Table 1" from Technical Document 4 (see chart and discussion,

---

70 Kevin Geoffry Birkett Dep. ("Birkett Dep.") at 605:7-20 (Exhibit 5).

71 *Id.* at 330:7-23.

72 *Id.* at 560:4-12. This theme, the centerpiece of AstraZeneca's efficacy message, is deceptive for two reasons. First, Seroquel was not compared to "everything," so the categorical negative that "nothing is more effective" is baseless. Second, AstraZeneca's comparisons of Seroquel and Haldol show that a correct application of Birkett's premise is in any patient for any psychiatric indication at any dose, Seroquel is no more effective than Haldol.

supra at 13-14; *see* Ex. 2), Mr. Birkett stated that he could not see in the chart "where Seroquel is seen as more effective than haloperidol."[73] Indeed, an AstraZeneca Sales Story Flow document discussed in Mr. Birkett's deposition stated in the notes at page two that "Seroquel produced greater improvement than Haloperidol, *but differences were not statistically significant*."[74]

Notwithstanding the positive spin the Company put on Seroquel's inefficacy, Dr. Wayne Macfadden, AstraZeneca's United States Medical Director for Seroquel and Director of Clinical Research from January 2004 to Summer 2006,[75] admitted in his deposition that to his recollection there had ***never been a study conducted*** that showed Seroquel was more effective than other SGAs or even FGAs. Dr. Macfadden also testified that it would be "false" for AstraZeneca's employees or representatives to say that Seroquel was more effective than other SGAs or FGAs.[76]

*2. **Risk (serious hazards) – "Smoke-and-mirrors"***

(a) **1997**: Weight gain, as noted, is a leading factor contributing to the onset of diabetes.[77] Lisa Arvanitas, Seroquel Product Physician, analyzed the severity of

---

[73] *Id.* at 577:20-24.

[74] Exhibit 6 at 2 (emphasis added). A Sales Story Flow document is generally provided to the Company's marketing firms to guide salespersons in "detailing" (making sales calls regarding Seroquel) on doctors, but the document is not itself used to detail doctors or shown to doctors. Birkett Dep. at 28:13-30-17.

[75] Wayne Macfadden Dep. at 17:13-18 (Exhibit 7).

[76] Macfadden Dep. at 718:3-15; 731:11-17, 20-24; 732:1, 13-24; 733:1-3, 7-15 (Ex. 7); *see also id.* at 716:7-19; 717:19-24 (Ex. 7). Macfadden also testified that he was aware of at least one study that concluded in part that Seroquel was no more effective than a placebo. Macfadden Dep. at 719:22-24; 720:1-24 (Ex. 7). In fact, "Trial 8," conducted by Dr. Joyce Small, concluded that "[t]he average low dose of 209 mg [of Seroquel] was no better than placebo but the mean high dose of 360 mg was superior to placebo." Draft Report by Joyce G. Small, M.D., *Quetiapine*, AZ/SER 1521228-1521256, at AZ/SER 1521232; *see* discussion *supra* at 8.

[77] *See* discussion, *supra* at 5-7.

Seroquel's critical association with weight gain[78] based on AstraZeneca's Study 15 in an internal Company email, noting the rapid, consistent, clinically significant, and dose-dependent nature of the weight gain. (Exhibit 10).

Study 15, to which the email refers, was a long-term study comparing three doses of Seroquel to haloperidol for the prevention of relapse in schizophrenia.[79] The Company considered it a "failed study" because it did not support the efficacy of Seroquel or haloperidol in the prevention of psychotic relapse in patients with schizophrenia.[80] Months earlier, Richard Lawrence, an AstraZeneca Commercial Strategist, circulated the following internal memorandum regarding Arvanitas and others' successful efforts at "spinning" to United States and Canadian investigators the results of Study 15 (a "cursed" study):

INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT

Tel No: 01625 517679

* * *

From: Richard Lawrence

Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimize (and dare I say venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

* * *

(Exhibit 13.)

---

78 *See* Donna K. Arnett, PhD Expert Report at 4-8 (analyzing studies conducted and submitted to the FDA with Seroquel's NDA, and concluding that "[s]ignficant weight gain was observed in the Phase II and Phase III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications") (Exhibit 9).

79 Martin Brecher Dep. ("Brecher Dep.") at 208:22-209:4 (Exhibit 11).

80 Barry Arnold Dep. at 367:1-9 (Exhibit 12).

(b) **1999**: AstraZeneca ultimately decided to "bury" Study 15, along with a number of others, as the following email from John Tumas, Seroquel U.S. Publications Director, shows:

> From: Tumas, John JA
> Sent: Monday, December 06, 1999 11:45 PM
> . . .
>
> Please allow me to join the fray.
>
> There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.
>
> That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.
>
> The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.
>
> . . .

(Exhibit 14.) The Velligan paper mentioned above consisted of an AstraZeneca-sponsored article (or "reprint") on only the cognitive function data from Study 15, making no mention of safety data from the Study nor revealing that the Company considered the Study to be "failed" or "cursed."[81] AstraZeneca has never made public the Study 15 safety data.

Additionally, at least by May 1999, the evidence shows that Company data had established the link between Seroquel-induced weight gain and diabetes/hyperglycemia. Dr. Joyce Small, who conducted "Trial 8" and was commissioned by AstraZeneca to write a paper on Seroquel efficacy and safety, found as follows:

> [W]eight gain was an adverse event experienced by two percent of quetiapine patients in the placebo controlled studies. Clinically significant weight gain, that is more than 7 percent increase in body weight, was seen more with

[81] *See* Ex. 14. The Velligan reprint was published in 2002 (three years after it was submitted) and it was shown, discussed, and/or distributed to Seroquel prescribers commencing that same year. *See, e.g.*, Pl. Linda Guinn's Resp. in Opp'n to AstraZeneca's Mot. for Summ. J. and Mem. of Law, filed concurrently herewith, at § III.C.1.

> quetiapine than placebo – 24 percent compared with four percent in the Borison et al. study. Weight gain appeared to be dose related in the Small et al. and Arvanitas et al., trials ranging from five percent for placebo, fifteen percent for low dose and twenty-four percent with high does quetiapine in the former. Likewise weight gain in the Arvanitas et al. study was proportional to dosage and exceeded amounts with haloperidol and placebo. Twenty-seven percent of quetiapine treated patients had significant weight gain compared with eighteen percent with chlorpromazine reported by Peuskens and Link.
>
> Adverse effects of atypical antipsychotics upon glucose regulation have been recognized recently mostly with clozapine. . . . . New onset diabetes has also been reported with olanzapine(45) [Zyprexa]. ***It appears that atypical neuroleptics may promote weight gain, insulin insensitivity and glucose intolerance by virtue of their antagonism of histamine and serotonin receptors.*** African-Americans are particularly vulnerable to these effects and individuals with personal or family histories of diabetes mellitus or obesity. ***As clozapine, olanzapine, and quetiapine cause the most weight gain, these drugs may be most likely to induce diabetes.*** Case reports with quetiapine have not appeared ***so far***.

(Exhibit 8 at AZ/SER 1521244-1521245; emphasis added.)[82]

Despite knowledge that Seroquel "may be [among the] most likely to induce diabetes," AstraZeneca delivered exactly the opposite message to doctors. In or about 1999, the Company circulated to doctors a brochure or "slim jim" (pamphlet) entitled "Managing Weight Gain and Diabetes in Schizophrenia," describing a "Patient Case Study From the files Michael J. Reinstein, MD." (Exhibit 15.) The patient presented as a 49-year old white male, unemployed with a long history of psychiatric hospitalizations and having been diagnosed with, among other illnesses, paranoid schizophrenia and bipolar disorder. (*Id.* at AZSER10427474.) Regarding the patient's response to Seroquel, the brochure stated: "Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on Olanzapine." (*Id.* at AZSER 10427476.) Then, the brochure quoted Dr.

---

[82] The timing of the study is established by Exhibit 14, in which John Tumas circulates Dr. Small's review of quetiapine for internal comment by Company officials in May 1999.

Reinstein's conclusions:

> Our laboratory data revealed a normalization of serum glucose levels ***which is valid proof of improvement of diabetes and metabolic stabilization.*** His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also very relieved that he no longer has to take daily insulin injections.
>
> * * *
>
> We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications.

(*Id.*; emphasis added.)

Dr. Reinstein's proclamations of weight loss and diabetes resolution in the sales brochure were supplemented by an AstraZeneca-sponsored "study" and resulting paper by Dr. Reinstein, also in 1999. (Exhibit 16.) In the purported study, Dr. Reinstein and his researchers "reviewed" medical charts of 65 randomly-selected schizophrenic patients who were taking the SGA clozapine initially, then had Seroquel added to their therapy. (*Id.* at 99.) According to the paper, the study resulted in all 65 patients showing statistically significant weight loss—"a 100% satisfactory response." (*Id.* at 99.) In addition, the paper reported that the 20 percent of patients who developed diabetes while taking clozapine alone "showed significant improvement of disease status with addition of [Seroquel]." (*Id.*) Dr. Reinstein reported that the "most common adverse event reported by patients was drowsiness." (*Id.*) The paper concluded that "[a]n unexpected, yet welcome, clinical effect of [Seroquel] is its apparent propensity to ***induce weight loss*** and ***improve glycemic control*** in patients who gain weight and develop diabetes on clozapine therapy." (*Id.* at 100.)

AstraZeneca seized upon these incredible messages, which were at odds with the

Company's understanding of Seroquel's relationship with weight gain and diabetes (as evidenced by the Small paper, for example) and deployed Dr. Reinstein to speak to doctors around the world about Seroquel's safety over 500 hundred times over the course of ten years. That AstraZeneca embraced and adopted Dr. Reinstein's findings as descriptive of the nature of Seroquel's metabolic risk profile is startling in light of its own assessment of the significant and numerous issues related to the quality of Dr. Reinstein's "research." According to AstraZeneca, at the time Dr. Reinstein was presenting his research to doctors, his lab was known to be guilty of such transgressions as (1) not getting informed consent from study participants, (2) modifications of protocols without permission, and (3) lack of adherence to Good Clinical Practices. (Exhibit 17.) Further, because Dr. Reinstein was "generally held in poor regard" among his peers in his hometown of Chicago, he was used by AstraZeneca to speak outside of the Chicago regional area. (*Id.*)

(c) **2000**: A year later, FDA notified AstraZeneca that, based upon review of post marketing safety data for SEROQUEL and other atypical antipsychotics, it was investigating a possible causal link between the SGAs and diabetes.[83] (Exhibit 18, "Discussion Document" prepared by Wayne Geller, M.D., AstraZeneca Medical Director, Drug Safety, at 2.) In or about June 2000, the Company convened a Safety Evaluation and Review Meeting ("SERM") concerning "SEROQUEL" and "DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCEMIA" as a result of FDA's inquiry. (Exhibit 18 at 1-2.) The Discussion Document prepared for the SERM meeting by Dr. Geller provided as follows:

---

[83] As part of its review, FDA requested AstraZeneca's pre-clinical, clinical, and postmarketing data. Therefore, it was AstraZeneca's data as of 2000 that prompted FDA to request the 2003 warning.

> Presently, the SEROQUEL Core Data Sheet (CDS)[84] does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycemia associated with SEROQUEL therapy. Safety data derived from clinical trials and spontaneous reports, despite often containing limited information, suggest the possibility of an association between SEROQUEL use and impaired glucose regulation including occasional reports of new onset diabetes mellitus. While none of those reports are absolutely steadfast, ***the number of reports is fairly sizeable. [C]onsideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.***
>
> * * *
>
> The SEROQUEL core data sheet (CDS) . . . does not include any listings for [new onset diabetes mellitus or the complications of diabetes mellitus identified by the FDA]. The following statement addresses the issue of weight gain with SEROQUEL:
>
> "As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominately during the early weeks of treatment."
>
> The SEROQUEL US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

(Exhibit 18 at 2; emphasis added.) The Discussion Document also stated that SGAs Zyprexa and Clozaril already warned of hyperglycemia and diabetes in their labels' "Warnings and Precautions" sections. (Exhibit 18 at 2-3.) Further, the Discussion Document provided synopses of diabetes and hyperglycemia-related adverse event reports that had been received by the Company to date (29 reports), which the document characterized as "fairly sizeable." (Exhibit 18 at 6-16.)

Either in advance of the June 2000 SERM meeting, or during the meeting, Dr. Martin

---

84 The CDS is the official company position on the safety and efficacy profile of a particular drug. It includes the core information about the drug that must be contained in every product label around the world for that drug. SERM is the body that determines whether or not changes need to be made to the CDS. SERM typically consists of safety physicians and regulatory officers. Prior to SERM, the Global Drug Safety Physician ("GDSP") for the particular drug at issue circulates a Discussion Document to the SERM body which summarizes the data on a particular issue. The GDSP typically presents that data during SERM. The SERM body then decides whether a change to the CDS is warranted. Wayne Geller Dep. ("Geller Dep.") at 999:12-24; 1000:1-20; 1001:19-24-1002:1 (Exhibit 19). If SERM decides to not change the CDS, the GDSP prepares a Safety Position Paper. Geller Dep. at 1124:17-24; 1125:1 (Ex. 19); Brecher Dep. at 947:14-948:12 (Ex. 11).

Brecher, AstraZeneca's then Medical Science Director, annotated by handwritten notes his copy of the Discussion Document Dr. Geller prepared. (Exhibit 20.)[85] Dr. Brecher "starred" certain of the adverse event reports.[86] Significantly, on the last page of the report, Dr. Brecher wrote: "*Seroquel may cause impaired glucose regulation in some individuals.*" (Exhibit 20 at 17; emphasis added.)

Following the June 2000 SERM meeting, Dr. Geller was charged with writing a "Safety Position Paper,"[87] indicating that SERM determined the CDS did not require a change, which, as noted, would have also required a Seroquel label change.[88] (Exhibit 21 at 1.) That position paper again individually summarized the diabetes/hyperglycemia-related adverse event reports that had been received. (Exhibit 21 at 5-11.) It again stated that the number of diabetes/hyperglycemia adverse event reports was "fairly sizeable." Significantly, Dr. Geller—by then AstraZeneca's Global Drug Safety Physician—concluded:

> While there were no reports of positive dechallenges and rechallenges,[89] **there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus** in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet [requiring a labeling change] based upon postmarketing and clinical trial safety data.

(Exhibit 21 at 11; emphasis added.)

On September 5, 2000, the Medicines Evaluation Board ("MEB"), which is the Dutch

---

85 Dr. Brecher testified that the handwritten notes appearing on Exhibit 20 were written by him either before or during the June 2002 SERM meeting. Brecher Dep. at 333:8-12 (Ex. 11).

86 Dr. Brecher testified that he could not remember why he starred certain adverse event reports, but he agreed they were presumably important to him. Brecher Dep. at 343:9-346:12 (Ex. 11).

87 Dr. Geller testified that he wrote the Safety Position Paper in the Fall of 2000. Geller Dep. at 459:23-24; 460:1-5 (Ex. 19).

88 *See* note 84, *supra.*

89 FDA describes positive dechallenge reactions as an adverse event that disappears on withdrawal of the medication, and a negative dechallenge as an adverse event that continues after withdrawal of the medication. A positive rechallenge signifies that the adverse event re-occurred on re-administration of the drug, and a negative rechallenge means the symptom did not re-occur after re-administration.

regulatory authority, sent a request to AstraZeneca for an overview and assessment of all reports of glucose metabolism disorders associated with Seroquel. (Exhibit 22). The Dutch serve as the reference member state for Seroquel for the European Union. Participating European countries follow Holland's lead when it comes to all Seroquel labeling decisions.[90] The MEB's request was forwarded to Dr. Geller. On September 18, 2000, Dr. Geller emailed the Safety Position Paper he prepared following the June 2000 SERM to Dorothee Weintjens, an AstraZeneca employee in The Netherlands, for transmittal to the MEB. A few days later, Dr. Geller faxed the same Safety Position Paper following her request for a signed version of the document. Ms. Weintjens confirmed her receipt of the facsimile and advised Dr. Geller that the Safety Position Paper was forwarded to the MEB. (Exhibit 23.) [redacted]

Meanwhile, AstraZeneca was responding to FDA's request for further safety information to assess the possibility of a causal association between Seroquel treatment and disturbances in glucose regulation.[92] (Exhibit 26.) In that response, AstraZeneca reported a conclusion directly contradictory to its own assessment: "Overall, following extensive reviews of all the preclinical, clinical, and postmarketing data, AstraZeneca believes that the diabetogenic potential for Seroquel is unlikely." (Ex. 26 at 12.) AstraZeneca told FDA that it estimates 623,000 patients have been exposed to Seroquel since its launch. During that time, 12 cases of new onset diabetes, 3 cases of diabetic ketoacidosis, 2 cases of

---

90 Brecher Dep. at 378:16-379:4 (Ex. 11).

[redacted]

92 *See* discussion, *supra* at 21.

hyperglycemia and no cases of hyperosmolar coma had been reported. (Ex. 26 at 4.) Yet, in his June 2000 Safety Position Paper, Dr. Geller listed 28 reports of diabetes mellitus, hyperglycemia, diabetic ketoacidosis, and non-ketonic hyperosmolar coma reported with Seroquel. (Ex. 21 at 5.) In an email dated November 20, 2001 (Exhibit 27 at 7), Dr. Geller disagreed that only 12 cases of diabetes mellitus have been reported with Seroquel use by 623,000 patients. He wrote that he presented this issue at the June 2000 SERM and at that time there were 27 reports of diabetes and 2 reports of hyperglycemia. (Ex. 27 at 7.) Ultimately, the smaller numbers were submitted to FDA. (Ex. 27 at 6.) Dr. Geller attempted to explain this discrepancy by testifying that AstraZeneca gave FDA exactly what FDA requested—i.e., post-marketing reports for new-onset diabetes, hyperosmolar coma, diabetic ketoacidosis, weight gain and hyperglycemia—which, while technically true, also allowed AstraZeneca to avoid reporting to FDA the other incidents contained in its database.[93]

Also in or about late 2000, when Seroquel's label included "weight gain" among the adverse reactions that were dose-dependent, Seroquel salespeople were armed with a reprint of a study led by Dr. Brecher (the Company's Medical Science Director) claiming, among other things, that there was "no correlation between higher doses [of Seroquel] and long-term mean weight changes." (Exhibit 28.) This claim conflicts in two ways with every version of Seroquel labeling since the inception of marketing. First, it implies that there is no weight gain associated with Seroquel treatment. Second, it directly contradicts the label's characterization of weight gain as a dose dependent adverse reaction.

(d) **2002-2006**: By November 2002, the Japanese government had

---

[93] Geller Dep. at 528:10-24; 529:1-24; 530:1-10 (Ex. 19).

reached a similar determination as Dr. Geller's Safety Position Paper about Seroquel and diabetes. (Exhibit 29.) Seroquel had been available in that country for 21 months. (Ex. 29.) Responding to 12 "serious cases (including 1 death) of hyperglycaemia, diabetic ketoacidosis, and diabetic coma" in that short 21-month period "where causality with [Seroquel] could not be ruled out," Japan's actions were swift and unequivocal. (Exhibit 29 at 1.) The Japanese authority mandated issuance of a "Dear Doctor" letter from AstraZeneca to prescribers in that country in November 2002, which stated in pertinent part:

DEAR DOCTOR LETTER
- EMERGENCY SAFETY INFORMATION -

November 2002
NO. 02-5

Dear Dr. Letter

Diabetic ketoacidosis and diabetic coma due to an increase in blood glucose level during administration of Seroquel® 25mg, 100mg tablets (quetiapine), an antipsychotic drug

Since February 2001 when Seroquel was started to be marketed, 12 serious cases (including 1 death) of hyperglycaemia, diabetic ketoacidosis, and diabetic coma where causality with the drug could not be ruled out have been reported . . . .

* * *

This drug should be cautiously administered with strict attention to the following instructions.

* * *

1. **Seroquel must not be administered to patients with diabetes or a history of diabetes.**
In diabetic patients or patients having a history of diabetes, blood glucose levels may elevate, which may rapidly aggravate metabolic conditions. This drug must not be given to such patients.

2. **During administration of Seroquel, the patient should be monitored carefully including measurement of blood glucose levels.**
During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured because marked elevation of blood glucose after administration of the drug may cause serious adverse reactions such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.

3. **Information on the adverse reactions and action to be taken must be fully explained to the patient and the family.**
Prior to administration of the drug, sufficient explanation should be provided to the patient and the family that significant adverse reactions including diabetic ketoacidosis and diabetic coma may occur. They should be instructed to stop administration of the drug and visit hospital if any symptoms such as thirst, polydipsia, polyuria, increased urinary frequency or others appear.

* * *

(Exhibit 29 at 1-2.)

Meanwhile, that same month, AstraZeneca furnished its salespersons with the

following "Objection Handler on Atypical antipsychotics and glucose dysregulation" for use in detailing United States' doctors regarding Seroquel, partly in response to the Japanese Dear Doctor letter:

Summary

- The literature contains much conflicting information concerning the prevalence of diabetes and glucose dysregulation with atypical antipsychotics. Most of the published evidence relates to clozapine and olanzapine.
- Product labels vary widely between countries concerning statements about diabetic risk—not only between products but for the same product in different countries.
- The company's safety database has reassuring data concerning Seroquel's diabetic potential and glucose dysregulation.

* * *

It is interesting to note the different approaches by the various companies in relation to their antipsychotic. The approaches can be broadly summarized as follows:

Lilly-have tried to imply that diabetes/glucose dysregulation is a **class effect** of atypicals (in other words if olanzapine is going to be singled out as a culprit they intend to brand all the atypicals as guilty as well)!

* * *

Company position

Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.

There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes.

There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.

(Exhibit 30 at 2, 7.) The "objection handler" obviously conflicts with (1) Dr. Brecher's handwritten notes from the 2000 SERM meeting (Ex. 20 at 17), (2) Dr. Geller's conclusion in the Safety Position Paper two years earlier, (Ex. 21) and (3) the Japanese's determination that the risk was sufficiently great to direct that diabetic patients must not be prescribed

Seroquel and instructing that Seroquel patients should receive careful blood monitoring (Ex. 29).

In 2003, Dr. Henry Nasrallah, a paid speaker and "key opinion leader" for AstraZeneca, published a paper called "A review of the effect of atypical antipsychotics on weight." (Exhibit 31). After characterizing Zyprexa, Seroquel's chief competitor among the SGA class, as associated with significant dose-related weight gain, Dr. Nasrallah reported that weight gain associated with Seroquel treatment was "neutral" over the long term and not dose-related. (*Id.* at 86-87, 89.) "Weight neutrality," as explained by Dr. Nasrallah, is supported by data from the Brecher 2000 study[94] showing that patients with low to moderate body mass index ("BMI") experienced "minimal weight gain" while patients at the upper end of the BMI range experienced "a statistically significant decrease in weight." (*Id.* at 90.) According to the paper, this phenomenon accounts for Seroquel's propensity to normalize weight in obese patients. (*Id.* at 91.) Critically, the paper acknowledges that "excessive weight gain may also lead to other adverse health effects, e.g. type II diabetes." (*Id.* at 92.)

In August 2005, a voicemail script from Christine Ney, Scientific Alignment Manager for Seroquel, instructed AstraZeneca Seroquel salespersons to "neutralize customer objections to SEROQUEL's weight and diabetes profile" by utilizing "messages that are supported by data" like the "Weight and Diabetes Sell Sheet." (Exhibit 32; *see also* Exhibit 33). But, FDA disapproved of the "Weight and Diabetes Sell Sheet" in its November 16, 2006 letter from the Division of Drug Marketing, Advertising, and Communications ("DDMAC") informing AstraZeneca that the "Weight and Diabetes Sell Sheet":

---

94 *See* discussion, *supra* at 25; *see* Ex. 31.

- Failed to warn doctors of the increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with Seroquel in its promotions, thus undermining FDA-approved labeling;
- Misrepresenting the incidence of diabetes in post-marketing adverse event reports; and
- Failing to include relevant risk information about Seroquel.

(Exhibit 34 at 4-6.) According to FDA, the marketing piece "undermine[d]" the approved diabetes warning. (*Id.* at 4.)

F. Seroquel's Labeling

When Seroquel was first approved and marketed in 1997 through 2003, Seroquel contained no "WARNING" of diabetes and hyperglycemia. The only mention of diabetes and hyperglycemia was buried under a section entitled "ADVERSE REACTIONS: Other Adverse Events Observed During the Premarketing Evaluation of Seroquel":[95]

> **Metabolic and Nutritional System:** ***Frequent*****:** peripheral edema; ***Infrequent*****:** weight loss; alkaline phosphatase increased, hyperlidemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare*****:** glycosuria, gout, hand edema, hypokalemia, water intoxication.
>
> **Endocrine System:** ***Infrequent*****:** hypothyroidism, diabetes mellitus; ***Rare*****:** hyperthyroidism.

(Exhibit 35 at 3431.)[96]

---

[95] The label at this time contained study results as to weight gain in the Adverse Reactions section as well, and indicated that that weight gain was dose-dependent.

[96] While this label was in effect, as noted previously, AstraZeneca:

- knew that Seroquel suffered from an efficacy problem, especially at low doses (*see* discussion, *supra* at 12-16);
- never conducted a study that showed that Seroquel had superior efficacy over any other antipsychotic (*see* discussion, *supra* at 16);
- knew that Seroquel users would experience rapid, consistent, clinically significant, and dose-related weight gain (*see* discussion, *supra* at 16-17);
- buried the safety results of Study 15 and other Seroquel studies, while parsing out favorable data from Study 15 for a published article (*see* discussion, *supra* at 16-17);

On September 11, 2003, FDA requested a class-wide hyperglycemia and diabetes warning for SGAs. (Exhibit 36.) AstraZeneca resisted this change, in a letter dated October 15, 2003. (Exhibit 37 at 1.) AstraZeneca explained to the FDA that the previous summer it "completed a comprehensive internal analysis of existing data and concluded that the available data do not establish a causal link between diabetes and Seroquel." (*Id.*) The FDA agreed to meet with AstraZeneca via teleconference on December 5, 2003, but perhaps because AstraZeneca then had Seroquel's second indication (this one for "acute bipolar mania") pending and within days of approval by FDA, AstraZeneca apparently decided not to press the issue at that time. Thus, the class label appeared as shown below:

- commissioned Dr. Small to write a (yet unpublished) paper on Seroquel, who concluded that because Quetiapine, among other SGAs, caused the most weight gain, it may also cause the most diabetes (*see* discussion, *supra* at 18-19);
- convened a SERM meeting, before or at which the Medical Safety Director for Seroquel handwrote the note "Seroquel may cause impaired glucose regulation in some individuals" (*see* discussion, *supra* at 21-23);
- concluded, through the Safety Position Paper written by Dr. Geller, that "*there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals*" (*see* discussion, *supra* at 23);
- [redacted] (*see* discussion, *supra* at 23-24); and
- issued, at the instruction of the Japanese authority, a "Dear Doctor" letter mandating that Seroquel not be prescribed for diabetics or persons with a history of diabetes, and that regular and careful blood monitoring be performed for all Seroquel patients (*see* discussion, *supra* at 25-26).

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hypersmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. 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, epidemiological studies suggest and 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 glucose control. Patients with risk factors of diabetes mellitus (eg, 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.

(Exhibit 36.) FDA also required that AstraZeneca send a "Dear Doctor" letter apprising doctors of the revised label. AstraZeneca sent a "Dear Doctor" letter on January 30, 2004, but modified the language requested by FDA, omitting a critical safety precaution for patients taking Seroquel: that blood monitoring be performed throughout the course of Seroquel treatment. A revised letter dated April 22, 2004 was sent, by then seven months after FDA first notified AstraZeneca regarding the requested label change. (Exhibit 38.) The label information reprinted in the widely used Physicians' Desk Reference was not updated until the 2005 publication of the book was released.

On June 8, 2007, another SERM meeting was convened to discuss Seroquel's association with diabetes. Three recent studies had been completed—Study 125, 126, and

127, with Studies 126 and 127 being efficacy studies for treating relapse of bipolar disorder, and Study 125 being a study of Seroquel's effect on glucose metabolism.[97] The minutes' two pages provided, in part:

> **Confidential**
>
> **1. Glucose Dysregulation**
>
> Following a review of all clinical trial data, including studies D1447C00125 [Study 125], D1447C00126 [Study 126], and D1447C00127 [Study 127], epidemiology literature, and post-marketing data, SERM recommended adding the following to Section 4.4 Special warnings and special precautions for use:
>
> **Increases in Blood Glucose and Hyperglycemia**
>
> Increases in blood glucose and hyperglycemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see also section 4.8 Undesirable effects).
>
> * * *

(Exhibit 39.) Then, albeit in confusing and misleading fashion, AstraZeneca finally admitted that its CDS should be revised to include the following—also necessitating a label change:

> * * *
>
> SERM also recommended adding the following to Section 4.8 Undesirable Effects.
>
Frequency	System Organ Class	Event
Common (≥1% - <10 %)	**Investigations**	**Blood glucose increased to hyperglycaemic level***

> ***Footnote**
>
> Fasting blood glucose ≥126mg/dL or a non fasting blood glucose ≥200mg/dL on at least one occasion.
>
> * * *

(Exhibit 39 at 2.) The statement "[b]lood glucose increased to hyperglycemic level" actually means ***diabetes***-level, because AstraZeneca defined "hyperglycemia" in the footnote as ***diabetes-level blood glucose***—i.e., fasting blood glucose ≥126mg/dL or a non fasting blood

[97] Brecher Dep. at 1017:1-8; 1034:24-1035:24 (Ex. 11). Although purportedly efficacy studies, according to Dr. Brecher, Studies 126 and 127 showed a four to zero diabetes occurrence ratio for Seroquel versus placebo.

glucose ≥200mg/dL.[98] (*Id.*)

Within two weeks, AstraZeneca notified FDA pursuant to the CBE provisions that it would be changing Seroquel's label "due to a review of clinical trial data." (Exhibit 40 at 1.) The trial data necessitating the label change consisted of Studies 125, 126, and 127. (*Id.*) In October 2007, AstraZeneca issued the (limited) labeling change for the "Hyperglycemia and Diabetes Mellitus" warning as follows (new text in italics):

> **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hypersmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel *(see **ADVERSE REACTIONS, Hyperglycemia**)*. 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, epidemiological studies suggest and 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 glucose control. Patients with risk factors of diabetes mellitus (eg, 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.

(Exhibit 41 at 14-15; italics added). Some ***80 paragraphs*** after the above paragraph in the "Warnings" section, the following was added under the "Adverse Reactions" section:

---

[98] *See* note 28, *supra.*

Hyperglycemia
In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure adjusted rate of any increased blood glucose (≥ 126 mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6%) of patients).

* * *

(Exhibit 41 at 35.) The significance of this data, buried in the Adverse Reactions section, is that in the two long-term trials, patients who took Seroquel for an average of 213 days were ***more than twice as likely*** to suffer ***diabetes-level hyperglycemia*** as those persons who took placebo (10.7% of patients versus 4.6% of patients).

FDA was not satisfied with AstraZeneca's most recent Seroquel label change, as indicated in FDA's June 2008 correspondence to AstraZeneca. (Exhibit 42.) FDA requested that the updated label be changed to add the additional information that "[t]he mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and –0.05 mg/dl for placebo," indicating that FDA desires for AstraZeneca to reveal that there was more than a 5-fold increase in blood glucose levels between those subjects taking Seroquel and those taking placebo. (Ex. 42.) FDA also asked that AstraZeneca add the statement: "Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of Seroquel on blood glucose may be underestimated." (Ex. 42.) In its letter, FDA supported the additional statement above as follows:

> Since the 2-week long-term placebo-controlled bipolar maintenance trial studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of

Seroquel on blood glucose could be underestimated.

(Ex. 42.)

Thus, FDA wanted to provide clarity that the already negative blood glucose results stated in the new label—based on studies that effectively prescreened participants who did not tolerate Seroquel—actually may be even worse than the label reveals. AstraZeneca has not made the labeling changes that the FDA has requested as of the date of this filing.

Plaintiffs contend that an adequate warning would have consisted at least of the following information contained in the "Warnings" section of the label:

- The "weight gain" information contained in the "Adverse Reactions" section of the 1997 to Present label should be moved to the "Warnings" section and should warn of the dose-dependent relationship between higher doses of Seroquel and higher incidences of weight gain, providing study outcomes for those higher doses. Such warning should also describe health consequences for which Seroquel-induced weight gain creates an increased risk, including hyperglycemia, diabetes, related complications, increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, and others. (Wirshing Decl. ¶ 8 (Exhibit 43); Plunkett Decl. ¶ 11 (Exhibit 44).)
- The so-called "class warning" label (including the cross-reference to the hyperglycemia data added to the Adverse Reactions section in October 2007) should be abandoned for a Seroquel-specific warning that clearly and easily identifies the level and severity of the risk of increased blood sugar (hyperglycemia) and diabetes in patients taking Seroquel, along with all related complications. The warning should state same level of diabetes risk that the AstraZeneca CDS modified in July 2007 states—i.e., that the risk of Seroquel patients suffering diabetes-level blood glucose is "common." (Wirshing Decl. ¶¶ 12-13 (Ex. 43); Plunkett Decl. ¶¶ 16-17 (Ex. 44); Br. at 32-33.)
- The warning should include the statement that persons who already have high blood sugar or suffer from diabetes should not be prescribed Seroquel. (See Br. at 26-27 (Japanese "Dear Doctor" letter).) The warning should mandate blood monitoring at the commencement of and regularly during Seroquel treatment to test for blood glucose elevations.

SEROQUEL SAFETY TIMELINE

8/1997	**Arvanitas email** analyzing consistent, dose-dependent weight gain in Study 15	*at 16*
9/1997	**Seroquel is approved** to treat "manifestations of psychotic disorders"; NO WARNING for weight gain, hyperglycemia, diabetes	*at 29*
5/1999	**Dr. Joyce Small** writes that quetiapine, like olanzapine and clozapine, causes most weight gain and may cause most diabetes	*at 18*
1999	**Dr. Reinstein's "case study" and paper** claiming Seroquel users' "weight loss" and diabetes resolution	*at 19*
5/2000	**FDA investigating** possible causal connection between SGAs and diabetes	*at 21*
6/2000	**SERM:** Dr. Geller writes Seroquel "*may cause impaired glucose regulation*"; Dr. Brecher writes "*Seroquel may cause impaired glucose regulation in some individuals*"; after SERM, Dr. Geller writes Safety Position Paper stating "*reasonable evidence*" Seroquel "*can cause impaired glucose regulation*"	*at 21*
8/2000	**Response to FDA** inquiry regarding SGAs and diabetes	*at 24*
9/2000	**Safety Position Paper** sent to Dutch authorities, [redacted]	*at 24*
11/2000	**Dr. Brecher's paper claiming no correlation** between higher doses of Seroquel and long-term mean weight changes	*at 25*
11/2002	**Japanese Dear Doctor** Letter; "**Objection Handler**" on diabetes: "no evidence" Seroquel causes or worsens diabetes	*at 26*
2003	**Dr. Nasrallah's paper** concluding that weight gain associated with Seroquel treatment was "neutral" over the long term and not dose-related.	*at 28*
9/2003	**"Class warning"**: FDA request for all SGAs (Qualified) first mention of hyperglycemia/diabetes in WARNING section	*at 30*
1/2004	**First Dear Doctor** letter in United States	*at 31*
4/2004	**Second Dear Doctor** letter in United States	*at 31*
2/2005	[redacted]	*n.66*
11/2006	**DDMAC letter** to AstraZeneca: "false and misleading" sales aid.	*at 28*
6/2007	**SERM** considers Seroquel CDS change—diabetes now "common" side effect; **AstraZeneca changes Seroquel label** on its own per CBE regulations WARNING cross-reference to diabetes-level hyperglycemia data in ADVERSE REACTIONS	*at 31*
6/2008	**FDA requests clearer, stronger language** regarding blood glucose study results on Seroquel label	*at 34*

II.
SUMMARY JUDGMENT STANDARD

The standard to be applied in reviewing a summary judgment motion is stated unambiguously in Rule 56(c) of the Federal Rules of Civil Procedure:

> The judgment sought should be rendered if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law.

As set forth in the Rule, summary judgment may be granted only where there is *no* genuine issue of material fact. Moreover, the moving party bears the burden of meeting this exacting standard. *Allen v. Tyson Foods, Inc.*, 121 F.3d 642, 646 (11th Cir. 1997). Once the moving party satisfies this burden, the burden shifts to the party opposing the motion to go beyond the pleadings and designate "specific facts showing that there is a genuine issue for trial." *Celotex v. Catrett*, 477 U.S. 317, 32 (1986). A factual dispute is genuine only if the evidence is such that a reasonable fact finder could return a verdict for the non-moving party. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).; *Denney v. City of Albany*, 247 F.3d 1172, 1181 (11th Cir. 2001). Thus, the court's focus in reviewing a motion for summary judgment is "whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." *Anderson*, 477 U.S. at 252.

In assessing whether the movant has met its burden, the court should view the evidence in the light most favorable to the party opposing the motion and should resolve all reasonable doubts about the facts in favor of the non-moving party. *Denney*, 247 F.3d at 1181. In determining whether to grant summary judgment, the court must remember that

"[c]redibility determinations, the weighing of the evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of the judge." *Anderson*, 477 U.S. at 255. "To the extent that evidence conflicts at summary judgment, the district court has an obligation to view all evidence and make all reasonable inferences in favor of the party opposing summary judgment." *Allen v. Bd. of Pub. Educ.*, 495 F.3d 1306, 1315 (11th Cir. 2007) (internal quotation marks and citation omitted).

III.
ARGUMENT & AUTHORITIES

A. Plaintiffs Have Adduced Sufficient Evidence of Causation.

While federal rules govern admissibility of evidence, including testimony offered by experts, those principles are "intimately intertwined" with substantive law doctrines supplied under *Erie* by the forum state. *Legg v. Chopra*, 286 F.3d 286, 291 (6th Cir. 2002). *See Daubert v. Merrell Dow Pharmaceuticals, Inc.* 43 F.3d 1311, 1320 (9th Cir.1995) ("In assessing whether the proffered expert testimony 'will assist the trier of fact' in resolving this issue, we must look to the governing substantive standard, which in this case is supplied by California tort law). This is particularly true in the area of tort analysis, given distinct state-law assessments as to the parameters of causation and the nature of proof required to satisfy its requirements. *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 761 (3rd Cir. 1994) (observing that "the substantive standard of causation can affect the standard of admissibility").

In addition to proving a product defect, a Florida product-liability plaintiff has the burden of proving proximate cause, which, as in most jurisdictions, incorporates an analysis of cause-in-fact. *See, e.g., Christopher v. Cutter Laboratories*, 53 F.3d 1184, 1191 (11th

Cir.1995). While the general test for cause-in-fact is "but for" causation, requiring a showing that "but for" the act or defect the injury would not have occurred, the focus changes to a "substantial factor" formulation when one or more causes are claimed to have "concurrently" caused an injury. The pertinent instruction to the jury provides:

> In order to be regarded as the legal cause of loss, injury or damage, negligence need not be the only cause. Negligence may be a legal cause of loss, injury, or damage even though it operates in combination with the act of another, some natural cause, or some other cause if such other cause occurs at the same time as the negligence and if the negligence *contributes substantially* to producing such loss, injury or damage.

Florida Standard Civil Jury Instruction 5.1(b) (emphasis added). *See also Hadley v. Terwilleger*, 873 So.2d 378, 380 Fla. 5th Dist. 2004). The purpose of the concurring cause instruction in a tort case is to negate the idea that a defendant is excused from the consequences of his or her fault by reason of some other cause concurring in time and contributing to the same damage. *Morton Roofing, Inc. v. Prather*, 864 So.2d 64, 68-69 (Fla. App. 5 Dist. 2003); *Hart v. Stern*, 824 So.2d 927, 930 (Fla. 5th Dist. 2002). The instruction applies specifically to toxic-exposure cases where multiple substances are alleged to have *concurrently* caused the plaintiff's injury, with the proper focus again on whether the defendant's product, along with other potential causative agents, was a "substantial factor in bringing about the injury." *Christopher*, 53 F.3d 1184 (11th Cir.(Florida.) (*citing Reaves v. Armstrong World Industries, Inc.*, 569 So.2d 1307, 1309 (Fla. Dist. Ct. App. 1990)). *Barrow v. Bristol-Myers Squibb,* 1998 WL 812318, *36 (M.D. Fla., October 29, 1998) (Fawsett, J.).

The "concurring cause" instruction is deemed equally appropriate and indeed mandated when a defendant's negligence is alleged to have acted in combination with a plaintiff's preexisting physical condition to produce an injury. *Thomason v. Gordon*, 782

So.2d 896, 898 (Fla. 5th Dist. 2001). *See Esancy v. Hodges*, 727 So. 2d 308 (Fla. 2d Dist. 1999) (requiring instruction where negligent operation of the defendant's motor vehicle combined with plaintiff's pre-existing back condition to cause her injury). The submission must be coupled with an aggravated injury instruction that permits the plaintiff to recover damages for any exacerbation of the underlying condition. *Morton Roofing, Inv. v. Prather,* 864 W.W.2d at 70. In cases in which apportionment between the defendant's act and the preexisting condition is not feasible because the injuries are "indivisible," the plaintiff is entitled to recover for the entire injury. *Gross v. Lyons*, 763 S.W.2d 276, 279-80 (Fla. 2000) ("When the tortious conduct of more than one defendant contributes to one indivisible injury, the entire amount of damage resulting from all contributing causes is the total amount of damages recoverable by the plaintiff.") The purpose of that rule is to prevent a subsequent wrongdoer from escaping responsibility "where his conduct contributed to the creation of the situation in which the problems of apportionment arose." *Hart v. Stern*, 824 So.2d 927, 932 (Fla. 5th Cir. 2002).

1. Plaintiffs Have Satisfied Their General Causation Burden Under Florida Law.

Plaintiffs' Response in Opposition to AstraZeneca's Motion to Exclude the General Causation Testimony of Plaintiffs' Generic and Case-Specific Witnesses and Supporting Memorandum of Law ("Plaintiffs' General Causation Response"), which is filed concurrently with this brief and incorporated herein by reference as if repeated in full, shows, among other things, that Seroquel causes or contributes to serious diseases, most significantly hyperglycemia and diabetes. Plaintiffs' general causation showing is supported by the universe of available scientific evidence, including data from AstraZeneca clinical trials, peer

reviewed literature and standard academic texts. In rendering opinions, Plaintiffs' general causation experts employed traditional, generally accepted methodologies to assess the relationship of Seroquel treatment with diabetes. Plaintiffs' experts faithfully applied those methodologies in arriving at their conclusions, as set forth in their Declarations, Reports and Depositions.

2. *Plaintiffs Have Satisfied Their Case-Specific Causation Burden Under Florida Law.*

Plaintiffs' Response in Opposition to AstraZeneca's Motion to Exclude the Specific-Causation Testimony of Plaintiffs' Case-Specific Causation Witnesses and Supporting Memorandum of Law ("Plaintiffs' Specific-Causation Response"), which is filed concurrently with this brief and is incorporated herein by reference as if repeated in full, shows that Seroquel caused or contributed to Plaintiffs' contraction of hyperglycemia and diabetes. In other words, Plaintiffs are part of the "collateral damage" of AstraZeneca's wrongful conduct.

The specific causation question is one of medical diagnosis, which falls squarely within the scope of clinical knowledge, training, and experience. It is appropriate, then, that the experts called upon to assess the specific causation question here are medical doctors who routinely treat populations that include persons like the Plaintiffs. Each claimant's case has been evaluated by an endocrinologist (Dr. Marks or Dr. Tulloch) who by training and experience has advanced knowledge about the cause and treatment of metabolic disorders, including hyperglycemia and diabetes. Also testifying in each case is a psychiatrist (Dr. Young, Dr. Abramson, or Dr. Perry) who, as a prescriber of drugs like Seroquel, is a first-line observer of the effects such medications have on subject patients.

These doctors pursued traditional methodologies to arrive at a diagnosis with regard to each Plaintiff: they reviewed medical histories and notes of physical examinations performed by other physicians; they gathered and scrutinized clinical data, including weight recordings and glucose measurements; they reviewed and analyzed existing peer-reviewed medical literature and AstraZeneca's own clinical trials, all pointing to the fact that Seroquel generally causes diabetes; and they considered what role other risk factors might have played in the development of disease in the particular cases. The analytic result in each instance is a reliable conclusion that the Plaintiff's ingestion of Seroquel, known generally to contribute to the development of diabetes, was in fact a causative agent here.

B. AstraZeneca Fails to Show That Implied Conflict Preemption Bars Plaintiffs' Claims.

For 100 years or more, persons injured by a drug manufacturer's unsafe product have successfully brought failure-to-warn lawsuits under state law. The civil justice system's chief purpose—to compensate people who are injured—has never been a role assumed by FDA. Cognizant of the important, complementary functions served by FDA regulations and state-law remedies, Congress has never included an express preemption provision in the Federal Food, Drug, and Cosmetic Act ("FDCA") or any amendment thereto, even as it enacted an express preemption provision for medical devices. *See* 21 U.S.C. § 301 *et seq.* (FDCA); *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1009 (2008) (recognizing congressional adoption of express preemption provision in the Medical Device Amendments of 1976). Nevertheless, AstraZeneca broadly asserts that FDA's regulation of prescription drugs preempts Plaintiffs' state law claims.

AstraZeneca's baseline argument is that "implied conflict preemption" bars Plaintiffs'

state law claims. AstraZeneca may prevail on its preemption argument only by demonstrating that Florida law "actually conflicts" with federal law. *English v. General Elec. Co.*, 496 U.S. 72, 79 (1990). It cannot make that showing, however, because state law tort claims *complement* applicable FDA regulations, but do *not conflict* with them. Furthermore, AstraZeneca fails to overcome the presumption against preemption by showing any intent by Congress or any authority Congress delegated to FDA to preempt state law failure-to-warn remedies. Finally, AstraZeneca's contention that Plaintiffs' Florida law claims "stand as an obstacle" to FDA's mission is unavailing. Not only does that argument ignore the complementary federal and state public safety roles, but among other infirmities, it grossly overstates the degree and effectiveness of FDA's direct evaluation and study of the safety of prescription drugs. Federal law does not, therefore, preempt Plaintiffs' state law tort remedies.

1. The Backdrop of FDA Regulation, Which Complements State Court Remedies, Presumes No Conflict Preemption With State Law.

Congress enacted the FDCA in 1938 "for the purpose of safeguarding the public health [and] preventing deceit upon the purchasing public." H.R. Rep. No. 75-2139, at 3 (1938); *see Kordel v. United States*, 335 U.S. 345, 349 (1948) ("[the FDCA's] high purpose [was] to protect consumers"); *United States v. Dotterweich*, 320 U.S. 277, 280, 282 (1943) (recognizing the FDCA protects the health and safety of consumers, which, "in the circumstances of modern industrialism, are largely beyond self-protection").[99] Since that time, the FDCA has prohibited selling misbranded or adulterated products in interstate

[99] *See also* Resp't' Br. in *Wyeth v. Levine* (hereinafter, "Resp't Br."), 2008 WL 3285388, at *7 (filed Aug. 7, 2008).

commerce. *See* FDCA §§ 301(a)-(c), 501-502, 52 Stat. 1042, 1049-51 (codified as amended at 21 U.S.C. §§ 331(a)-(c), 351-352). A predecessor of the bill that became the FDCA included a private right of action for injured consumers. *See* H.R. 6110, 73d Cong. § 25 (1933). Congress omitted that provision from the enacted version, however, following witness testimony questioning its necessity[100] in light of long-standing state-law consumer protection remedies.[101]

To further ensure public safety and the FDCA's purpose of requiring accurate labeling bearing adequate warnings, *see* 21 U.S.C. §§ 331(a)-(c), 352(a), (f), long-standing FDA regulations have not only permitted, but required, drug manufacturers to update their labels to provide physicians with the most current information about serious hazards associated with their products, *see, e.g.*, 21 C.F.R. § 1.110(d) (1955) (authorizing "supplemental application proposing changes in "labeling"), *cited in* Resp't Br., 2008 WL 3285388, at *7. In 1965, FDA required that certain safety-based labeling changes should be

---

[100] *See, e.g., Food, Drugs, and Cosmetics: Hearings on S. 1944 Before a Subcomm. of the S. Comm. on Commerce*, 73d Cong. 400 (1933) (statement of W.A. Hines) (recommending federal right of action "be stricken from the bill on the ground that it is unnecessary" because "common-law right of action exists"), *quoted in* Resp't Br., 2008 WL 3285388, at *4.

[101] As discussed further *infra* at 46-57, the FDA too has historically viewed state tort remedies as complementary to the agency's regulation of drug manufacturers. The agency's longstanding position was that civil damages cases helped to uncover risks that were unknown to the agency at the time of approval; they also provide an important additional layer of consumer protection against unsafe products. In 1997, former FDA Chief Counsel Margaret Jane Porter stated:

> FDA's view is that FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection. FDA regulation of a device cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product such as a critical medical device may fail to identify potential problems presented by the product. Regulation cannot protect against all possible injuries that might result over time. Preemption of all such claims would result in the loss of a significant layer of consumer protection.

H. Comm. on Oversight & Gov't Reform, *Hearing on Should FDA Regulation Bar State Lawsuits?*, 110th Cong. (May 14, 2008); *see also* David A. Kessler & David C. Vladek, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 463 (Jan. 2008); Margaret Jane Porter, *The Lohr Decision: FDA Perspective & Position*, 52 Food & Drug L.J. 7, 11 (Jan. 1997).

implemented "at the earliest possible time," permitting a manufacturer to augment labeling with an "additional warning, contraindication, side-effect, and precaution information" when it submitted a supplemental application covering the change, without waiting for FDA approval. 30 Fed. Reg. 993, 993-94 (1965) (promulgating 21 C.F.R. § 130.9(d)(1), (e) (1965)), *cited in* Resp't Br., 2008 WL 3285388, at *7.

Thus, consistent with congressional intent to protect consumers and public health by prohibiting false and misleading labels under the FDCA, that regulation today provides that a drug manufacture can make "[c]hanges [in] labeling"—*without FDA approval*—"[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "[t]o add or strengthen and instruction about dosage and administration that is intended to increase the safe use of the product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); Resp't Br., 2008 WL 3285388, at *7. Known as the "changes being effected" or "CBE" regulation, such labeling change can be implemented when FDA receives the supplemental application reflecting the change and before FDA acts on that application. 21 C.F.R. § 314.70(c)(6). Importantly, FDA has also long mandated that drug makers revise labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e).[102] As FDA explained when promulgating that regulation, "it is *essential* to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it"; "the act requires labeling to include warnings about both *potential* and verified hazards"; and the agency "believes that practicing physicians will welcome such information so that they can make their best

[102] *See* notes 57-65, *supra*.

informed medical judgments in the care of their patients." 44 Fed. Reg. 37,434, 37,433, 37,447 (1979) (emphases added), *quoted in* Resp't Br., 2008 WL 3285388, at *8.

Therefore, as discussed in greater detail below, the consumer safety-oriented purpose of the FDCA and FDA regulations—which are devoid of any remedy when a manufacturer's noncompliance causes injury—are enhanced, but not conflicted, by state tort lawsuits that supply a cognizable state-law remedy to redress such injury. Additionally, AstraZeneca has not shown, and cannot show, that Congress intended to preempt state-law warnings lawsuits and, therefore, has not overcome the well-settled presumption against preemption.

(a) If There Is No Conflict, There Is No Conflict Preemption.

AstraZeneca's fundamental premise allegedly supporting conflict preemption here is wrong. AstraZeneca argues, without citation to authority, that "[c]onflict preemption *clearly applies* where—as here—a federal agency has specifically examined an issue and determined how best to balance competing objectives." (Mem. at 26; emphasis added.) But that is not the test. Only if AstraZeneca shows that Florida law "actually conflicts" with federal law may AstraZeneca prevail on its preemption defense. *English*, 496 U.S. at 79.

No real conflict exists here, though. An "actual conflict" exists when "it is impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002). Conflict preemption analysis is not, therefore, a "'freewheeling judicial inquiry into whether a state statute is in tension with federal objectives,' but an inquiry into whether the ordinary meanings of state and federal law conflict." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431,

459 (2005) (Thomas, J., concurring in the judgment in part and dissenting in part) (quoting *Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part and concurring in the judgment)) (citation omitted), *quoted in* Resp't Br., 2008 WL 3285388, at *8.

The FDCA and applicable federal regulations emphasize safety as a paramount goal, establishing that:

- Introduction of any "misbranded" drug would be "prohibited," 21 U.S.C. § 331(a);
- A drug label would be "misbranded" if "false or misleading in any particular," *id.* § 352(a);
- Such labeling would be misbranded if it lacked "adequate warnings against use . . . [that] may be dangerous to health . . . as are necessary for the protection of users . . . ," *id.* at 352(f);
- A drug manufacturer can make "[c]hanges [in] labeling"—without FDA prior approval—"[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product," 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); and
- A drug manufacturer is required "to include a warning as soon as there is a reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved," *id.* § 201.57(e).

See Resp't Br., 2008 WL 3285388, at *26.

Under Florida law, as in states generally, "a manufacturer of prescription drugs or products discharges its duty to warn by providing the physician with information about risks associated with those products." *Christopher v. Cutter Labs.*, 53 F.3d 1184, 1192 (11th Cir. 1995).[103] State law claims that the manufacturer failed to discharge its duty to warn parallel federal misbranding requirements and regulations mandating a warning change as soon as

[103] An indispensible "corollary" to that duty is that the warning given must be "adequate"—i.e., accurate, clear, and unambiguous, as discussed *infra* at 59-68. *See id.* (citing *Felix v. Hoffmann-LaRoche, Inc.*, 540 So.2d 102, 104 (Fla. 1989)).

there is reasonable evidence of an association of a serious hazard with a drug. *Cf.* 21 U.S.C. § 352(f); 21 C.F.R. § 201.57(e); *see* Resp't Br., 2008 WL 3285388, at *26-27.

Moreover, as Judge Weinstein recognized in the parallel *Zyprexa* MDL, "FDA labeling regulations and state law adequacy of warning claims have existed harmoniously from the time the FDCA was first enacted." *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 275 (E.D.N.Y. 2007). It is clear that a state may not, by positive statutory enactment, require a "drug manufacturer to include a warning with the labeling for its product that the FDA previously rejected as scientifically unsubstantiated." *Id.* Such a requirement could, indeed, expose a manufacturer to misbranding liability under 21 U.S.C. § 352. However, jury verdicts do not impose mandatory labeling requirements on drug manufacturers. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495-97 (1996). Jury verdicts simply impose civil judgment. *In re Zyprexa*, 489 F. Supp. 2d at 277. In response to a jury verdict, a manufacturer can either seek to change its labeling through the above-cited federal provisions facilitating such change, or it can leave its label as is despite the verdict. *Id.*

Judge Weinstein's reasoning comports with what the Supreme Court has said on many occasions—i.e., that federal law preempts state law when "compliance with both federal and state regulations is a physical impossibility." *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963). That rarely met test, however, does not require preemption so long as compliance with federal and state law is "theoretically possible." *California Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 291 (1987) (internal quotation marks omitted). Here, AstraZeneca can comply with both a damages judgment in a failure-to-warn case and the FDCA and FDA regulations. Florida law duties are consistent with

federal law, because nothing in the FDCA or FDA regulations prohibits manufacturers from proposing stronger warnings or later strengthening them to promote the drug's safe use. Alternatively, AstraZeneca could comply with a Florida judgment without changing its label.

Further, as noted, jury verdicts and adequacy of warning claims serve an important safety function parallel to FDA regulation. *Id.* "State law adequacy of warning claims may alert the FDA to potential inadequacies in product labeling." *In re Zyprexa*, 489 F. Supp. 2d at 277. As the Supreme Court has noted, "labels will evolve over time, as manufacturers gain more information about their products' performance in diverse settings. [T]ort suits can serve as a catalyst in this process . . . ." *Bates*, 544 U.S. at 451 (rejecting preemption challenge to state-law claims that herbicide labeling warnings were inadequate, notwithstanding express preemption provision).

Thus, as demonstrated above, the complementary rather than conflicting roles of FDA and state warnings law is firmly supported by FDA regulations. AstraZeneca complains that the potential civil jury finding that a warning is inadequate infringes on FDA authority. (Mem. at 25-31.) But, as previously shown, it does not. Indeed, the CBE provisions discussed above contemplate that an approved warning may, at any point in the post-approval period, be inadequate. *Cf.* 21 U.S.C. § 352(f); 21 C.F.R. § 201.57(e). Those provisions are testament to even FDA's understanding that its approved labeling may not convey all available, legitimate safety information. Because this is the crux of all state-law warnings claims in general, and Plaintiffs' claims specifically, FDA regulation and the claims at issue do not conflict.

Lastly, AstraZeneca's argument that Plaintiffs' claims must be dismissed because

FDA has considered and rejected proposed strengthened warnings has no basis in fact. AstraZeneca did not propose inclusion of warnings related to increased risks of hyperglycemia and diabetes in Seroquel's labeling. Rather, FDA requested that AstraZeneca include a hyperglycemia and diabetes warning in late 2003. (Ex. 36.) FDA has never considered and rejected a stronger warning than that mandated in 2003—on the other hand, AstraZeneca did propose weaker language with which FDA disagreed. (Ex. 37; *see also* Wirshing Decl. ¶ 16 (Ex. 43).) Therefore, as the district court in *Perry v. Novartis Pharmaceutical Corporation* recognized, "it is more in keeping with the narrow scope of preemption to allow state law to require the addition of warnings so long as there has been no specific FDA determination" regarding a particular warning. 456 F. Supp. 2d 678, 685 (E.D. Pa. 2005).

(b) AstraZeneca Has Not Overcome The Legal Presumption Against Implied Conflict Preemption.

AstraZeneca also sidesteps recognition that preemption is "fundamentally a question of congressional intent." *English*, 496 U.S. at 78-79; *see Puerto Rico Dep't of Consumer Affairs v. Isla Petroleum Corp.*, 485 U.S. 495, 503 (1988) ("There is no federal pre-emption *in vacuo*, without a constitutional text or a federal statute to assert it."). Accordingly, the "purpose of Congress is the ultimate touchstone of pre-emption analysis." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted); *see* Resp't Br., 2008 WL 3285388, at *25. Congress does not "cavalierly pre-empt state-law causes of action." *Medtronic*, 518 U.S. at 485. In fields traditionally occupied by the states, such as health and safety regulation, there is a strong presumption against federal preemption. *Id.*; *New York State Conference of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.*, 514

U.S. 645, 654-55 (1995); *Hillsborough County v. Automated Med. Labs. Inc.*, 471 U.S. 707, 715 (1985).

Congress has never enacted a prescription-drug preemption provision, despite numerous opportunities to do so. Its enactment of a preemption provision for medical devices, but not drugs, strongly signals its intent to preserve state-law remedies against pharmaceutical manufacturers. *See Riegel*, 128 S. Ct. at 1009 ("Congress could have applied the preemption clause" in the Medical Device Amendments of 1976 "to the entire FDCA," but it "instead wrote a pre-emption clause" that applies only to medical devices"); *see also id.* at 1017 (Ginsburg, J., dissenting) ("Nothing in the FDCA's text or legislative history suggested that FDA preclearance would immunize drug manufacturers from common-law tort suits."); Resp't Br., 2008 WL 3285388, at *27. The Supreme Court has "never assumed lightly that Congress has derogated state regulation, but instead ha[s] addressed claims of pre-emption with the starting presumption that Congress does not intend to supplant state law." *New York State Conference*, 514 U.S. at 654-55. That presumption against preemption "provides assurance that the federal-state balance will not be disturbed unintentionally by Congress or unnecessarily by the courts." *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (citation and internal quotation marks omitted); *see also Medtronic*, 518 U.S. at 485.

Notwithstanding AstraZeneca's contention that FDA's position on preemption should control, "an agency cannot supply, on Congress's behalf, the clear legislative statement of intent required to overcome the presumption against preemption." *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 97 n.9 (2d Cir. 2006); *see Bates*, 544 U.S. at 449 ("The long history of tort litigation against manufacturers of poisonous substances adds force to the

basic presumption against preemption. If Congress had not intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."); *Medtronic*, 518 U.S. at 487 ("It is, to say the least, difficult to believe that Congress would, without comment, remove all means of judicial resources for those injured by illegal conduct.").

AstraZeneca's contrary argument, primarily based on *Geier v. American Honda Motor Company*, is unavailing because that case is distinguishable in several important respects. *See* 529 U.S. 861 (2000). First, *Geier* is not a drug case, nor does it purport to decide the presumptive scope and force of the FDCA and FDA regulations. Instead, *Geier* decided whether state law superseded federal passive restraint regulations for automobiles issued by the federal Department of Transportation ("DOT"). *Id.* at 865-66. Second, *Geier* was a *design defect* case with no "failure-to-warn" claims at issue. *Id.* at 864. Third, the preemptive force of DOT regulations at issue in *Geier* was buttressed by nearly 30 years of DOT's consistent research and efforts to employ passive restraints and airbags on automobiles, as opposed to FDA's nascent, and conflicting, regulations and opinion, discussed *infra*.

Thus, it has long been presumed that state laws—particularly those such as the provision of tort remedies to compensate for personal injuries—are not to be preempted by a federal statute unless it is the clear and manifest purpose of Congress to do so. *See Medtronic*, 518 U.S. at 480, *Geier*, 529 U.S. at 894 (Souter, J., dissenting). Evidence of the legislative intent must be derived from the text of an act of Congress. *See Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999). An executive agency's creation of its own

authority to preempt state law would amount to usurpation of Congress's constitution-based ability to delegate such authority, or to withhold it. In the words of Justice Scalia, "[a]gencies may play the sorcerer's apprentice but not the sorcerer himself." *Alexander v. Sandoval*, 532 U.S. 275, 291 (2001). Therefore, as further discussed below, FDA's recent, conflicting position changes regarding preemption are an inadequate substitute for congressional intent.[104]

2. *AstraZeneca's Obstacle-Preemption Arguments Are Unavailing.*

AstraZeneca makes no showing of clear and manifest congressional intent to preempt state law claims such as those Plaintiffs bring, as shown above. Instead, it argues in sweeping fashion that "a lay jury *second guess*[ing] the FDA's expert judgments and strik[ing] a *different balance* conflicts with FDA's authoritative federal determinations." (Mem. at 28; emphasis original.) Therefore, AstraZeneca contends, "any jury's imposition of state-law based on AstraZeneca's use of the FDA-approved labeling for Seroquel would necessarily *stand as an obstacle* to FDA's expert determinations that its federally mandated labeling strikes the appropriate balance." (Mem. at 28; emphasis original.)

Ignoring the parallel objectives of federal and state law and the long history of litigation against drug manufactures, AstraZeneca claims that FDA comprehensively regulates the content of a drug's labeling and carefully "balances" the risks and benefits in

---

[104] AstraZeneca argues in a footnote (Mem. at 25 n.22) that the presumption against preemption should not apply here because federal statutes have regulated the drug industry for a number of years. But, in *Bates* and *Lohr*, federal regulation had existed since 1910 and 1938, respectively, *see Bates*, 544 U.S. at 437; *Lohr*, 518 U.S. at 475, and the Supreme Court nonetheless applied its presumption against preemption. AstraZeneca also argues that plaintiffs' presumption against preemption argument won only a single dissenting vote in the Supreme Court's most recent examination of preemption in the FDCA context. (Mem. at 25 n.22 (citing Justice Ginsberg's dissent from *Riegel*). Of course, as this Court and AstraZeneca are aware, *Riegel* involved an express preemption provision in the Medical Device Amendments of 1976, so the presumption against preemption (which applies to implied conflict preemption, as here) could not have applied because Congress's intent was manifested by the enacted amendments themselves.

determining what information should appear on that labeling and how the information should be expressed. (Mem. at 25-31.) More specifically, AstraZeneca claims that FDA performed careful and complete balancing of the risks at issue in this litigation—weight gain, hyperglycemia, and diabetes. (Mem. 27-31 & n.24.) Such contentions overstate FDA's oversight and direct analysis of drug safety, while overlooking the complementary role that state tort law has long played in that regime. AstraZeneca's arguments also wrongly infer that FDA labeling is "set in stone" after a drug's initial approval. Finally, they ignore the factual record and documentary evidence establishing that FDA never considered and rejected a stronger warning than what AstraZeneca proposed for Seroquel.

First, the assertion that FDA "balances" what warnings should appear in a drug's labeling is incorrect. Like Florida law, federal law requires manufacturers to warn of *all* known risks of a drug. *See* 21 U.S.C. § 352(f); 21 C.F.R. § 201.57(e); *see also* Resp't Br., 2008 WL 3285388, at *51. According to FDA, "it is essential to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it," and "the act requires labeling to include warnings about both potential and verified hazards." 44 Fed. Reg. at 37,443, 37,447 (emphasis added), *quoted in* Resp't Br., 2008 WL 3285388, at *51. Thus, nothing in the statute or regulations empowers FDA to permit a manufacturer to withhold information about a substantiated risk (such as the greatly increased risk of weight gain, hyperglycemia, and diabetes for Seroquel users) on the ground that providing such information might deter beneficial uses of the drug or "overwarn" about a drug's potential risks. (Mem. at 28.) *See* Resp't Br., 2008 WL 3285388, at *50.

Moreover, FDA does not test drugs. Inst. of Med. of the Nat'l Academies, *The*

Future of Drug Safety: Promoting and Protecting the Health of the Public 34-38, 152 (2007) (hereinafter, "Inst. of Med. Rpt."); *see also* Kessler & Vladek, *supra* note 101, at 469-71. Manufacturers conduct relatively limited clinical trials to support FDA new drug applications. *Id.*; Kessler & Vladek, *supra* note 101, at 470 ("[p]remarket human trials generally involve only a few thousand subjects, and study design necessitates a careful control of the conditions of the stud[ies]," which are "supervis[ed] and controll[ed]" by "[d]rug companies"; "[t]hese conditions are a far cry from those that face a drug once it is approved and widely prescribed by thousands of doctors"). Because study participants are healthy adults, the trials do not reveal adverse reactions affecting, for example, pregnant, elderly, or sick patients, and because of the studies' relatively brief durations, they do not uncover side effects with long latency periods. *See* Inst. of Med. Rept. at 37-38, *cited in* Resp't Br., 2008 WL 3285388, at *48. Thus, it is unsurprising that a 1990 Government Accounting Office report found that more than half of the drugs FDA approved between 1976 and 1985 had serious post-approval risks surface. U.S. Gen. Acct. Off., Rpt. to the Chairman, Subcomm. on Human Resources and Intergovernmental Relations, Comm. on Gov't Operations, House of Representatives, *FDA Drug Review: Post Approval Risks 1976-85*, at 3 (Apr. 1990), *cited in* Resp't Br., 2008 WL 3285388, at *48; *see* Kessler & Vladek, *supra note* 101, at 472 ("The FDA does have a program in place for post-market surveillance of approved drugs, but that program has been chronically under-funded by Congress, and according to recent studies by the Institute of Medicine and the Government Accountability Office, has not performed well.")

Additionally, the manufacturer proposes the language for the drug's labeling, which

FDA reviews and approves. 21 U.S.C. § 355(d) (2005); 21 C.F.R. §§ 201.56, 201.57, 201.80 (2006). After FDA has approved a drug with manufacturer-proposed labeling, the manufacturer bears primary responsibility for analyzing safety information and evaluating needed labeling modifications in response to that information. *See* 21 C.F.R. §§ 201.57(e), 314.80(b); *see also* Resp't Br., 2008 WL 3285388, at *48. FDA's post-approval authority is limited because FDA could not force a manufacturer to make a labeling change.[105] Although most risks will become known after FDA approval, FDA's regulatory powers are most limited during a drug's post-approval lifespan. *See* Kessler & Vladek, *supra* note 101, at 471-73.

Second, AstraZeneca's position is premised on the flawed inference that FDA-approved labeling is immutable. But, as amply shown above, federal law did not compel the particular warning AstraZeneca used for Seroquel. Either in the initial proposed labeling for Seroquel before FDA approved the drug or after approval, AstraZeneca could have adequately warned of increased risks of weight gain, hyperglycemia, and diabetes consistent with the FDCA. Indeed FDA has long make clear that labeling rules present no obstacle to manufacturers' providing warnings to doctors and patients through labeling, advertising, or "Dear Doctor" letters as soon as the manufacturer discovers risks that are not clearly stated on the label. *See, e.g.*, 21 C.F.R. §§ 201.57(e), 314.80(b); *see also* Kessler & Vladek, *supra* note 101, at 473.[106] To the extent that AstraZeneca contends that once FDA approved Seroquel's labeling the Company was powerless to change it, that bold assertion finds no support in the FDCA, and cannot be reconciled with FDA's regulatory scheme requiring such

---

105 *See* discussion, *supra* at 9-10.

106 *See* note 51 and accompanying discussion, *supra*.

changes to strengthen inadequate warnings.

Third, FDA never considered and rejected a stronger warning regarding Seroquel's association with weight gain, hyperglycemia, and diabetes. The opposite is true. FDA considered and requested a stronger warning in 2003, and considered and accepted a stronger warning in 2007.

3. Recent CBE Amendments Do Not Preempt Plaintiffs' Claims.

Finally, AstraZeneca argues that the CBE provisions only apply to "newly discovered risks" and that such provisions may only be used when the information motivating the label change is "new" or was not previously available to the agency. (Mem. at 32.) AstraZeneca also assumes—incorrectly and without support—that FDA's recent rule changes regarding when a drug company may add or strengthen a warning apply to Plaintiffs' claims.

AstraZeneca's position that a CBE supplement must be based on information about a "newly discovered risk"—as opposed to a manufacturer's reevaluation or analysis of existing risk information—conflicts with FDA's own proposal to codify its "new information" on the CBE regulation. The proposed rule defines "newly acquired information" to include "new analyses of *previously submitted* data." 73 Fed. Reg. 2853 (2008) (emphasis added), *quoted in* Resp't Br., 2008 WL 3285388, at *40. Thus, even under FDA's proposed rule, AstraZeneca could have re-analyzed data on safety of Seroquel and implemented a stronger warning via the CBE regulation in response to any of its internal analyses discussed herein.

Congress's recent FDCA amendments align with that understanding of what information can be considered "new" in the labeling change context. The 2007 FDCA amendments provide FDA with limited authority to order labeling changes based on "new

safety information," § 901(a), 1212 Stat. 924 (codified at 21 U.S.C. § 355(o)(4)(A)), which is defined to include "scientific data" about "a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (*that may be based on a new analysis of existing information*) since the drug was approved," § 901(b), 121 Stat. 927-28 (emphasis added) (codified at 21 U.S.C. § 355-1(b)(3)(A)). *See* Resp't Br., 2008 WL 3285388, at *41. Thus, Congress too has recognized that because risk information about a drug evolves over time, it makes no sense to limit labeling changes to those based wholly on information not available when FDA last considered the labeling. *See* Karen E. Lasser *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J.A.M.A. 2215, 2218-19 (May 1, 2002) (providing examples of drugs that were withdrawn from the market based on adverse effects that had appeared in pre-market trials).

AstraZeneca's argument regarding "new" risks and information also runs counter to its own conduct under the CBE provisions. As noted above (Br. at 31-35), in the summer 2007, AstraZeneca took it upon itself to review recent study results in SERM, then immediately propose to FDA and effectuate *on its own, without waiting for FDA approval* the current Seroquel label. (*Id.*) Pursuant to AstraZeneca's own language informing the FDA of the CBE label amendment, the "labeling is being updated due to a review of clinical trial data." (Ex. 40.) Moreover, the trial data to which AstraZeneca referred in its letter did not constitute "newly discovered risks" (Mem. at 32), but simply provided "new information on SEROQUEL and hyperglycemia." (Ex. 40.) Importantly, AstraZeneca's unilateral actions in summer 2007 to change Seroquel's labeling belie its litigation-inspired position that it is powerless to do so. Thus, whatever the merits of AstraZeneca's argument, and they

are scant, it is betrayed by facts.

In sum, AstraZeneca has not established that Plaintiffs' claims are preempted as a matter of law. The Court should deny summary judgment on that basis.[107]

C. Plaintiffs' Claims Are Not Barred By Florida's Learned Intermediary Doctrine.

Next, AstraZeneca argues that all Plaintiffs' claims fail under Florida's "learned intermediary doctrine." Contrary to AstraZeneca's characterization of the applicable test under the doctrine, however, to defeat summary judgment Plaintiffs need only (1) raise a fact issue relative to whether Seroquel's warning was "accurate, clear, and unambiguous" in order to send that question to the jury, *Felix v. Hoffmann-LaRoche, Inc.*, 540 So.2d 102, 105 (Fla. 1989); and (2) show that, notwithstanding the inadequacy of the warning, the prescribers' independent knowledge of the information that would have been contained in an *adequate warning* did not break the causal chain, *Christopher*, 53 F.3d at 1192; *Tatum v. Schering Corp.*, 795 F.2d 925, 927 (11th Cir. 1986), *cited with approval in Christopher*, 53 F.3d at 1192.

Florida has recognized the learned intermediary doctrine since 1989. The Florida Supreme Court adopted the rule in *Felix v. Hoffmann-LaRoche, Inc.*, 540 So.2d 102, 104 (Fla. 1989). *Felix* involved the plaintiff mother's claim that the acne medicine Accutane, which she was prescribed and consumed while pregnant, caused her child to be born with severe birth defects that led to the infant's death. *Id.* at 103. The "critical issue in the case was whether the manufacturer of the drug furnished adequate warnings of the dangers of using the drug during pregnancy." *Id.* Approving the learned intermediary doctrine under

---

[107] Plaintiffs' hereby incorporate by reference as if repeated in full the earlier preemption briefing filed by other plaintiffs in this MDL (Doc. 365).

Florida law, the supreme court stated that the "prescribing physician, acting as a 'learned intermediary' between the manufacturer and the consumer, weighs the potential benefits against the dangers in deciding whether to recommend the drug to meet the patient's needs." *Id.* at 104. Further, recognizing that the manufacturer's warning to physicians must be "adequate," *see Buckner v. Allergan Pharms., Inc.*, 400 So.2d 820, 822 (Fla. Ct. App. 1981), the court observed that ***"in many instances the adequacy of warnings concerning drugs is a question of fact" for a jury to determine.*** *Id.* at 105. The court explicitly held that only "where the warning is ***accurate, clear, and unambiguous***" may a warning be deemed "adequate as a matter of law." *Id.* at 104-105 (emphasis added); *Upjohn Co. v. MacMurdo*, 562 So.2d 680, 681-82 (Fla. 1990) (same).

Before undertaking its analysis of whether AstraZeneca has met its learned intermediary summary judgment burden,[108] the Court should be mindful of the following critical points of Florida learned intermediary law and their proper application to the facts of Plaintiffs' cases:

- In *Felix*, "there [was] no contention that the warning given in [the] case ***contained any misstatements***" and no adverse event reports involving the injury plaintiff (or her infant) sustained prior to plaintiff's ingestion of the drug. 540 So.2d at 104 (emphasis added). Without evidence that the warning was insufficient, it was deemed "adequate as a matter of law." *Id.* at 105.
  - ➢ Here, Plaintiffs plainly allege and the evidence shows that AstraZeneca's warning was inadequate and contained numerous misstatements, and substantial evidence further demonstrates that through purportedly reliable means (e.g., clinical trials), the Company knew of greatly increased diabetes and hyperglycemia risks that were not shared with the medical community, the FDA, or the public. Moreover, AstraZeneca actively undermined the effectiveness of any warning it gave through marketing and overpromotion of Seroquel, which a reasonable juror may conclude impacted the doctors' decision to prescribe Seroquel.

---

[108] *See* note 111, *infra.*

- Under Florida law, a prescriber's so-called "independent knowledge" of the risks at issue may break the "causal link" between the doctor's prescription of the drug and a plaintiff's injury. *Felix*, 540 So.2d at 105. However, courts applying Florida law have imposed an "increased threshold that must be met when attempting to qualify the prescribing physician as a learned intermediary after being exposed to misrepresentative product warnings." *Zanzuri v. G.D. Searle & Co.*, 748 F. Supp. 1511, 1518 (S.D. Fla. 1990); *Christopher*, 53 F.3d at 1192 (citing *Zanzuri*'s statement of the independent knowledge requirement under Florida law); *see also In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 247, 249, 257-58 (E.D.N.Y. 2006). The task of attaining "learned intermediary" status in the face of a manufacturer's misstatements about its product's safety "becomes Herculean," and if not met, summary judgment is inappropriate. *Zanzuri*, 748 F. Supp. at 1518.
  - ➢ Here, AstraZeneca has not, and cannot, meet the increased threshold for qualifying Plaintiffs' prescribers as learned intermediaries in the face of the "universe" of misinformation about Seroquel's safety promulgated for years by the Company; a doctor's "general" knowledge or experience under this standard is simply insufficient.
- In any event, the Eleventh Circuit's interpretation of the Florida learned intermediary doctrine demands that AstraZeneca show that Plaintiffs' prescribers "had independent knowledge of the risk that the adequate warning [as alleged by Plaintiffs] should have communicated." *Christopher*, 53 F.3d at 1192 (citing *Felix*, 540 So.2d at 105; *Zanzuri*, 748 F. Supp. at 1517) (emphasis added).
  - ➢ Here, Plaintiffs have identified, at least in part, what an adequate Seroquel warning should have stated. (Br. at 35.) AstraZeneca has not shown that Plaintiffs' prescribers had independent knowledge of that adequate warning. Again, a physician's general knowledge or experience is insufficient unless the physician has substantially the same knowledge as the adequate warning should have conveyed.
- Florida learned intermediary law, as interpreted by Eleventh Circuit courts, requires that in order for a physician to be ascribed learned intermediary status, s/he must testify "without contradiction" that s/he was aware of "all the risks associated with the" drug. *Beale*, 492 F. Supp.2d at 1371.
  - ➢ Plaintiffs' prescribers' testimony is at best conflicting on this issue, rendering summary judgment inappropriate.

Further, AstraZeneca's attempt to break the causal link between an inadequate warning and Plaintiffs' injuries is unsupported by Florida law and runs counter to Eleventh Circuit and other precedent instructing that reasonable jurors may reach competing

conclusions based upon inferences drawn from the record.[109]

As shown below and in their Responses, Plaintiffs have each met his/her learned intermediary summary judgment burden. AstraZeneca is not entitled to summary judgment on learned intermediary grounds.

1. Seroquel's Warning Is Not Adequate As A Matter Of Law Because Plaintiffs Have Raised A Genuine Issue Of Material Fact Regarding the Warning's Accuracy, Clarity, and Unambiguousness.

Genuine issues of material fact preclude the Court's finding that the warnings given by AstraZeneca to physicians about Seroquel's risks were adequate as a matter of law. As noted above, in order for the Court to make such a finding, it must determine that the warning given was "accurate, clear, and unambiguous." *Felix*, 540 So. 2d at 105. Otherwise, as here, the question of warning adequacy must go to the jury. *Id.*

(a) The Jury Must Decide The Adequacy Of Unclear, Inaccurate, or Ambiguous Warnings.

Courts interpreting the Florida learned intermediary doctrine have helped define the outer boundaries of the rule. Premised on *Felix*, the United States District Court for the Southern District of Florida in *Zanzuri v. G.D. Searle & Co.* determined that a "qualified" or otherwise unclear or ambiguous warning could not be considered "adequate as a matter of [Florida] law." 748 F. Supp. at 1516. The *Zanzuri* court recognized that *Felix* deemed the warning concerning acne medication adequate as a matter of law where it warned physicians that the product should *not* be prescribed to "patients who are pregnant or intend to become pregnant while undergoing treatment." *Id.* (quoting *Felix*, 540 So.2d at 103) (internal quotation marks omitted). The *Zanzuri* court then compared the warning accompanying the

---

[109] *See* discussion, *infra* at _.

intrauterine contraceptive device ("Cu-7") at issue in that case:

> Unlike the categorical negative—"should not be prescribed"—present in the *Felix* warning, the warning accompanying the Cu-7 merely warns . . . that ***"[a]n increased risk of pelvic infection associated with the use of IUDs has been reported".*** The warning continues that "[w]hile unconfirmed, this risk appears to be greatest for young women who have never had a baby . . .". Far from a model of clarity, the Cu-7 warning is the very example of a qualified warning, the adequacy of which must be resolved through a highly intensive factual inquiry. *Zanzuri*, 748 F. Supp. at 1516. Thus, the court found that the Cu-7 warning *mentioned* the risks associated with the use of the Cu-7, only going so far as to state "merely that incidents of pelvic inflammatory disease (PID) have been 'reported', and that the reports of such problems are 'unconfirmed'." *Id.* at 1517.

One of plaintiff's experts testified by affidavit that defendant's warnings did not adequately convey the increased risk of PID, and that defendant tried to "minimize or negate" any warnings present in the physician package insert and patient brochure. *Id.* Such warnings "did not present data to the physician or patient upon which they could make a judgment as to the comparative risk of developing pelvic inflammatory disease while wearing an IUD, versus such risk when using other forms of contraception," the expert opined. *Id.* Thus, the court determined that plaintiff's experts raised disputed issues of material fact sufficient to defeat defendant's contention regarding the legal adequacy of the warning. *Id.*; *see also Amore v. G.D. Searle & Co.*, 748 F. Supp. 845, 851-52 (S.D. Fla. 1990) (finding, as in *Zanzuri*, that the Cu-7 warning was "[f]ar from a model of clarity" and the "very example of a qualified warning"); *Adams v. G.D. Searle & Co.*, 576 So. 2d 728, 731 (Fla. Ct. App. 1991) (adequacy of Cu-7 warning a "question of fact for the jury"); *cf. Mitchell v. VLI Corp.*, 786 F. Supp. 966, 969-970 (M.D. Fla. 1992) (denying summary judgment as to adequacy of warning in package insert of defendant's over-the-counter contraceptive sponge, a sample of which plaintiff obtained from her doctor, who testified that

it was his office procedure to inform patients that allergic reactions such as simple burning, itching, or redness had been experienced; "[w]hile it is uncontroverted that [plaintiff] suffered an allergic reaction and the inserts mention "allergic reaction," neither insert is clear or unambiguous as to what constitutes an allergic reaction [i.e.—] . . . whether the scope of an allergic reaction would encompass a chronic infection that could ultimately necessitate a hysterectomy . . .").

The Florida appellate court and federal district courts adjudicating the adequacy of those warnings, however, are not alone in their determination that ambiguities and unclear language in a warning, or misinformation from the manufacturer that confounds the warning, render the adequacy of such warning a jury question. Relying on *Felix*, *Zanzuri*, and *MacMurdo*, Judge Weinstein in the *Zyprexa* MDL recognized that "whether a prescription drug warning adequately informs prescribing physicians of the risks inherent in the drug is one of fact, ordinarily determined by a jury" under Florida law. *In re Zyprexa*, 489 F. Supp. 2d 230, 266 (E.D.N.Y. 2006) (citing *MacMurdo*, 562 So.2d at 683). "Where the warning is 'accurate, clear, and unambiguous,' its adequacy becomes a question of law." *In re Zyprexa*, 489 F. Supp. 2d at 266 (quoting *Felix*, 540 So.2d at 105).

Judge Weinstein found that "[d]isputed questions of fact exist concerning the issue of whether the warning provided by [defendant] to [plaintiff's] physician was adequate, ***particularly when viewed in light of the position its salespeople were taking, to convey the risks of weight gain, hyperglycemia, and diabetes.***" *In re Zyprexa*, 489 F. Supp. 2d at 279 (emphasis added). The plaintiff's prescriber had testified that he was aware of the risks and benefits of Zyprexa, and believed the benefits to outweigh the risks. *Id.* at 256-57. The

Zyprexa court then weighed the testimony of the defendant's sales representatives who called on the plaintiff's prescriber, determining that their statements to the doctor regarding Zyprexa, weight gain, diabetes, and hyperglycemia had rendered the warning ambiguous:

> Q: In the time frame 2000 to 2003 did any physician ever say to you, [y]our competition is saying Zyprexa is the worst offender for weight gain?
> A: Every day.
> Q: And how did you respond to that physician?
> A: Well, Eli Lilly, at that point they had a detail piece that showed a comparison between Risperdal, Zyprexa, Depakote, Clozaril. It just showed basically a comparison between the two of weight gain and increase in the risk of that. And that's what you showed. I just went over it. I didn't focus on it. It's a class effect and the doctors knew it was a class effect; they was just trying to pull your chain. I didn't waste my time on that to these doctors.
>
> * * *
>
> Q: What was your understanding, in the class of atypical antipsychotics, where Zyprexa ranked in terms of being an offender for weight gain?
>
> * * *
>
> A: Yes, rank it either one, two, or three. It was pretty much-you know, according to the studies of what we had, it basically caused it no more than Clorazil or any of the rest of them. It was a class effect.
>
> * * *
>
> Q: You testified a few times in your deposition that diabetes was comparable for all atypical antipsychotics?
> A: Yes.
> Q: Do you remember saying that?
> A: I sure do, yes.
>
> * * *
>
> Q: Okay. I take it that at some point in time, and we've kind of talked about this already, the issue of the association between Zyprexa and diabetes or causing diabetes came to your attention and was something that you were taught about and learned about and talked to doctors about; is that correct?
>
> * * *
>
> A: What I would say is with regard to Zyprexa, quote/unquote, causing diabetes, I don't think that I've ever seen any material that shows a direct connection between Zyprexa causing diabetes. However, as we've talked about previously, we did have a body of evidence that suggested that chronic severe mentally ill patients tend to be in a population or a subpopulation of a general population that are more prone to higher instances of hyperglycemia and diabetes.
> Q: And would that fact be one of the responses that you would talk to a doctor about if you were discussing whether there was a relationship between

diabetes and Zyprexa.

* * *

A: I think similar to what I said earlier with regard to if somebody said they had a concern about diabetes and Zyprexa, I would share with them, like I mentioned earlier, the data that we had suggested, that while it's an epidemic—while diabetes is an epidemic in the general population, it appeared that this particular subset of the population tend to be prone to increased risk of diabetes. But we never, at least the data that we had at our disposal didn't show any particular increased risk for patients on any given atypical antipsychotic.

Id. at 257-58. The ambiguities and inaccuracies conveyed to plaintiff's prescriber by the defendant's salespeople regarding Zyprexa's association with weight gain and diabetes sufficiently countered the defendant's position that plaintiff's prescriber was indisputably aware of the risk of weight gain and diabetes. *Id.* at 247. "Plaintiff[] [has] . . . sufficiently under summary judgment standards . . . demonstrated that reasonable minds may differ on this point." *Id.*

Judge Weinstein concluded:

> The strong constitutional right to a jury precludes a pretrial finding that *no* reasonable juror could find for any plaintiff except when a reasonable treating physician must have been fully aware of Zyprexa's dangers and those of competing drugs. Genuine issues exist as to material facts regarding the prescribing physicians' state of knowledge about the risks of diabetes and excessive weight gain associated with Zyprexa in [plaintiff's] . . . case[] defendant moves to dismiss.

Id.[110]

---

[110] AstraZeneca's warning regarding the diabetes risk inherent in Seroquel was diluted by the company's conduct relative to its promotion of the drug. In *Beale*, on which AstraZeneca so heavily relies, the district court recognized that numerous other jurisdictions, including the United States Court of Appeals for the Fourth Circuit, as well as California and Pennsylvania state courts, have approved an "overpromotion" exception to the learned intermediary doctrine. 492 F. Supp. 2d at 1377. However, the *Beale* court found plaintiffs' cases factually distinguishable because the plaintiffs had adduced no evidence of defendant's salespersons' interaction with or influence on plaintiffs' prescribers:

> In each of [plaintiffs' cited] cases, the courts found that drugs were overpromoted by salesmen known as "detail men," who visited physicians' offices and encouraged physicians to prescribe the drug. During these

In contrast, the cases on which AstraZeneca relies in support of the purported legal adequacy of Seroquel's warning are distinguishable from a pleadings and/or evidentiary standpoint. The record in *Felix* (Mem. at 37, 39), as noted, reflected that "***there [was] no contention [by the plaintiff] that the warning given in [the] case contained any misstatements***." 540 So.2d at 104 (emphasis added). Furthermore, the court determined that "[w]hile there have been subsequent incidents of children born with birth defects after their mothers ingested Accutane, there had been no Accutane related [birth defect incidences] in human infants prior to the ingestion of the drug in this case." *Id.* Based on those unique factual circumstances, not present here, the *Felix* court determined that the Accutane warning was adequate as a matter of law. *Id.* at 105.

Also distinct is *Beale v. Biomet, Inc.* (Mem. at 39), in which (AstraZeneca fails to note) the plaintiffs "did not provide any evidence that the warnings were, in themselves inadequate" and, more specifically, "did not provide any expert affidavits stating that the warnings were inadequate . . . ." 492 F. Supp. 2d 1360, 1370 (S.D. Fla. 2007).

Likewise, in *Upjohn Co. v. MacMurdo*, "no medical expert testified that the package insert was insufficient to put a doctor on notice that the symptoms displayed by [plaintiff] in January of 1975 could result from the use of [the drug at issue]." 562 So.2d at 683; *see also E.R. Squibb & Sons, Inc. v. Farnes*, 697 So.2d 825, 827 (Fla. 1997) (reinstating trial court's

---

> visits, the detail men often provided information regarding the drug which contradicted the warnings on the package insert of the drug, and made the drug appear much safer than it actually was. The physicians prescribing the drug testified that they were influenced by the representations of the detail men, and prescribed the drug much more freely than they would have without those representations.

Id. Because there were no comparable fact issues in the plaintiffs' case, the *Beale* court held that the plaintiffs had failed to raise a genuine issue of fact to support their position that the overpromotion exception should apply in this case . . . ." *Id.* at 1378. Yet the court implicitly recognized that such an exception may apply under Florida law. *Id.*; *accord Zanzuri*, 748 F. Supp. at 1518.

grant of new trial in defendant's favor, where plaintiff had failed to counter "extensive evidentiary support" that plaintiff's physician had received an adequate warning; "the key piece of information, i.e., that flu vaccines . . . had not been associated with [the identified risk], *was uncontroverted*" and plaintiff's expert offered "no particular basis, other than personal preference, for his opinion that the warning was inadequate") (emphasis added). Moreover, the "adequate warning" in *MacMurdo* consisted not only of "mentions" of the risk in the label's Adverse Reactions section, but also specific information about the risk in the Precautions section. Given the redundancy of the evidence in defendant's favor, and the lack of qualified expert testimony to support Plaintiff's position, the court remanded the case for entry of judgment in defendant's favor.

(b) Plaintiffs' Evidence Demonstrates That Seroquel's Warning Is Not Adequate As A Matter Of Law.

The expert testimony of William C. Wirshing, M.D. and Laura M. Plunkett, Ph.D., DABT, shows that Seroquel's various labeling incarnations have never carried a weight gain, hyperglycemia, or diabetes warning that may be considered adequate as a matter of law. As shown in Dr. Wirshing's Declaration, which is incorporated by reference (Ex. 43):

- The Seroquel label has never adequately warned of weight gain, given the alarming potential for Seroquel to cause clinically significant weight gain and the serious and even life-threatening health consequences likely to stem from that weight gain; the "weight gain" information should be relocated to the Warnings section, and should include a brief description of the negative health effects of such weight gain (Wirshing Decl. ¶¶ 6-7; Ex. 43);
- Seroquel's pre-2004 label did not warn of the risk of hyperglycemia and diabetes; those words were simply mentioned under the category "infrequent" in the adverse reactions section, along with *hypo*glycemia and weight loss; this is simply no warning at all, given the life-threatening nature of the side effects (Wirshing Decl. ¶¶ 9-10; Ex. 43);
- The 2004-2007 "class warning" is inadequate because it fails to account for the level

of risk attributable to Seroquel, which is "extraordinary" according to clinical trials comparing Seroquel to other antipsychotics; the "class warning" is also inadequate because not all SGAs are created equal, and examples such as aripiprazole and ziprasidone have not been shown to cause the extreme weight gain that is associated with Seroquel (Wirshing Decl. ¶¶ 12-13; Ex. 43);

- Also, the 2007 label change, with its cross-reference from the Warning section to the Adverse Reaction section, then indentifying diabetes-level hyperglycemia as merely "high blood sugar" or "hyperglycemia, appears to have been designed to be intentionally confusing; FDA has requested revisions to strengthen this label, but AstraZeneca has not thus far complied (Wirshing Decl. ¶¶ 16-18; Ex. 43); and
- AstraZeneca undermined and diluted any "warning" it gave relative to Seroquel through the promotion of materials to Plaintiffs' prescribers suggesting that Seroquel is "weight neutral," causes "minimal weight gain," has a "favorable weight profile," caused "weight loss," or helped to cure or alleviate diabetes; the truth was that 23-33% of Seroquel users were gaining clinically significant weight, and the Company was aware of the hyperglycemia/diabetes link to Seroquel as early as 1999 (Wirshing Decl. ¶¶ 6, 8, 11; 14; 16 Ex. 43).

Dr. Wirshing concludes:

> 19. Overall, the inadequacy of Seroquel's labeling and accompanying misstatements of the risks associated with its use make it prohibitively difficult for a physician relying on such information to appreciate the true nature of Seroquel's risks and discuss those risks with his or her patients.
>
> 20. Furthermore, in my opinion, AstraZeneca's warnings for Seroquel appear to have been designed to obscure known risks associated with the drug, rather than to clearly, accurately, and unambiguously communicate risks to prescribing physicians in a frank, explanatory manner such that they would have ready access to such critical information in treating their patients.

(Wirshing Decl. ¶¶ 19-20; Ex. 43). Dr. Plunkett, a food and drug regulatory expert, also reaches similar conclusions as Dr. Wirshing, but based upon the Company's awareness of "reasonable evidence of an association with" Seroquel and weight gain, hyperglycemia, and diabetes over time under 21 C.F.R. § 201.57(e). (Plunkett Decl. ¶¶ 8-21; Ex. 44.) Thus, apart from the facial inadequacies of Seroquel's labeling incarnations, Plaintiffs have also produced sufficient summary judgment evidence to send the issue of warning adequacy or inadequacy to the jury.

Lastly, as shown above and proven in Plaintiffs' individual Responses, AstraZeneca's so-called "warning" must be considered "*in light of the position its salespeople were taking, to convey the risks of weight gain, hyperglycemia, and diabetes.*" *In re Zyprexa*, 489 F. Supp. 2d at 279 (emphasis added); *see also Zanzuri*, 748 F. Supp. at 1518. In addition, as shown above, federal law broadly defines "labeling" to include separate literature (including advertising) sent by the manufacturer that supplemented or explained materials sent with the drug itself. Plaintiffs have each demonstrated that any weight gain, hyperglycemia, or diabetes AstraZeneca was obligated or tried to give was undermined by promotion of Seroquel that was inconsistent with those warnings. For the above reasons, Seroquel's warnings of weight gain, hyperglycemia, and diabetes should not be deemed adequate as a matter of law.

2. *Plaintiffs' Prescribers Did Not Possess Sufficient, Independent Knowledge Of The Risks An Adequate Warning Would Reveal To Sustain Summary Judgment Under Florida Law.*

Florida law recognizes an "independent knowledge" exception to the learned intermediary rule, which AstraZeneca asserts breaks the "causal link" between the Company's failure to provide an adequate warning and Plaintiffs' Seroquel ingestion and resulting injury. (Mem. at 36-37, 41-44.) *See Zanzuri*, 748 F. Supp. at 1517; *Felix*, 540 So.2d at 105. In addition, AstraZeneca argues that other categories of Plaintiffs' prescribers' testimony (e.g., that the physician testified that "he still would have prescribed" Seroquel despite the information omitted or misstated in the warning) also break the causal link between AstraZeneca's failure to warn and Plaintiffs' injuries, but those arguments find no

support under Florida law.[111]

First, given the "universe of [mis]information" that AstraZeneca itself created regarding Seroquel's risks and benefits, the Court should hold Plaintiffs' prescribers to a higher evidentiary threshold before anointing them "learned intermediaries." *See Zanzuri*, 748 F. Supp. at 1518. AstraZeneca has not met that higher threshold in proving that Plaintiffs' prescribers qualify as learned intermediaries. Second, and in any case, the record lacks evidence that Plaintiffs' prescribers had sufficient independent knowledge of the adequate warning (including the actual degree or extent of risk of injury) that Plaintiffs allege should have been given. *See Christopher*, 53 F.3d at 1192 (recognizing that question is whether prescriber had independent knowledge of the risk that the adequate warning, as

---

[111] Correspondingly, AstraZeneca tries mightily to shift the burden of proving its own affirmative defense of learned intermediary to Plaintiffs, an effort plainly contrary to Florida law notwithstanding the cases interpreting ***Georgia*** law and ***Texas*** law that AstraZeneca cites. (Mem. at 41 ("To establish proximate cause under the learned intermediary doctrine, plaintiffs must prove that their prescribing physician *would not have* prescribed Seroquel for them *but for* the allegedly inadequate warnings of the risks at issue." (emphasis original) (citing *Porter v. Eli Lilly & Co.*, No. 08-11335, 2008 WL 4138115, at *1 (holding that ***"[u]nder Georgia law***, [plaintiff] was required to prove that, but for the alleged inadequate warning, [decedent's prescriber] would not have prescribed [the drug] to decedent") (emphasis added) and *Ackerman v. Wyeth Pharms.*, 526 F.3d 203, 208 (5th Cir. 2008) (***"[U]nder Texas law***, . . . the plaintiff must show . . . that but for the inadequate warning, the treating physician would not have used or prescribed the product.") (emphasis added))).) AstraZeneca also relies on other Florida federal cases for similar propositions. But, the fact remains that *Felix* simply does not go so far as to identify a specific causation burden that plaintiffs bear under the learned intermediary rule. *See* 540 So.2d at 105 (holding only that the physician's independent knowledge of risks, where the language of the warning is uncontroverted, may break causal chain).

Plaintiffs do not dispute that they assume a causation burden with respect to their failure-to-warn and other claims, and have set forth above the applicable causation test under Florida law. However (setting aside AstraZeneca's above mischaracterizations of applicable Florida law), to the extent that AstraZeneca raises the question of which party shoulders the burden of establishing that the "causal link" is *broken* under the Florida learned intermediary doctrine, that party is indisputably AstraZeneca. *See, e.g., Christopher*, 53 F.3d at 1193 ("[Defendant] contends that in order to sustain *its burden on the learned intermediary defense*, it needed only to prove that [plaintiff's prescriber] had substantially the same knowledge of the . . . risk as would have been disclosed in [an adequate warning].") (emphasis added); *id.* at 1195 ("Given the importance of this [jury] instruction to [defendant's] primary defense [of learned intermediary] * * * the district court erroneously instructed the jury on [defendant's] defense."); *Walls v. Armour Pharm. Co.*, 832 F. Supp. 1467, 1482 (M.D. Fla. 1993) ("Because [defendant] raises the 'learned intermediary' doctrine as an affirmative defense, [defendant] bears the burden of proof on this issue."), *rev'd on other grounds sub nom Christopher*, 53 F.3d 1184; *Barrow v. Bristol-Myers Squibb Co.*, No. 96-689-ORL-19B, 1998 WL 812318, at *31 (M.D. Fla. Oct. 29, 1998) (Fawcett, J.) ("Defendant has failed to carry its burden to prove its learned intermediary defense in that the evidence fails to show that [plaintiff's physician] knew or should have known of the risks.").

alleged by the plaintiff, should have communicated); *see also Tatum*, 795 F.2d at 927. Further, the evidence shows that many of Plaintiffs' prescribers equivocated in their testimony with respect to their knowledge of an adequate warning and/or the point in time at which they acquired such knowledge, creating a fact issue. *See, e.g., Zanzuri*, 748 F. Supp. at 1517 ("physician [must be] an intermediary sufficiently informed to interrupt the causal link of liability . . . as a matter of uncontroverted fact"); *Barrow*, 1998 WL 812318, at *31 (finding that defendant failed to show that plaintiff's physician had "substantially the same" knowledge as an adequate warning *before* plaintiff received her treatment from physician). Lastly, Plaintiffs raise a fact issue with respect to possible bias of certain prescribers because of their former or current financial relationship with AstraZeneca, which a jury is entitled to weigh in evaluating the prescribers' testimony. *Anderson*, 477 U.S. at 255 (1986).

(a) AstraZeneca Has Not Shown That Plaintiffs' Prescribers Had Independent Knowledge Of The Risks An *Adequate* Warning Would Have Conveyed.

As mentioned, the Eleventh Circuit requires, in order for a physician to be shown to have "independent knowledge" for learned intermediary purposes, s/he must have "had independent knowledge of the risk that the *adequate warning* ***should have communicated.***" *Christopher*, 53 F.3d at 1192. Plaintiffs contend that an adequate warning would have consisted at least the information identified *supra* at 35.

Here, as shown in Plaintiffs' individual Responses, AstraZeneca simply cannot meet that evidentiary burden. (*See* Plaintiffs' Responses § III.C.2.(a).) Therefore, AstraZeneca is unable to establish Plaintiffs' prescribers' independent knowledge of the information an adequate warning would have conveyed, and summary judgment is not appropriate on that

basis.

(b) AstraZeneca's Misstatements About Seroquel's Risks Prevented Plaintiffs' Doctors From Accomplishing The "Herculean" Task Of Supplementing The Warning And Refuting AstraZeneca's Misstatements.

Zanzuri dismissed defendant's argument that, under *Felix*, plaintiff's prescriber had acquired independent knowledge of the risks associated with use of the Cu-7. Defendant argued that the prescriber had acquired independent knowledge of the risks from his general experience as a gynecologist, his subscription to professional journals, and his hospital residency, where he frequently prescribed and inserted the Cu-7. *Id.* The court found that "[t]he record does indeed indicate that [plaintiff's prescriber] was ***generally informed*** as to the dangers associated with the Cu-7." *Id.* (emphasis added.) However, the court held that "the record as presented gives this Court reason to pause before casting [plaintiff's prescriber] in the leading role of an independently informed learned intermediary." *Id.* Unlike *Felix*, plaintiff had unequivocally argued that the warning provided for the Cu-7 contained misrepresentations that misled the medical community as to the magnitude of the risks involved with Cu-7 use. *Id.* (comparing the Florida Supreme Court's observation in *Felix* that there was "no contention that the warning given in this case contained any misstatements" (*Felix*, 540 So.2d at 104)). *Zanzuri* also found the plaintiff's expert had testified that defendant "***mischaracterized the relationship and incidence of PID [defendant] knew or should have known existed.***" *Zanzuri*, 748 F. Supp. at 1518. (emphasis added.) Additionally, plaintiff's expert opined that the defendant's "medical studies and record keeping were inadequate . . . to determine the actual rate of PID experienced with the use of the device." *Id.* ("[Defendant] reported an inaccurate rate to the FDA and used the

inaccurate rate as a basis for some of its statements in the patients [sic] booklet and physicians [sic] inserts."). *Id.*

Concluding that defendant's misinformation prevented a finding that it had provided an "accurate, clear, and unambiguous" warning as a matter of law:

> Although the line drawn between misstatements in the warning, and general inadequacy of the warning may at first blush seem enigmatic and elusive, close inspection reveals considerable persuasive force behind the increased threshold that must be met when attempting to qualify the prescribing physician as a learned intermediary after being exposed to misrepresentative product warnings. In his deposition, [plaintiff's prescriber] admits that he relied heavily on the literature supplied by [d]efendant in forming his opinion as to the risks associated with Cu-7. The "independent knowledge" category of the learned intermediary doctrine is necessarily premised on the ability of the physician to move beyond the educative deficiencies of the product warning in forming a realistic opinion of the product's risks through an independent research of professional journals. If [d]efendant's literature were merely inadequate, yet devoid of material misstatements, it is entirely conceivable that the prescribing physician could reach the fully informed state of a "learned intermediary" through independent reading. ***When, however, the universe of information from which the physician must piece together a conception of the totality of the risks involved with a product includes misstatements by the product manufacturer, the physician's task becomes Herculean, for he or she must not only supplement the warning, but actually refute the errors communicated by the manufacturer.***

Id. (emphasis added); accord, *In re Zyprexa*, 489 F. Supp. 2d at 247 (denying summary judgment under Florida learned intermediary law where defendant failed to show that plaintiff's prescribers were fully informed of all risks associated with Zyprexa and competing drugs, "particularly when viewed in light of the position its salespeople were taking[,] to convey the risks of weight gain, hyperglycemia, and diabetes";[112] *Beale*, 492 F. Supp. 2d at 1377-1378 (recognizing "overpromotion" and "dilution" exceptions to the learned intermediary rule).

---

112 *See* discussion, *supra* at 64-66.

Again, more than ample evidence in each of Plaintiffs' cases demonstrates the influence AstraZeneca's Seroquel sales messages had on Plaintiffs' prescribers and the concomitant dilutive effect those promotional measures had on any warnings. (*See* Plaintiffs' Responses §§ III.C.1, III.C.2.(b); *see also* Wirshing Decl. ¶¶ 8, 11, 14 (Ex. 43); Plunkett Decl. ¶¶ 12, 15, 18 (Ex. 44).) The Court should not enter summary judgment based on the prescribers' so-called independent knowledge where AstraZeneca actively sought to corrupt and obfuscate crucial health risk warnings.

(c) Plaintiffs' Prescribers' Testimony Regarding Their Independent Knowledge Of The Risks Was, At Best, Inconsistent, Raising A Fact Issue.

Further, Plaintiffs' prescribers must have testified "without contradiction" that they were "aware of all the risks associated with the" drug. *Beale*, 492 F. Supp.2d at 1371. Because certain of Plaintiffs' prescribers have not done so, summary judgment is inappropriate for this additional reason. (*See* Plaintiffs' Responses § III.C.2.(c).)

(d) Certain Of Plaintiffs' Prescribers Were Biased In Favor Of AstraZeneca Through Their Previous Employment By The Company And Other Relationships.

Next, a number of Plaintiffs' prescribers testified that they had financial relationships with AstraZeneca prior to their testifying in this case, establishing a fact question as to credibility and bias relative to those witnesses' testimony. "Credibility determinations, the weighing of the evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of a judge, whether he is ruling on a motion for summary judgment or for a directed verdict. The evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor." *Anderson*, 477 U.S. at 255 (1986); *see Lane v.*

Celotex Corp., 786 F.2d 1526, 1528 (11th Cir. 1986) ("The district court must not resolve factual disputes by weighing conflicting evidence, since it is the province of the jury to assess the probative value of the evidence."). As the United States District Court for the District of Minnesota emphasized in *In re Guidant Corp. Implantable Defibrillators Prods. Liab. Litig.*, MDL No. 05-1708, 2007 WL 2023569, at *5 (D. Minn. July 6, 2007), "the law does not turn a blind eye to [a doctor's] bias or interest," but views a doctor's statements "in conjunction with his ties and/or relationship to [a manufacturer]." *Id.* (citing *Motus v. Pfizer, Inc.*, 196 F.Supp.2d 984, 997 (C.D. Cal. 2001) ("explaining that summary judgment would not be warranted if plaintiff had presented evidence putting the physician's credibility in question.")).

A large number of Plaintiffs' prescribers were employed as speakers by or had other paid roles (jobs) within or contracted by AstraZeneca. Because this fact creates a witness credibility issue for the jury, the Court should not enter summary judgment on this ground. (*See* Plaintiffs' Responses § III.C.2.(d).)

(e) AstraZeneca's Contrived Efforts to Interrupt the Causal Chain of Plaintiffs' Failure to Warn Claims Are Unsupported by Eleventh Circuit and Florida Law and Require the Court to Invade the Province of the Jury.

Plaintiffs have adduced summary judgment evidence, the components of Seroquel's deceptive warnings related to diabetes were communicated to Plaintiffs' prescribing physicians. This evidence is alone sufficient to create a fact issue regarding whether Seroquel's inadequate warning was the proximate cause of Plaintiffs' injury. (*See* Plaintiffs' individual Response Briefs § III.C.)

Nevertheless, AstraZeneca sets forth a laundry list of other causal "breaks" that

purportedly bar Plaintiffs' ability to prove that AstraZeneca's deceptive and illegal conduct caused their injuries. (Mem. at 41-44.) Quite apart from the "independent knowledge" exception recognized in *Felix* and *Christopher*, AstraZeneca's other causation arguments suffer from the same fundamental flaw: they are unsupported by any binding Florida or Eleventh Circuit authority. [113] Moreover, specifically with respect to AstraZeneca's

---

[113] AstraZeneca takes numerous licenses with its case attributions throughout its brief, particularly with respect to expanding causation tests applicable to the Florida learned intermediary doctrine. For example,

- AstraZeneca cites *Porter v. Eli Lilly & Co.* with determinate frequency, with nary a mention that the Eleventh Circuit interpreted and applied Georgia law in that case, as mentioned above in note 111.
- Repeatedly citing *Stupak v. Hoffmann-La Roche, Inc.*, No. 8:05-CV-926T30TBM, 2007 WL 2350561, at *3 (M.D. Fla. Aug. 17, 2007). AstraZeneca overlooks the fact that the court curiously decided the causation issue relative to the learned intermediary rule based exclusively on Wisconsin and New York law. Moreover, the court observed that the plaintiff's prescriber *was unaware of the risk of suicide* associated with the drug Accutane, but nevertheless shielded the defendant under the learned intermediary doctrine, in plain contravention of *Felix*, because he said he would continue to prescribe the drug. *Id.* at *3-*4. The court also noted that plaintiff offered no evidence to refute the prescriber's testimony. *Id.* at *3.
- The Florida appeals court in *Cornelius v. Cain* simply determined, pursuant to *Felix*, that plaintiff's prescribers "were both independently aware of the risks and benefits of prescribing [the drug at issue]." No. CACE 01-020213(02), 2004 WL 48102, at *4-*5 (Fla. Ct. App. Jan. 5, 2004) (citing *Felix*). The opinion does not reveal that the prescribers "still would have prescribed" the drug.
- AstraZeneca relies on *Alexander v. Danek Medical, Inc.*, 37 F. Supp. 2d 1346, 1350 (M.D. Fla. 1999) for the proposition that "[P]laintiffs cannot prove the requisite causal link between any allegedly inadequate warning and their drug ingestion and alleged injury" where "the prescribing physician '*still would have prescribed*' the drug for plaintiff despite allegedly omitted information." (Mem. at 42.) However, the Middle District of Florida simply concluded that Alexander's surgeon "knew of the risk of nerve damage" and "knew of the risk of a poor clinical outcome." *Alexander*, 37 F. Supp. 2d at 1349-50. Based on that independent knowledge, Alexander could not "show that the inadequacy of the manufacturer's warning affected [his surgeon's] use of the product." *Id.* at 1350. There was no testimony by plaintiff's surgeon that he "still would have [performed the surgery]" despite any alleged inadequate warnings. *Id.* at 1349-50.
- *Beale* plainly decided the learned intermediary question in defendant's favor based upon the surgeon's independent knowledge of the risks, citing *Felix* as the lone Florida state court decision on which the *Beale* court relied. 492 F. Supp. 2d at 1371. To the extent that *Beale* applied a standard that also considered whether the doctor "would have taken the same course of action even with the information plaintiff contends should have been provided," that standard is one articulated by the Eleventh Circuit under Georgia, rather than Florida, law. *See id.* (citing *Ellis v. C.R. Bard, Inc.*, 311 F.3d 1272, 1283 n.8 (11th Cir. 2002)). AstraZeneca's own citations to *Ellis* further neglect to mention the case interprets and applies Georgia law. That aside, AstraZeneca self-servingly abbreviates the full quote from *Ellis*, which states "regardless of the sufficiency or insufficiency of the warnings at issue . . . ***[w]here a learned intermediary has actual knowledge of the substance of the alleged warning*** and would have taken action even with the information the plaintiff contends should have been given,

hypotheticals asked in depositions of Plaintiffs' prescribers—largely following the theme "if you knew then what you know now, would you still prescribe Seroquel?"—fail to break the causal link, or have any effect on the case other than to raise additional fact questions precluding summary judgment.

---

courts typically conclude that the learned intermediary doctrine applies or that the causal link is broken and the plaintiff cannot recover." 311 F.3d at 1283 n.8 (emphasis added). Plaintiffs, of course, contend (and have adduced evidence to overcome summary judgment) that their prescribers did not have independent knowledge of all the information an adequate warning would have provided. *See* Plaintiffs' individual Responses at § III.C.2.A.

- In *Timmons v. Purdue Pharma Co.*, No. 8:04-CV-1479-T-26MAP, 2006 WL 263602, at *4 (M.D. Fla. Feb. 2, 2006) the court determined that the causal link was broken because "all four [plaintiff's] physicians testified that they were independently aware of the risks of addiction to [the drug at issue]." *Id.* at *4. Additionally, all four physicians testified that plaintiff did not suffer from the condition he complained of in his lawsuit. *Id.* Plaintiffs' doctors did not mention whether they still would have prescribed the drug for plaintiff, and none of them "purport[ed] to say" whether the additional warning would have made any difference to them. *Id.*

- *Edgar v. Danek Medical, Inc.* observed that "[a] physician's independent awareness of th[e] risks . . . disrupts probable cause and obviates any liability for a manufacturer's failure to warn," citing *Christopher* and *Felix*. No. 96-2451-CIV-T-24A, 1999 WL 1054864, at *6 (M.D. Fla. Mar. 31, 1999). (The *Edgar* court did apply a "but for" causation standard, which Plaintiffs have shown above is improper for this case. *See* discussion, *supra* at 38-42.) The opinion does not reveal that the surgeon still would have performed the surgery.

- The *Wilson v. Danek Medical, Inc.* court determined that "[t]here is abundant unrebutted evidence that [plaintiff's physicians] were well aware of the risks and dangers inherent in use of the [medical device]." No. 96-2460-CIV-T-17B, 1999 WL 1062129, at *5 (M.D. Fla. Mar. 29, 1999). Therefore, the learned intermediary doctrine barred plaintiff's failure to warn claim. The court further held that the *Bellofatto v. Danek Medical, Inc.* exception to the learned intermediary doctrine (similar to *Zanzuri*, requiring a higher evidentiary threshold be met for learned intermediary status) did not apply because the doctors stated that they did not rely on materials from the manufacturer in forming their opinions. *Wilson*, 1999 WL 1602129, at *5. That is different, of course, from testimony that actual exposure to adequate warnings or disclosures from the manufacturer would not have "made a difference" or "affected" the prescribing decision. (Mem. at 42.)

- *Colville v. Pharmacia & Upjohn Co.* simply concluded that "[b]ecause [plaintiff's prescriber] was aware of the risk factor and did not have a specific conversation with [p]laintiff about it, [p]laintiff has failed to show that the inadequacy of the manufacturer's warnings was a proximate cause of her [injury]," regardless of whether the doctor later continued to prescribe that medicine to other patients. 565 F. Supp. 2d 1314, 1322 (N.D. Fla. 2008). The question is whether the prescriber had independent knowledge of the risks stated in an adequate warning at the time s/he prescribed it for the plaintiff, not whether s/he continued that same course of treatment with other patients.

With respect to AstraZeneca's reliance on non-Florida cases, what is good for the goose is good for the gander: "No Florida court has *ever* applied [the other jurisdictions' causal tests AstraZeneca identifies in it Memorandum at 43] in the prescription drug context under Florida law—which is dispositive under federalism principles and governing Eleventh Circuit authority in these diversity cases." (Mem. at 45, citing cases.)

In *Tatum*, for example, the purported "learned intermediary" prescriber testified that he knew about the general risk of death associated with the prescription drug Solganol, but he did not know the particulars that an adequate warning would have conveyed—e.g., the percentage of patients who suffered injury and the rate of incidence of fatality. 795 F.2d at 927 (applying Alabama learned intermediary doctrine), *cited in Christopher*, 53 F.3d at 1192. From that knowledge set, the Eleventh Circuit correctly concluded:

> The knowledge that Dr. Karst did have—that Solganol could kill—does not preclude a factfinder's concluding that had Dr. Karst known of the actual degree or extent of risk of death or other serious adverse effect, he would not have prescribed the drug for Mrs. Tatum in particular, or for other patients in general having the same state of severity of diagnosis or prognosis as Mrs. Tatum. ***Nor does it preclude a factfinder's concluding that had Dr. Karst informed Mrs. Tatum of the information plaintiff says should have been conveyed to him, Mrs. Tatum would not have agreed to the treatment.***

Tatum, 795 F.2d at 927-28 (emphasis added). Because in *Tatum* a reasonable juror could find for the plaintiff, it was error to hold by summary judgment that proximate cause did not exist. *Id.* at 928; *see In re Prempro Prods. Liab. Litig.*, Nos. 4:03CV1507-WRW, 4:05CV00497, 2006 WL 1981902, at *3 (E.D. Ark. July 13, 2006);[114] *see also Golod v. Hoffman La Roche*, 964 F. Supp. 841, 857 (S.D.N.Y. 1997);[115] *cf. Athridge v. Aetna Cas. &*

---

114 I'm not convinced that a physician's testimony regarding what he or she would have done in 20/20-hindsight should be considered absolute. It appears to me that such testimony may well hinge on credibility, which is for the jury decide. I'm inclined to hold with the idea that "unless a physician's claim that she would have prescribed a drug even if adequately warned is self-disserving, the credibility of such a claim is generally a jury question not to be resolved on a motion for summary judgment.

115 Defendants contend that any inadequacy of its warning was not a proximate cause of Golod's injuries because Dr. Grossman, who prescribed Tegison for Golod, has testified that he believes Hoffman's warnings are adequate despite Golod's blindness and has not changed his practices in prescribing Tegison since her injury. However, unless a physician's claim that she would have prescribed a drug even if adequately warned is self-disserving, the credibility of such a claim is generally a jury question not to be resolved

Sur. Co., 474 F. Supp. 2d 102, 105 (D.D.C. 2007) ("Under Federal Rule of Evidence 602, witnesses must have personal knowledge about which they testify. Additionally, under Rule 701(a), a lay witness's testimony must be 'rationally based on the perception of the witness.' Speculative testimony as to what a witness would have done under different circumstances cannot possibly be based on the witness's perception.").

Thus, Plaintiffs' prescribers' conjecture as to whether they would have prescribed, or continued to prescribe, Seroquel *had the facts been different than what is presented in the record* is simply improper grounds to sustain summary judgment. Under *Tatum*, despite Plaintiffs' prescribing doctors' after-the-fact judgment as to whether they would recommend beginning or continuing Seroquel treatment in the face of an adequate warning, jurors could reasonably conclude that Plaintiffs, upon receipt of such information, would have refused to begin or continue Seroquel treatment.

In any event, because such speculative testimony requires the Court to draw inferences in favor of the moving party, summary judgment on that basis would be error. *See Anderson*, 477 U.S. at 255 ("Credibility determinations, the weighing of the evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of the judge."); *Allen*, 495 F.3d at 1315 ("To the extent that evidence conflicts at summary judgment, the district court has an obligation to view all evidence and make all reasonable inferences in favor of the party opposing summary judgment.") (internal quotation marks and citation omitted).

---

on a motion for summary judgment. Here, because Dr. Grossman is not a defendant in this action, his statement is not self-disserving in any meaningful way.

D. AstraZeneca Is Not Entitled To Summary Judgment On Plaintiffs' Intentional and Negligent Misrepresentation Claims.

Each of AstraZeneca's attacks on Plaintiffs' fraud claims falls short. Under Florida law, intentional misrepresentation has four elements: "(1) a false statement concerning a material fact; (2) the representor's knowledge that the representation is false;[116] (3) an intention that the representation induce another to act on it; and, (4) consequent injury by the party acting in reliance on the representation." *Webb v, Kirkland*, 899 So. 2d 344, 346 (Fla. Dist. Ct. App. 2005) (quoting *Johnson v. Davis*, 480 So. 2d 625, 627 (Fla. 1985)). "Fraud also includes the intentional omission of a material fact." *Ward v. Atlantic Sec. Bank*, 777 So. 2d 1144, 1146 (Fla. Dist. Ct. App. 2001); *accord Charles v. Florida Foreclosure Placement Ctr.*, LLC, 988 So. 2d 1157, 1160 (Fla. Dist. Ct. App. 2008).

AstraZeneca admits that Plaintiffs may prevail on their fraud-based claims by proving that either they or their prescribers observed and relied on AstraZeneca's material misstatements about Seroquel. (*See* Mem. at 47-50). Plaintiffs do not attempt to show that they observed or relied on AstraZeneca's material misstatements and omissions about Seroquel, nor does Florida law require them to do so. *Albertson v. Richardson-Merrell, Inc.*, 441 So. 2d 1146, 1149-51 (Fl. Dist. Ct. App. 1983) (finding that plaintiff who ingested the drug Bendectin could maintain an action for fraud against manufacturer of drug and its sales representative when they failed to disclose material information or had made material representations to prescribing physician but not to plaintiff), *cited in Barrow* 1998 WL

[116] Negligent misrepresentation, in contrast, requires that a "defendant made a misrepresentation of material fact that he believed to be true but which was in fact false," and that "the defendant was negligent in making the statement because he should have known the representation was false." *Romo v. Amedex Ins. Co.*, 930 So. 2d 643, 653 (Fla. Dist. Ct. App. 2006); *see Simon v. Celebration Co.*, 883 So. 2d 826, 832 (Fla. Dist. Ct. App. 2004). Otherwise, intentional and negligent misrepresentation do not differ under Florida law. *Compare Johnson v. Davis*, 480 So. 2d 625, 627 (Fla. 1985), *with Romo*, 930 So. 2d at 653.

812318, at *45 (M.D. Fla. Oct. 29, 1998) (applying Florida law and stating: "The fact that MEC made the misrepresentations, and omitted material information in its representations, to Plaintiff's physician and not directly to Plaintiff does not preclude recovery by Plaintiff against MEC for such misrepresentations and omissions."); *see Alexander v. Danek Med., Inc.*, 37 F. Supp. 2d 1346, 1350 (M.D. Fla. 1999). Rather, Plaintiffs base their fraud claims on their prescribers' having relied on false statements AstraZeneca made to them about Seroquel's safety and efficacy, and (2) AstraZeneca's failure to disclose information to their prescribers about Seroquel's safety and efficacy.

1. Plaintiffs Have Raised Sufficient Summary Judgment Evidence Regarding Whether Their Prescribers Heard or Saw AstraZeneca's False Statements About Seroquel's Efficacy and Safety.

Plaintiffs' summary judgment evidence refutes AstraZeneca's contention that Plaintiffs' fraud claims fail for lack of evidence that their prescribers' ever saw or heard any material misstatements by AstraZeneca about Seroquel. As shown in the individual summary judgment Responses filed concurrently, each Plaintiff has identified sufficient summary judgment evidence on the issue of whether AstraZeneca failed to disclose material information to Plaintiffs' prescribers.

2. Plaintiffs Have Summary Judgment Evidence Showing that Their Prescribers Relied on AstraZeneca's Material Misrepresentations and Omissions.

Plaintiffs' summary judgment evidence also refutes AstraZeneca's contention that Plaintiffs' fraud claims fail for lack of evidence that their prescribers' justifiably relied on AstraZeneca's material misstatements or omissions. As shown in the individual summary judgment responses filed concurrently, each Plaintiff has met his or her summary judgment

burden on this issue.

3. *Plaintiffs Have Met Summary Judgment Causation Burden, If Any, Relative to Their Fraud and Misrepresentation Claims.*

AstraZeneca incorrectly asserts that Florida law requires Plaintiffs to prove proximate causation in order to prevail on their intentional and negligent misrepresentation claims. (Mem. at 50-51.) For example, in *Cahill v. American Jets International Inc.*, the Florida Court of Appeal for the Fourth District reversed the trial court's grant of summary judgment on plaintiff's fraud-based claims on the ground that proximate causation is not an essential element of fraud under Florida law. 755 So. 2d 688, 689 (Fl. Dist. Ct. App. 1999) (per curiam). The *Cahill* court agreed with plaintiff that "because summary judgment was granted only with respect to the proximate cause issue and thereby disposed of only the negligence count, the trial court erred in entering final judgment on all counts." *Id.* The *Cahill* court concluded that "[b]ecause the summary judgment disposed of only the negligence count, the counts for breach of contract, fraudulent inducement, and fraudulent misrepresentation are still pending." *Id.*

In *Lopez v. Rica Foods, Inc.*, the Eleventh Circuit recently reversed dismissal of plaintiffs' fraudulent and negligent misrepresentation claims for the same reason. The *Lopez* court rejected the district court's holding that plaintiffs were required to plead that defendant's misrepresentations proximately caused their damages, stating: "To adequately plead causation in a fraud claim under Florida law, a plaintiff must only allege damage or injury as a result of the misrepresentation." 277 F. App'x 931, 932-33 (11th Cir. 2008) (per curiam) (citing *Lance v. Wade*, 457 So. 2d 1008, 1011 (Fla. 1984). The *Lopez* court noted that in *Lance*, the Florida Supreme Court listed "'reliance on the representation to the injury

of the other party'" as the fourth element of fraud. *Id.* at 933 (quoting *Lance*, 457 So. 2d at 1011). Indeed, immediately after identifying the elements of fraud, the *Lance* court stated: "In summary, there must be an intentional material misrepresentation upon which the other party relies to his detriment." 457 So. 2d at 1011.[117] Noticeably absent from the *Lance* court's discussion of the elements of fraud is any reference to proximate causation.

Even if Florida law did require a showing of proximate causation in fraud-based claims, however –which it does not– Plaintiffs have raised a fact issue regarding whether AstraZeneca's material misstatements and omissions proximately caused Plaintiffs' Seroquel ingestion and resulting injuries, as shown above and in the individual Responses filed herewith.[118]

---

[117] None of the cases AstraZeneca cites stand for the proposition that Florida law requires proof of proximate causation in fraud-based claims. (Mem. at 47, 50.) In *Allison v. McGhan Med. Corp.*, the Eleventh Circuit applied Georgia law and not Florida law. 184 F.3d 1300 (11th Cir. 1999). In *Beale*, the district court did not indicate that proximate causation is an element of a fraud-based claim. 492 F. Supp. 2d at 1374-75 (holding that plaintiffs' negligent misrepresentation claim inadequate as a matter of law because plaintiffs' failed to identify a false statement made by defendant). Likewise, in *Soler v. Secondary Holdings, Inc.*, the Florida District Court of Appeal for the Third Circuit made no reference to proximate causation. 771 So. 2d 62, 69-70 (Fla. Dist. Ct. App. 2000) (holding that plaintiff's fraudulent misrepresentation claim was inadequate as a matter of law because plaintiff did not detrimentally rely on a false statement). In *Hasenfus v. Secord*, the Eleventh Circuit stated that a surviving spouse of an experienced combat pilot and Air Force Academy graduate who died while working as a pilot in covert air missions to resupply the Contras in Nicaragua. 962 F.2d 1556, 1558 (11th Cir. 1992). The court referred to proximate causation in transitioning from its discussion of plaintiff's negligence claim to its discussion of her misrepresentation claim. *Id.* at 1561. The court explained that plaintiff's claim failed because there was no evidence showing that her husband had *relied* on a misrepresentation about the quality of the plane. *Id.*

[118] AstraZeneca relegates its attack on Plaintiff's fraud pleadings to footnote 44. (Mem. at 48 n.44.) Without identifying any particular deficiency in Plaintiffs' Original Complaint, AstraZeneca asserts that Plaintiffs' have not pled their fraud claims with the particularity required by Federal Rule of Civil Procedure 9(b). *Id.* Contrary to AstraZeneca's assertion, the fraud allegations contained in Plaintiffs' intentional and negligent misrepresentations claims satisfy Rule 9(b)'s particularity requirement. *See Wagner v. First Horizon Pharm. Corp.*, 464 F.3d 1273, 1278 (11th Cir. 2006) ("In a complaint subject to Rule 9(b)'s particularity requirement, plaintiffs retain the dual burden of providing sufficient particularity as to the fraud while maintaining a sense of brevity and clarity in the drafting of the claim, in accord with Rule 8."); *Brooks v. Blue Cross & Blue Shield of Fla., Inc.*, 116 F.3d 1364, 1371 (11th Cir. 1997) (per curiam) ("'Rule 9(b) must be read in conjunction with Rule 8(a) [of the Federal Rules of Civil Procedure], which requires a plaintiff to plead only a short, plain statement of the grounds upon which he is entitled to relief.'") (quoting *O'Brien v. Nat's Prop. Analyst Partners*, 719 F. Supp. 222, 225 (S.D.N.Y. 1989)); 2 Moore's Federal Practice, ¶ 9.03[1][a] at 9-17 (3d

E. Plaintiffs' Raise a Genuine Issue of Material Fact Regarding Whether Seroquel's Design Was Defective.

1. Florida Law Recognizes Two Alternative Tests For Establishing That A Product's Design Is Defective.

In Florida, a product's design can be found defective under either the "consumer expectation" test or the "risk-benefit" test.[119] *See Tran v. Toyota*, 420 F.3d 1310, 1312-14 (2005) (acknowledging that "consumer expectations" test and "risk-utility" tests are alternative bases for design defect liability under Florida law); *Jennings v. BIC Corp.*, 181 F.3d 1250, 1255-56 (11th Cir. 1999) (holding that a lighter lacking a child-proof feature was not defective because neither test of defectiveness could be satisfied); *Liggett Group, Inc. v. Davis*, 973 So. 2d 467, 473 (Fla. Dist. Ct. App. 2007) (applying "two issue rule" to design defect claim because jury rendered general verdict based on two alternative theories of

---

ed. 1999) (footnote omitted) ("While the purpose of Rule 9(b) is to provide detailed notice of the circumstances constituting fraud, each and every alleged misrepresentation need not appear in the pleadings.").

Further, Rule 9(b) analysis is not limited to pleadings, particularly at the summary judgment stage. *Tello v. Dean Witter Reynolds, Inc.*, 494 F.3d 959, 972-73 (11th Cir. 2007) ("While '[a]llegations of date, time or place satisfy the Rule 9(b) requirement that the *circumstances* of the alleged fraud be pleaded with particularity,' we have acknowledged that 'alternative means are also available to satisfy the rule' in substantiating fraud allegations." (quoting *Durham v. Bus. Mgmt. Assocs.*, 847 F.2d 1501, 1512 (11th Cir. 1988) (holding that "allegations contained in the amended complaint and the affidavit before the district court on the motion for summary judgment satisfy the requirements of Rule 9(b)" by alleging that plaintiffs corresponded by mail with defendants in a securities fraud action))); *see also United States ex rel. Clausen v. Lab. Corp. of Am.*, 290 F.3d 1301, 1310 n.18 (11th Cir. 2002) ("[T]his Court has found challenged complaints—read together with other documents in the record—to be sufficient [to satisfy Rule 9(b)]."); *cf.* Fed. R. Civ. P. 12(b)(6) ("If . . . matters outside the pleading are presented to and not excluded by the court, the [Rule 12(b)(6)] motion shall be treated as one for summary judgment and disposed of as provided in Rule 56, and all parties shall be given reasonable opportunity to present all material made pertinent to such a motion by Rule 56."). Plaintiffs' summary judgment evidence regarding their prescribers' reliance on AstraZeneca's false statements and failure to disclose information about Seroquel's safety and efficacy, together with the fraud allegations in Plaintiff's Original Complaint, satisfy the particularity requirement of Rule 9(b).

[119] Plaintiffs have alleged that "Seroquel was defective in design and/or formulation in that, when it left the hands of Defendants and/or its representatives, the foreseeable risks of serious harm posed by the drug outweighed its alleged benefits. The foreseeable risks of serious harm were so great that Plaintiffs, and the general public, having known of such foreseeable risks and alleged benefits, would not have ingested Seroquel." (Original Compl., ¶ 30.) Despite pointing out that Plaintiffs "include negligent 'design[]' in their broader negligence claims, AstraZeneca does not address Plaintiffs' allegation that AstraZeneca breached its duty to use reasonable care in designing Seroquel," (Mot. 54 n.51 (quoting Guinn Compl. ¶ 36)).

liability, the "ordinary consumer" test and the "risk benefit" test); *Force v. Ford Motor Co.*, 879 So. 2d 103, 106-07 (Fla. Dist. Ct. App. 2004) (discussing alternative nature of the two test for design defectiveness).

Under the consumer expectation test, "a product is defectively designed if the plaintiff is able to demonstrate that the product did not perform as safely as an ordinary consumer would expect when used in the intended or reasonably foreseeable manner." *Force v. Ford Motor Co.*, 879 So. 2d 103, 106 (Fla. Dist. Ct. App. 2004); *accord Pinchinat v. Graco Children's Prods., Inc.*, 390 F. Supp. 2d 1141, 1148 (M.D. Fla. 2005). Under the risk-benefit test, "a product is defectively designed if the plaintiff proves that the design of the product proximately caused the plaintiff's injuries and ***the defendant fails to prove*** that on balance, the benefits of the design outweigh the risk of the danger inherent in the design."[120] *Force*, 879 So. 2d at 106 (emphasis added); *accord Pinchinat*, 390 F. Supp. at2d at 1148. "[B]oth tests require application of the objective standard to determine the defective nature of

---

[120] The Florida Standard Jury Instructions confirm that Plaintiffs are not required to identify a specific "defect" in Seroquel's design. See In re Standard Jury Instructions (Civil Cases), 435 So. 2d 782, The design defect instruction provides: "

> A product is defective . . . if by reason of its design the product is in a condition unreasonably dangerous . . . . A product is unreasonably dangerous because of its design if the product fails to perform as safely as an ordinary consumer would expect when used as intended or in a matter reasonably foreseeable by the manufacturer or the risk of danger in the design outweighs the benefits.

Fla. Std. Jury Instr. (Civil) PL 5 (internal brackets omitted). The design defect instruction should not be interpreted, however, as a comment on the burden of proof at the summary judgment stage. As the committee responsible for drafting Florida's Standard Jury Instructions stated:

> The committee is of the view that, in Florida, the ultimate burden of persuasion in cases submitted to the jury remains with the plaintiff. . . . PL 5 therefore allocates that burden to the plaintiff. The charge is not intended to control issues of the burden of proof or sufficiency of the evidence for directed verdict purposes.

Fla. Std. Jury Instr. (Civil Cases), Note on Use, cmt. 5 (internal citations omitted). Because a motion for summary judgment is tantamount to a pretrial motion for a directed verdict, instruction PL 5 does not affect the burden of proof at the summary judgment stage.

the product. The consumer expectation test requires consideration of the ordinary consumer's expectations. The risk-benefit analysis requires consideration of the 'normal public expectation of danger.'" *Jennings v. BIC Corp.*, 181 F.3d 1250, 1255 (11th Cir. 1999) (quoting *Hobart Corp. v. Siegle*, 600 So. 2d 503, 504 n.3 (Fla. Dist. Ct. App. 1992)). As such, there is no merit to AstraZeneca argument that Plaintiffs must identify a defect in Seroquel's chemical composition[121] or some other identifiable "defect" in Seroquel's design to withstand summary judgment on their design defect claims.[122]

AstraZeneca is not entitled to summary judgment on Plaintiffs' design defect claims because (1) Plaintiffs have raised a fact question on proximate causation, as shown above and in the individual summary judgment responses filed herewith, and (2) AstraZeneca bears the burden of proving that Seroquel's benefits outweigh its risks at the summary judgment stage. Even if Plaintiffs bear the burden of proof on risk-benefit analysis at the summary judgment stage, however, Plaintiff's experts' testimony presents more than a scintilla of evidence and raises a fact question regarding both tests for a defective design. Plaintiffs' expert Dr. Donna

---

[121] AstraZeneca's reliance on *Timmons v. Purdue Pharma Co.* is misplaced, as this Court merely pointed out that plaintiff "does not make a case for the defectiveness of the chemical composition of Oxycontin" and did not hold that Florida law requires a plaintiff to identify a defect in chemical composition in design defect claims involving prescription drugs. No. 08:04-CV-1479-T-26MAP, 2006 WL 263602, at *4 (M.D. Fla. Feb. 2, 2006). Moreover, because Seroquel is still under patent, neither Plaintiffs nor their experts have knowledge of Seroquel's precise chemical composition.

[122] Contrary to AstraZeneca's suggestion, *West v. Caterpillar Tractor Co.* does not stand for the proposition that plaintiffs must identify a specific defect in a product's design to prevail in every design defect claim brought under Florida law. 336 So. 2d 80 (Fla. 1976). In *Edward M. Chadbourne*, the Florida Supreme Court quoted *West* and explained: "As adopted by this Court, an action sounding in strict liability requires the plaintiff to prove that (1) a product (2) produced by a manufacturer (3) ***was defective or created an unreasonably dangerous condition*** . . . ." 491 So. 2d at 551 (emphasis added). Further, the two other cases AstraZeneca cites in support of this proposition are inapposite because they involved medical devices, not prescription drugs. See *Alexander v. Danek Med., Inc.* 37 F. Supp. 2d 1346, 1349-50 (M.D. Fla. 1999) (granting summary judgment on design defect claim because plaintiff did not identify defect in metallic fixation devices used to treat lumbar spine disease); *Savage v. Danek Med.,*, 31 F. Supp. 2d 980, 983-84 (M.D. Fla. 1999) (granting summary judgment on design defect claims because plaintiff did not identify defect in bone screws implanted during back surgery).

Arnett testified as to her belief that "there are other alternatives out there that are metabolically safer" than Seroquel.[123] Dr. Arnett explained that "[i]n light of the fact that there were other drugs without those metabolic abnormalities that could be used to treat psychoses, in that respect Seroquel was unsafe."[124] Likewise, Plaintiffs' expert Dr. Laura Plunkett testified as to her belief that "there are safer alternatives" to Seroquel.[125] Dr. Plunkett further opined: "I believe that if you look at Seroquel, it should not be a first-line agency necessarily because the metabolic risks of this drug are different from some of the other risks, and that is above and beyond the neuromuscular risks."[126]

2. *Under Florida Law, Plaintiffs Are Not Required To Identify A Safer Alternative Design of Seroquel.*

AstraZeneca's contention that Plaintiffs must identify a safer alternative design to withstand summary judgment on their design defect claims is unavailing. As the Florida Court of Appeal for the Fourth District recently explained: "We find no case which holds that a plaintiff is required to show a safer alternative design in order to prevail on a strict liability design defect claim. Rather, it appears to be one factor which can be demonstrated and argued to the jury." *Liggett Group, Inc. v. Davis*, 973 So. 2d 467 (Fla. Dist. Ct. App. 2007). While section 2(b) of the Restatement (Third) of Torts: Products Liability arguably requires a plaintiff to identify a safer alternative design, strict liability claims in Florida are still governed by section 402A of the Restatement (Second) of Torts, which does not require identification of a safer alternative design. *West v. Caterpillar Tractor Co.*, 336 So. 2d 80,

---

123 Second Deposition of Donna K. Arnett, M.S.P.H., dated Oct. 7, 2008 ("Arnett 1st Dep."), at 253:5-7 (Exhibit 46).

124 *Id.* at 253:15-18 (Ex. 46).

125 First Deposition of Laura M. Plunkett, Ph.D., DABT, dated Oct. 2, 2008 (Plunkett 1st Dep."), at 132:12-13 (Exhibit 47).

126 *Id.* at 132:13-17 (Ex. 47).

87 (Fla. 1976) (adopting "the doctrine of strict liability as stated by the A.L.I. Restatement (Second) of Torts § 402A"); *see also Liggett*, 973 So. 2d at 473 ("[T]he Restatement (Third) of Torts has not yet been adopted in Florida."); *McConnell v. Union Carbide Corp.*, 937 So. 2d 148, 151 n.4 (Fla. Dist. Ct. App. 2006) ("We purposefully forbear from any reliance on the Restatement (Third) of Torts and its risk-benefit analysis until the supreme court has recognized it as correctly stating the law of Florida."); *Force*, 879 So. 2d at 107 ("[T]he Restatement (Third) position has not been adopted by any appellate court in Florida."). [127]

3. Plaintiffs' Experts' Testimony Does Not Undermine Their Design Defect Claims.

AstraZeneca blurs the distinction between design defectiveness and proximate causation by arguing that Plaintiffs cannot establish any design defect under Florida law

---

[127] In fact, the Florida Supreme Court is currently considering (1) whether a plaintiff is required "to establish an alternative safer design in order to prevail on a design defect claim for an inherently dangerous product, and (2) whether Florida should "adopt the Restatement (Third) of Torts for design defect cases." *Liggett Group, Inc. v. Davis*, 973 So. 2d 684, 685 (Fla. Dist. Ct. App. 2008) (mem.) (granting motion to certify these two questions to the Florida Supreme Court).

AstraZeneca's reliance on *Edic v. Century Prods. Co.* is misplaced. 364 F.3d 1276, 1279-80 n.2 (11th Cir. 2004). Although the *Edic* court indicated that Florida law requires a plaintiff to identify a safer alternative design to prevail on a design defect claim, the court only cited *Scheman-Gonzalez v. Saber Manufacturing Co.* as authority for that proposition. *Id.* (citing *Scheman*, 816 So. 2d 1133, 1139 (Fla. Dist. Ct. App. 2002). In *Scheman*, however, the Florida's Fourth District Court of Appeal simply found the Restatement (Third) of Torts "instructive." 816 So. 2d at 1139; see also (citing in support of this proposition merely found the Restatement (Third) of Torts "instructive." *Id.*; *see also Liggett*, 973 So. 2d at 478 (Warner, J., concurring) ("We found the Restatement (Third) of Torts 'instructive' in. *Scheman* . . . . However, whether Florida should adopt the position of this new restatement is an issue that our supreme court should decide." (internal citation omitted)).

None of the other cases cited by AstraZeneca stand for the proposition that a plaintiff must identify a safer alternative design to prevail on a design defect claim under Florida law. *See Kohler v. Marcotte*, 907 So. 2d 596, 599-600 (Fla. Dist. Ct. App. 2005) (quoting but not applying Restatement (Third) of Torts § 2 in reversing denial of directed verdict for component manufacturer); *Warren ex rel. Brassell v. K-Mart Corp.*, 765 So. 2d 235, 237-38 (Fla. Dist. Ct. App. 2000) (quoting but not applying Restatement (Third) of Torts § 2 in negligent entrustment case); *Adams v. G.D. Searle & Co.*, 576 So. 2d 728, 732-33 (Fla. Dist. Ct. App. 1991) (applying Restatement (Second) of Torts § 402A). In *Marzullo v. Crosman Corp.*, plaintiffs alleged that a BB gun was defectively designed because it had more firepower than they or any other reasonable person would have expected. 289 F. Supp. 2d 1337, 1342 (M.D. Fla. 2003). In granting summary judgment in favor of defendant on the ground that muzzle velocity was "not a condition of the gun and, by definition, cannot be a defective or unreasonably dangerous condition," the *Marzullo* court simply noted that plaintiffs did not identify a safer alternative design. *Id.* at 1343.

based on (1) a temporal relationship between use of the product and injury, or (2) the assertions of experts that Seroquel can cause injury or death, or that the reported rate of injuries from Seroquel use is significantly higher than the rate of other antipsychotics. (Mem. at 55-56.) Further, although either of these factors alone might not be sufficient to establish that a product's design is defective, AstraZeneca does not argue that these factors taken together, or in combination with other factors, cannot establish that a product's design is defective under Florida law.

Lastly, AstraZeneca's argument that Plaintiffs' design defect claims are inadequate as a matter of law because their experts are not of the "opinion that no reasonable physician would ever prescribe Seroquel for any patient or any class of patients" fails both for lack of evidentiary support and because it is based on section 6(c) Restatement (Third) of Torts, which has not been adopted in Florida. (Mem. at 56-57 (citing Restatement (Third) of Torts: Products Liability § 6(c)).[128] For the same reason, AstraZeneca's suggestion that Plaintiffs' design defect claims cannot survive summary judgment because some of their prescribers still prescribe Seroquel is unavailing.

CONCLUSION

For all the foregoing reasons, as well as the reasons stated in Plaintiffs' General

---

[128] Section 6(c) of the Restatement (Third) of Torts: Products Liability, which Florida has not adopted, provides:

> A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.

AstraZeneca also cites *Beale* as support for this proposition, but the *Beale* court did provide any authority for its suggestion that a plaintiff cannot prevail on a design defect claim under Florida law in the face of evidence that a prescription drug is appropriate for some patients. 492 F. Supp. 2d at 1369 n.11.

Causation Response and Plaintiffs' Case-Specific Causation Response, incorporated herein by reference, AstraZeneca's Motions for Summary Judgment should be denied.

DATED: November 24, 2008

Respectfully submitted,

By: /s/ K. Camp Bailey

F. Kenneth Bailey Jr.
K. Camp Bailey
Fletcher V. Trammell
Robert W. Cowan
BAILEY PERRIN BAILEY
440 Louisiana St., Suite 2100
Houston, Texas 77002
(713) 425-7100 Telephone
(713) 425-7101 Facsimile
kbailey@bpblaw.com
cbailey@bpblaw.com
ftrammell@bpblaw.com
rcowan@bpblaw.com
Co-Lead Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 24th day of November, 2008, I electronically filed the foregoing: PLAINTIFFS' OMNIBUS LEGAL MEMORANDUM RESPONDING IN OPPOSITION TO ASTRAZENECA'S SUMMARY JUDGMENT MOTIONS IN THE FLORIDA TRIAL POOL "GROUP ONE" CASES with the Clerk of the Court by using the CM/ECF system which will send a Notice of Electronic Filing to the counsel listed on the attached Service List.

/s/ Robert W. Cowan
Robert W. Cowan

Marjorie Shiekman at Dechert LLP — via email: Marjorie.shiekman@dechert.com
Louise Moyer at Dechert, LLP — via email: louise.moyer@dechert.com