

**UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION**

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This Document Relates to: All Cases

**ASTRAZENECA’S BRIEF IN SUPPORT OF PARTIAL SUMMARY JUDGMENT
IN ALL MDL CASES BASED ON FEDERAL PREEMPTION**

AstraZeneca LP and AstraZeneca Pharmaceuticals LP (“AstraZeneca”) have briefed and argued federal preemption as it applies to the Florida “Group One” cases. *See* Omnibus Legal Memorandum In Support Of AstraZeneca’s Summary Judgment Motions In The Florida Trial Pool “Group One” Cases, filed on November 3, 2008 (Doc. No. 1113; hereinafter “Omnibus Br.”). On March 12, 2009, this Court ordered AstraZeneca (Doc. No. 1366) to brief federal preemption as to *all* MDL cases, in light of the United States Supreme Court’s recent decision in *Wyeth v. Levine*, 555 U.S. ___, 2009 WL 529172 (Mar. 4, 2009) (“*Levine*”), addressing preemption of state-law inadequate warning claims. Accordingly, this brief seeks partial summary judgment in all MDL cases on the following two failure-to-warn and inadequate warning claims asserted by the Plaintiffs in this MDL (“Plaintiffs”):

- (1) Plaintiffs’ claim that AstraZeneca violated state laws by failing to *abandon the classwide diabetes and hyperglycemia warning* crafted by the federal Food and Drug Administration (“FDA” or the “Agency”) and mandated by FDA for all atypical antipsychotic medications, including Seroquel, and by failing instead to implement some different warning based on Seroquel-specific data. AstraZeneca seeks a ruling that this claim is preempted by FDA’s federally mandated warning through June 2007, when

AstraZeneca completed its analysis of glucose regulation data from two recent clinical studies, Trials 126 and 127; and

- (2) Plaintiffs' claim that AstraZeneca violated state laws by failing to include in its Seroquel labeling a *contraindication*, such as that mandated by the Japanese Government for Japan, instructing that *Seroquel should not be used by those with diabetes or a history of blood glucose problems*. AstraZeneca seeks a ruling that this claim is preempted through the present date.

This brief does not seek relief on all preemption grounds that might apply to these cases, or as to all time periods, because some claims may be preempted on grounds that depend on the facts of a particular case and the state law applicable to that case. AstraZeneca understands the Court's recent Order to seek supplemental briefing on preemption of those state-law inadequate warning claims that remain preempted after *Levine*, and which are now ripe for resolution by this Court on an MDL-wide basis. Thus, AstraZeneca respectfully reserves briefing on other aspects of its federal preemption defense that cannot now be determined on an MDL-wide basis. For instance, AstraZeneca reserves preemption briefing on Plaintiffs' "design defect" claims and any "fraud on the FDA" claims or theories – because consideration of preemption as to these claims and theories depends on case-specific facts as well as the underlying state law governing each Plaintiff's claims.¹ AstraZeneca also reserves briefing on Plaintiffs' diabetes and hyperglycemia

¹ To cite but one example, the Supreme Court in *Buckman Co. v. Plaintiffs' Legal Comm.* held that "state-law fraud-on-the-FDA claims conflict with, and are therefore impliedly preempted by, federal law." 531 U.S. 341, 348-39, 351 (2001). In those cases governed by Michigan or Texas state law (among other states), AstraZeneca maintains that Plaintiffs' failure-to-warn claims will be barred by state statutes providing that a pharmaceutical company that has provided FDA-approved labeling cannot be held liable under state-law inadequate warning claims, subject to an exception where Plaintiffs prove that the defendant committed a fraud on FDA in connection with FDA-approved labeling. Whether and to what extent *Buckman* operates to preempt application of the statutory "exception" in those Seroquel cases governed by such state statutes is a context-specific ruling that should await further briefing and consideration in appropriate Seroquel cases on a properly focused record at a later time. *See, e.g., Garcia*

warning claims for the periods after June 2007 and prior to FDA's federally mandated classwide warning (because those arguments will arise only in a smaller subset of MDL cases depending on the dates of each individual's Seroquel usage, and might also be raised on motions *in limine*), as well as any Plaintiffs' weight-gain warning theories (because they likewise should be considered in the context of the actual case-specific facts and theories asserted by each Plaintiff). In those individual cases where the remaining aspects of AstraZeneca's preemption defense actually arise, AstraZeneca will file individual motions for summary judgment or motions *in limine* at the appropriate time in each case.

This brief is thus limited to two of Plaintiffs' claims that will affect all of the MDL cases. Below, AstraZeneca shows that the regulatory record here, unlike that in *Levine*, clearly supports AstraZeneca's preemption arguments as to the two inadequate warnings claims that are the subject of this supplemental preemption briefing.

I. INTRODUCTION

In *Wyeth v. Levine*, the United States Supreme Court considered whether federal law preempted an individual's claim that FDA-approved labeling was insufficient to warn her doctor of the risks of administering a drug via a particular method (called an "IV-push"). The drug at issue was Phenergan, which provides relief from nausea. If an IV-push is administered incorrectly, Phenergan "causes irreversible gangrene" that can lead, as it did for Ms. Levine, to the loss of a limb. 2009 WL 529172, at *2. Ms. Levine contended that, given the huge risks of the IV-push method as compared to less-risky alternatives, and Phenergan's modest benefits, the warnings about an IV-push were inadequate.

v. *Wyeth-Ayerst Labs.*, 385 F.3d 961, 967 (6th Cir. 2004); *Ledbetter v. Merck & Co.*, 2007 WL 1181991, **2-6 (Tex. Dist. Apr. 19, 2007).

The Supreme Court rejected Wyeth's preemption defense. The Court found no clear evidence in the record that FDA would have rejected a stronger warning had Wyeth proposed one. *Id.* at *9. To the contrary, the record showed "that the FDA had *not* made an affirmative decision to preserve the IV-push method," and had given no more than "passing attention to the issue" of how strong the warning should be. *Id.* at *4, *9 (emphasis added). The record also contained data that the Court found both Wyeth and FDA could have analyzed, but did not – including "at least 20 incidents prior to [plaintiff's] injury in which a Phenergan injection resulted in gangrene and an amputation." *Id.* at **8-9. The Court therefore concluded that Wyeth – which had waited until after trial to raise the preemption defense – had not presented "clear evidence" that FDA would not have approved a stronger warning about the risks of an IV-push method, or shown that allowing Levine's claim would frustrate the achievement of Congress's and the Agency's goals. *Id.* at *9, *13.

Although the Supreme Court rejected Wyeth's preemption defense on the limited record before it, the Court did not reject preemption. Rather, the Court separately analyzed the two types of implied conflict preemption – impossibility and frustration of congressional purpose – and found, after a detailed factual review, that neither applied in Ms. Levine's case. The Court took care to acknowledge, however, that in another case, with different facts, preemption may be warranted. *See, e.g., id.* at *13.

The factual record here is the opposite of that in *Levine*, and therefore warrants preemption. Here the Agency neither gave mere "passing attention" to the issue nor failed to analyze relevant data. To the contrary, FDA expressly took responsibility upon itself *both* for deciding what the data showed about the relationship between Seroquel and diabetes, and for articulating its conclusions as to what the Seroquel labeling should say on this very point.

First, FDA asked for, received, and analyzed glucoregulatory data relevant to the relationship between Seroquel and hyperglycemia and diabetes. Second, after studying this and other data, *FDA itself* then wrote a carefully crafted classwide warning on this precise issue, applicable to all drugs in the class, and mandated that AstraZeneca include that warning exactly as directed by FDA in Seroquel's labeling. Unlike the Phenergan labeling at issue in *Levine*, the Seroquel labeling therefore reflects FDA's considered judgment on the association between Seroquel and hyperglycemia and diabetes based on FDA's own careful assessment of the underlying science. At that point, it is clear that AstraZeneca could not have obtained approval from FDA for labeling expressing a materially different scientific judgment about the relationship between Seroquel and hyperglycemia and diabetes than what FDA determined and mandated, because AstraZeneca did not have evidence supporting a "stronger" warning.

AstraZeneca did not have evidence supporting a diabetes or hyperglycemia label change until it assessed the results of Trials 126 and 127. Thus, at the very least, from the period between FDA's mandated warning, and AstraZeneca's assessment of the results of Trials 126 and 127, federal law preempts claims that AstraZeneca should have provided a different warning about the relationship between Seroquel and diabetes. It would have been impossible for AstraZeneca to have obtained approval from FDA for a different warning, because AstraZeneca lacked the evidence to support it. Moreover, allowing state-law claims that may require a regulated entity to abandon FDA-mandated classwide labeling and instead publish a scientific judgment about a drug's linkage to adverse events that is different from the one that FDA expressly arrogated to itself to determine, and which it did determine on a classwide basis, would – in these circumstances – frustrate Congress's purposes and objectives in delegating regulatory authority to FDA.

Accordingly, as explained further below, this Court should grant AstraZeneca's motion for partial summary judgment on the narrowed grounds of implied conflict preemption that AstraZeneca presses herein in the wake of *Levine*.

II. SUMMARY OF RELEVANT SEROQUEL FDA REGULATORY HISTORY

AstraZeneca incorporates by reference its discussion of the FDA regulatory framework and the extensive FDA regulatory history concerning Seroquel that was set forth at pages 6 through 17 of its Omnibus Legal Memorandum (Doc. No. 1113). The FDA Seroquel regulatory history is undisputed before this Court. In what follows, AstraZeneca highlights particular aspects of the undisputed FDA regulatory history for Seroquel that are directly implicated by the implied conflict preemption arguments advanced below in Part IV.A. and IV.B., *infra*. The undisputed record establishes that – since FDA first approved Seroquel in 1997 – FDA and AstraZeneca have engaged in a detailed study of the risks of diabetes and hyperglycemia that may be associated with Seroquel. FDA's review and analysis of the underlying science has been part of its broader analysis of all other medicines in the "class" of atypical antipsychotic medications, and in 2003 culminated in FDA's determination to create and to mandate a particular classwide warning concerning the risks of diabetes and hyperglycemia – which FDA crafted itself based on its own determinations about the underlying science and found to be in the public interest, and which remains in effect to this day.

A. FDA's September 2003 Class Labeling Change

In September 2003, based on years of study concerning glucose-related risks of Seroquel and atypical antipsychotic use (*see* Omnibus Br. at 13-14), FDA mandated a classwide diabetes/hyperglycemia labeling change for all atypical antipsychotic medications, including Seroquel. Sept. 11, 2003 Ltr. from Russell Katz, M.D. (FDA) to AstraZeneca (hereinafter "Sept. 11, 2003 FDA Ltr.") (Exhibit ("Ex.") 1) at 1. For the first time, in late 2003, FDA concluded

that risk disclosure about diabetes and hyperglycemia should be in the labeling's "Warnings" section, not the "Adverse Reactions" section where those risks had previously been addressed in Seroquel's FDA-approved labeling. *Id.* at 1-2. The diabetes/hyperglycemia warning carefully calibrated and imposed by FDA provides:

WARNINGS . . .

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar 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, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. . . .

Jan. 12, 2004 final approved labeling (Ex. 2) at 9.

As FDA explained when promulgating the classwide warning that FDA wrote itself, the Agency's labeling change reflected and embodied its expert conclusions about what the scientific data would support. Sept. 11, 2003 FDA Ltr. (Ex. 1) at 2 (stating that the "labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus"). Specifically, in mandating as a matter of federal law that AstraZeneca provide FDA's classwide warning concerning the risks of hyperglycemia and diabetes, FDA determined that its review of the relevant science required certain qualifications or caveats to be included in the

“Warnings” – including that: (i) “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”; and (ii) “the *relationship* between atypical antipsychotic use and hyperglycemia-related adverse events *is not completely understood*.” *Id.* at 1 (emphasis added). FDA also required the labeling to warn physicians to monitor patients with “established diagnos[e]s of diabetes” or “risk factors” for the condition. *Id.*

Consistent with FDA’s directive to submit revised labeling incorporating the FDA-drafted classwide “Warnings,” *see id.* at 2, AstraZeneca did so in November and December, 2003. *See* Jan. 12, 2004 Ltr. from Russell Katz, M.D. (FDA) to AstraZeneca (hereinafter “Jan. 12, 2004 FDA Ltr.”) (Ex. 3) at 1 (discussing AstraZeneca’s submissions). On January 12, 2004, FDA approved the revised Seroquel labeling implementing FDA’s classwide “Warnings,” and explicitly required as a matter of federal law that Seroquel’s final labeling “must be identical.” *Id.*; *see* Jan. 12, 2004 final approved labeling (Ex. 2); *see generally* *Levine*, 2009 WL 529172, at *4.

B. FDA’s Continued Evaluation And Reaffirmation Of Its Classwide Warning

When FDA mandated its classwide labeling change, the Agency recognized that the classwide warning it wrote and required to be given “reflect[ed] the currently available information” about diabetes-related risks; at the same time, FDA “acknowledge[d] that additional labeling changes may be required as new information becomes available.” Sept. 11, 2003 FDA Letter (Ex. 1) at 2 (outlining issues related to diabetes risk that “require[d] additional research”). Consistent with this directive, AstraZeneca and FDA remained in a continuing dialogue over these risks with respect to Seroquel, while FDA also continued to study these risks across the entire class of atypical antipsychotic medications. For instance, on April 8, 2004,

FDA requested that all atypical manufacturers submit data related to “an association between metabolic abnormalities and the use of atypical[s].” Apr. 8, 2004 Ltr. from Russell Katz, M.D. (FDA) to AstraZeneca (Ex. 4) at 1. AstraZeneca complied. *See* Excerpts of AstraZeneca’s Response to FDA Request for Information: Metabolic Abnormalities (July 9, 2004) (Ex. 5). In June 2005, FDA conducted another updated literature review of all atypical antipsychotics. *See* Review of Clinical Data (June 1, 2005) (Ex. 6). FDA’s reviewing officer noted that, although there had been a number of studies published since the Agency’s 2003 literature review and imposition of FDA’s classwide warning, “there does not appear to be clear evidence *to support changes in our position about this relationship*” between atypical antipsychotics and diabetes. *Id.* at 11-12 (emphasis added). FDA committed itself to further study of the risks. *See id.* at 12.

C. Based On The Evaluation Of New Scientific Data In 2007, AstraZeneca Revised Its Labeling Concerning Diabetes And Hyperglycemia-Related Risks

AstraZeneca continued to study the safety and efficacy of Seroquel. In particular, two long-term placebo-controlled clinical trials (Trials 126 and 127) designed to assess Seroquel’s efficacy for treatment of bipolar maintenance produced data relevant to glucose-related risks. *See, e.g.*, Study Synopsis, Trial 126 (June 19, 2007) (Ex. 7) at 1, 12, http://www.astrazenecaclinicaltrials.com/_mshost2715844/content/content/resources/media/2958892/4205558; Study Synopsis, Trial 127 (June 19, 2007) (Ex. 8) at 1, 11, http://www.astrazenecaclinicaltrials.com/_mshost2715844/content/content/resources/media/2958892/4205572; *see also* Deposition of Martin Brecher, M.D. (Ex. 9) (“Brecher Dep.”) at 411, 1035-36.

The last patients completed Trials 126 and 127 in October 2006 and September 2006, respectively. *See* Study Synopsis, Trial 126 (Ex. 7) at 1; Study Synopsis, Trial 127 (Ex. 8) at 1. The data from these studies were then collected from the hundreds of participating study centers, entered into databases for analysis, and subjected to numerous other data management

procedures designed to extract usable data (*e.g.*, unblinding the data). *See* Excerpt of Trial 126 Clinical Study Report (Ex. 10) at §5.6.3; Excerpt of Trial 127 Clinical Study Report (Ex. 11) at §5.6.3. Only after completing these procedures was AstraZeneca able to begin studying data from Trials 126 and 127. *See* Brecher Dep. (Ex. 9) at 45-46 (testifying that a usable data set was available in late 2006).

After conducting a “standard analysis” of the trial data “in late 2006 and early 2007,” in February 2007, the company “began an intensive review of the glucose results” from the trials. *Id.* at 45-47; *see also id.* at 47-48 (explaining that in February, AstraZeneca concluded that “questions around Seroquel and glucose metabolism . . . necessitated further analysis”). AstraZeneca spent the next three months conducting additional analyses of this data. *Id.* at 48-49; *see id.* at 59-62, 1037-38 (discussing analyses). The company then held a Safety Evaluation and Review Meeting (“SERM”) on June 8, 2007, to evaluate comprehensively glucose risks associated with Seroquel. *See* Deposition of Ronald Leong, M.D. (Ex. 12) at 251; *see also* Brecher Dep. (Ex. 9) at 1038-39. A week later, AstraZeneca finalized its core data sheet, concluding that the exposure adjusted rate of increased blood glucose (≥ 126 mg/dl) was 18.03 per 100 patient years taking Seroquel (10.7%) versus 9.53 for placebo. *See* AstraZeneca, *Clinical Overview: Glucose Dysregulation in Patients Treated With Seroquel* (June 2007) (Ex. 13) at 16; *see also* Brecher Dep. (Ex. 9) at 1038-39 (explaining that the SERM “concluded that the core data sheet needed to be changed” in light of Trials 126 and 127).

Within two weeks, AstraZeneca modified the Seroquel labeling to reflect this information; on June 22, 2007, AstraZeneca submitted a Changes Being Effected (“CBE”) supplement to FDA to present that new glucose data in Seroquel’s labeling. *See* June 22, 2007 Ltr. from AstraZeneca to FDA (Ex. 14) at 1-2; *see also* Brecher Dep. (Ex. 9) at 1038-41

(discussing what prompted the CBE submission). The revised labeling retained FDA's classwide warning, but immediately following that warning, AstraZeneca added a cross-reference to the new glucose data from Trials 126 and 127, which were detailed in the Adverse Reactions section of the labeling where FDA previously had approved the inclusion of detailed information from other clinical trials. *See* July 2007 labeling (Ex. 15) at 14-15, 35; *see* Excerpt of AstraZeneca 2.7.4 *Summary of Clinical Safety* (July 3, 2007) (Ex. 16) at 100 (setting forth same glucose data). Notably, Plaintiffs have conceded that AstraZeneca's CBE Supplement reflected *new* information on Seroquel and hyperglycemia resulting from a review of "recent study results." Plaintiffs' Omnibus Legal Memorandum Responding In Opposition To AstraZeneca's Summary Judgment Motions In the Florida Trial Pool "Group One" Cases (Doc. No. 1334; hereinafter "Pls.' Omnibus Resp.") at 58.

AstraZeneca implemented the new labeling in July 2007. A year later, on June 25, 2008, FDA concluded that the CBE supplement was "approvable" – *i.e.*, the labeling changes AstraZeneca previously implemented had been proper. *See* June 25, 2008 Ltr. from Thomas Laughren, M.D. (FDA) to AstraZeneca (Ex. 17) (hereinafter "June 25, 2008 FDA Ltr.") at 1.² FDA left in place the classwide warning, including the cross-reference AstraZeneca added to the hyperglycemia data. *See id.*³

² In the interim, FDA also had approved supplemental new drug applications involving Seroquel XR for the treatment of schizophrenia and schizophrenia maintenance in May and November 2007. *See* Nov. 15, 2007 Ltr. from Thomas Laughren, M.D. (FDA) to AstraZeneca (Ex. 18) at 1-3, <http://www.fda.gov/cder/foi/appltr/2007/022172s000ltr.pdf>. That labeling contained the same classwide warning discussed above. *See, e.g.*, November 2007 labeling (Ex. 19), <http://www.fda.gov/cder/foi/label/2007/022172lbl.pdf>; *see also* May 13, 2008 Ltr. from Thomas Laughren, M.D. (FDA) to AstraZeneca (Ex. 20) at 1 (approving July 2007 sNDA submission, including labeling incorporating the CBE changes), <http://www.fda.gov/cder/foi/appltr/2008/020639s025,se1-037,s038,s040ltr.pdf>; May 2008 labeling (Ex. 21), <http://www.fda.gov/cder/foi/label/2008/020639s025s037s038s040lbl.pdf>.

³ In the "approvable" letter, FDA also requested that AstraZeneca add language to the Adverse Reactions section of the labeling about the mean change in glucose from baseline in the Trial 126 and 127 patients, as well as in the previously conducted placebo-controlled short-term clinical trials. June 25, 2008 FDA

Meanwhile, as part of its ongoing study of Seroquel and its possible effect on glucose regulation, FDA requested that AstraZeneca provide a report collecting certain metabolic data gathered in placebo-controlled studies. *See* Jan. 8, 2008 Ltr. from Thomas Laughren, M.D. (FDA) to AstraZeneca (Ex. 22) (hereinafter “Jan. 8, 2008 FDA Ltr.”). In June 2008, AstraZeneca submitted to FDA an 1100-plus page report, presenting the data requested by FDA.

In October 2008, AstraZeneca submitted a supplemental new drug application for pediatric use. On December 4, 2008, AstraZeneca submitted a CBE supplement based on its review of pediatric safety data. On December 18, 2008, after studying AstraZeneca’s submissions, FDA requested that the company make changes to the “Warnings and Precautions” section of the labeling. Dec. 18, 2008 Ltr. from Thomas Laughren, M.D. (FDA) to AstraZeneca (Ex. 23) at 1 ¶ 2; *see id.* at 1 (accepting submission of “new safety information . . . as a CBE supplement, but “requesting that [AstraZeneca] reformat the information for better integration in the overall label”).⁴ FDA did not require AstraZeneca to make any changes to the longstanding classwide warning regarding diabetes and hyperglycemia-related risks, which FDA wrote and imposed in 2003. *See id.* at 1-2. FDA simply determined that the data for glucose changes that AstraZeneca had previously added to the Adverse Reactions section should “be elevated to the Warnings/Precautions section of the labeling,” *id.* at 1 ¶ 2, and that data for weight and lipid changes should be moved to the Warnings and Precautions section of the label. *Id.*

Ltr. (Ex. 17) at 1-2; *see also id.* at 2 (requesting AstraZeneca note limitations of study design in Trials 126 and 127); *id.* at 2-3 (requesting additional glucose data).

⁴ FDA recently revised its regulations governing labeling, and in doing so collapsed the formerly independent sections “Warnings” and “Precautions” into one section of the labeling entitled, “Warnings and Precautions.” *Compare* 21 C.F.R. § 201.57(c)(6) (effective June 30, 2006); *with* 21 C.F.R. § 201.57(e) (effective to June 29, 2006) (“Warnings”) *and id.* § 201.57(f) (“Precautions”).

AstraZeneca submitted new labeling complying with FDA's December 18, 2008 letter on January 26, 2009 and implemented that labeling. *See* January 2009 labeling (Ex. 24) at 1, 3-4, http://www.astrazeneca-us.com/cgi-bin/az_pi.cgi?product=seroquel&country=us&popup=no.

III. SUMMARY JUDGMENT STANDARD

AstraZeneca incorporates by reference the basic summary judgment standard as set forth on pages 18 through 19 of its Omnibus Legal Memorandum (Doc. No. 1113).

Summary judgment must be granted where, as here, the record evidence reveals “that there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law.” FED. R. CIV. PROC. 56(c). Pursuant to Rule 56(b), AstraZeneca may move “for summary judgment on all *or part* of [any] claim” asserted by Plaintiffs. FED. R. CIV. PROC. 56(b) (emphasis added). Indeed, partial summary judgment is appropriate to resolve individual legal claims within a larger action, or to resolve discrete legal “issues” within individual claims. *Barker v. Norman*, 651 F.2d 1107, 1123 (5th Cir. 1981) (emphasizing that, especially in cases involving “complicated fact patterns and multiple causes of action,” courts may grant summary judgment “as to some causes of action but not as to others, or *as to some issues but not as to others*”) (emphasis added);⁵ *Stillman v. Travelers Ins. Co.*, 88 F.3d 911, 914 & n.4 (11th Cir. 1996) (approving authority of district court to enter partial summary judgment, where appropriate, to “narrow[] the issues”); *accord In re Healthsouth Corp. Ins. Litig.*, 308 F. Supp. 2d 1253, 1265-67 (N.D. Ala. 2004). It is hornbook law that courts may grant motions for “partial summary ‘judgment’” in a ruling that “dispose[s] of only a single issue relevant to a

⁵ Fifth Circuit decisions prior to September 30, 1981 are binding precedent in the Eleventh Circuit. *Bonner v. City of Pritchard*, 661 F.2d 1206, 1209 (11th Cir. 1981) (en banc).

claim” and thereby serves to “resolve significant questions” and “focus the litigation on the true matters in controversy.” 11 MOORE’S FEDERAL PRACTICE – CIVIL § 56.40[1], [2] (2009).

Here, a partial summary judgment ruling that eliminates preempted claims and theories will “aid significantly in preventing the waste of private and judicial resources and time.”

Barker, 651 F.2d at 1123; *see also, e.g., Luna Gaming - San Diego LLC v. Dorsey & Whitney, LLP*, 2009 WL 587801, *2 (S.D. Cal. Mar. 6, 2009) (granting partial summary judgment “on Plaintiff’s negligent misrepresentation claim to the extent that it is based on events occurring before March 29, 2000”); *Brown v. McGraw-Hill Companies, Inc.*, 2007 WL 2479685, *9 (N.D. Iowa Aug. 29, 2007) (granting partial summary judgment “for the time period up to and including December 31, 2002”).

IV. ARGUMENT

The Supreme Court’s decision in *Wyeth v. Levine*, 555 U.S. ___, 2009 WL 529172 (Mar. 4, 2009), sets forth the framework for evaluating a preemption defense to a claim that a manufacturer failed adequately to warn of the risks of taking a prescription drug. First, preemption applies when it is “impossible” for the defendant “to comply with [a] state-law duty . . . without violating federal law.” *Id.* at *5 (citing *Fidelity Fed. Sav. & Loan Ass’n v. de la Cuesta*, 458 U.S. 141, 153 (1982)). Second, preemption applies when a “state tort action creates an unacceptable ‘obstacle to the accomplishment and execution of the full purposes and objectives of Congress.’” *Id.* (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)); *accord Crosby v. Nat’l Foreign Trade Council*, 530 U.S. 363, 372 (2000).

In *Levine*, the Court concluded that FDA’s approval of the Phenergan labeling did not preempt a state law challenge to the adequacy of the warnings about use of the IV-push method, given the “sparse” regulatory record and scant attention FDA had given to the particular risks

relevant to the plaintiff's claims. *Id.* at **3-4, 8-9. Here, in contrast, a clear and extensive evidentiary record demonstrates that FDA would not have approved material changes to Seroquel's labeling that Plaintiffs contend were required by state law. Moreover, the changes Plaintiffs seek here would have interfered with FDA's decision to address the relationship between Seroquel and diabetes and glucose control through a specific classwide warning that FDA itself prepared.

A. FDA's Mandated Classwide Diabetes And Hyperglycemia Warning Preempts Plaintiffs' State Law Claims For A Different Warning On That Subject At Least Until June 2007, When AstraZeneca Had New Data To Support A CBE Supplement

Plaintiffs' first inadequate warning claim that is the subject of AstraZeneca's current preemption motion in the wake of *Levine*, and which this Court may determine at this time on an MDL-wide basis, alleges that Seroquel's labeling was inadequate because AstraZeneca should have "abandoned" FDA's classwide warning addressing the risks about which Plaintiffs complain and instead provided a materially different Seroquel-specific warning based on risk data specifically pertaining to Seroquel. Pls.' Omnibus Resp. at 35. That claim is clearly preempted by federal law, including *Levine*.

1. Under The "Impossibility" Conflict Preemption Standard In *Levine*, And On This Record, Plaintiffs' State-Law Warning Claims About Diabetes And Hyperglycemia Are Preempted

In *Levine*, the defendant argued it was "impossible" to comply with FDA's federal labeling requirements for Phenergan and the additional state-law warning requirements the plaintiff claimed were required under state law. *See* 2009 WL 529172, at *7. But the Court concluded that defendant had "offered no such evidence" that this was true. *Id.* at *9. Specifically, the Court said that defendant needed "clear evidence that the FDA would not have approved" a stronger warning about the risks of administering Phenergan through the IV-push

method, and that “[o]n the record before us,” the Court saw “no such evidence.” *Id.* (emphasis added).

The Supreme Court’s scrutiny of the regulatory record in *Levine* makes clear that the defense of implied preemption turns on the *particular FDA regulatory record* with respect to the medicine at issue. Specifically, the *Levine* Court rejected the defendant’s preemption arguments because:

- (i) FDA had paid “no more than passing attention” to the strength of the warning about the IV-push method of drug administration;
- (ii) In the nearly 20 years following Phenergan’s initial approval, and for another 17 years after a 1981 FDA submission, FDA only “sparse[ly]” and “intermittently corresponded” with defendant regarding any aspect of the drug’s labeling;
- (iii) During that time, FDA did not mandate any different labeling or otherwise communicate with defendant about the labeling except on one occasion when, in response to a proposed change that the Court found did not materially strengthen the warning, FDA, without analysis, instructed defendant to “retain verbiage in current label”;
- (iv) Defendant “d[id] not argue that it supplied the FDA with an evaluation or analysis concerning the specific dangers” at issue;
- (v) Although it was unclear on the “limited” record “what newly acquired information Wyeth had or should have had about the risks of IV-push administration,” the plaintiff, Ms. Levine, introduced evidence of “at least 20” incidents where IV-push administration had led to gangrene and amputations since FDA first addressed the labeling;
- (vi) All conceded that the drug, when improperly injected into an artery, caused gangrene and caused Ms. Levine’s injury; and

(vii) “FDA had not made an affirmative decision,” in light of all of the above, that the evidence failed to support a stronger warning about the risks of administering Phenergan by the IV-push method.

2009 WL 529172, at **2-4, 8-9; *see also id.* at *13 (Breyer, J., concurring).

On that regulatory record, the Court concluded that, “as amputations continued to occur, Wyeth could have analyzed the accumulating data and added a stronger warning about IV-push administration of the drug.” 2009 WL 529172, at *8.

The regulatory record here stands in stark contrast to that in *Levine*. All of the elements that were missing in the regulatory record in *Levine* are present here. The regulatory record here shows that:

- FDA did not give merely “passing attention” to the strength of a company-crafted warning (*Levine*, 2009 WL 529172, at *9), but rather undertook, over several years, what the Agency itself described as a “comprehensive review” and “thorough assessment” of the diabetes and glucose-related risks about which Plaintiffs complain, which culminated in FDA’s September 2003 decision to mandate a classwide warning. *See Omnibus Br.* at 13 (quoting Ex. 11 thereto).
- Correspondence was not intermittent and sparse; during and after this review, FDA actively gathered data and analyses from all manufacturers of this class of drugs; and AstraZeneca “supplied the FDA” (*Levine*, 2009 WL 529172, at *9) with multiple evaluations and analyses addressing precisely the risks about which Plaintiffs complain. *See Omnibus Br.* at 13 (discussing Ex. 12 thereto, noting AstraZeneca’s submission entitled “safety information [t]o assess the possibility of a causal association between

Seroquel treatment and disturbances in glucose regulation”); *see also* pp. 6-8, *supra* (discussing revisions to label drafted and requested by FDA).

- Issues of causation are not conceded, but rather – as the language of FDA’s classwide warning illustrates – are highly complex and uncertain, and require and have received the Agency’s ongoing attention and expert evaluation.
- FDA itself has made an affirmative decision as to the warning physicians should receive, by deciding *itself* to craft the precise diabetes and hyperglycemia warning that Plaintiffs attack as inadequate under state law, *see* pp. 6-8, *supra*.
- FDA has further mandated under federal law that its carefully calibrated classwide warning must be provided by AstraZeneca in Seroquel’s labeling exactly as directed by FDA beginning in January 2004 – a warning that FDA determined to “reflect the currently available information about antipsychotic use and diabetes mellitus.” Sept. 11, 2003 FDA Ltr. (Ex. 1) at 2.

This record thus presents the polar opposite of what the Supreme Court found in *Levine*. Here, the Court must consider the preemptive effect of a warning that reflects the Agency’s own considered effort to evaluate the scientific basis for risks created by an uncertain relationship between a drug and certain side effects, and to balance the risks and benefits of how best to present its conclusions on that subject. This is precisely the level of FDA engagement that was missing in *Levine*. Indeed, the Agency’s engagement could not have been greater than it was here, because the Agency itself conducted the scientific analysis and then wrote the classwide warning that Plaintiffs now attack.

Consider the alternative for which Plaintiffs argue. According to Plaintiffs, state law required AstraZeneca immediately to “abandon[]” that FDA-crafted class warning and instead

provide some unspecified but materially different Seroquel-specific warning about diabetes and hyperglycemia. Pls.' Omnibus Resp. at 35. AstraZeneca could not have done that, because FDA certainly would have disapproved it. AstraZeneca had no new evidence or new analyses of existing evidence that FDA had not considered when FDA made its judgment; all of this had already been provided to FDA. AstraZeneca therefore had no evidentiary basis to support any decision to substitute some unspecified new warning for FDA's carefully considered scientific judgment.

The undisputed regulatory record therefore contains the "clear evidence" missing in *Levine* – *i.e.*, evidence that FDA "would not have approved" a decision or proposal by AstraZeneca literally to *abandon* FDA's mandatory classwide diabetes warning in favor of whatever Seroquel-specific warning Plaintiffs would have preferred. *Levine*, 2009 WL 529172, at *9. With Seroquel, unlike with Phenergan, FDA itself independently and exhaustively analyzed all of the relevant evidence and reached a final judgment as to the precise warning that physicians should receive, which it mandated AstraZeneca to give exactly as directed by FDA. It would have been "impossible" for AstraZeneca both to comply with FDA's mandate under federal law to publish FDA's classwide warning while at the same time *abandoning* that same FDA warning. *Id.* It is difficult to imagine a more stark preemptive conflict between federal and state law.

2. Plaintiffs' State-Law Claims Are Also Preempted Because They Impermissibly Frustrate The Achievement Of Congressional Objectives

Even if there were some doubt whether it was "impossible" for AstraZeneca to comply with both federal and state law – and there is none – the matters at issue here would still be preempted under the "obstacle" form of preemption. The objectives and purposes of Congress would be improperly frustrated where, as here, the Agency has specifically considered the proper

presentation and strength of the warning at issue in later litigation. *Levine* explicitly “recognize[s] that some state-law claims might well frustrate the achievement of congressional objectives.” 2009 WL 529172, at *13. For example, in his concurring opinion, Justice Breyer suggested that such a conflict may occur where a plaintiff’s inadequate warnings claim under “state tort law” would “interfere with the FDA’s desire to create a drug label containing a *specific set of cautions and instructions.*” *Id.* (Breyer, J., concurring) (emphasis added). That is what happened here.

Indeed, here, FDA not only had a “desire” to “create a drug label containing a specific set of cautions and instructions,” *id.*, the Agency *acted* upon that desire by writing the labeling itself. After years of carefully and comprehensively studying the issue across the drugs in the class of atypical antipsychotic medications, FDA exercised its congressionally delegated authority to mandate classwide labeling concerning the alleged risks of diabetes and hyperglycemia, and even took the extraordinary step of *itself* crafting the precise terms of the classwide warning. *See* pp. 6-8, *supra*. The Agency’s close review continued over time. In 2005, the FDA reviewer stood by the *specific set of cautions and instructions* embodied in its classwide warning, and explicitly rejected the proposition (advanced now by Plaintiffs in this litigation) that the classwide warning should be altered to differentiate risk information among the different atypical antipsychotics. *See* pp. 8-9, *supra* (discussing FDA reviewer’s conclusions in June 2005 that the existing data made differentiation between the drugs unsound). Indeed, even after reviewing the new evidence in AstraZeneca’s 2007 CBE, the Agency still adhered to its view that the classwide warning should be given and merely supplemented that warning with then-available new information. *See* June 25, 2008 FDA Ltr. (Ex. 17) at 1-2. Plaintiffs’ state-law claims attacking the adequacy of FDA’s “specific set of cautions and instructions” therefore stand as an obstacle

to FDA's desire to create and maintain a warning applicable to all atypical antipsychotics, which communicates what FDA determined to be the appropriate balancing of risks and benefits across this entire class of FDA-approved atypical antipsychotic medications.

This record stands in sharp contrast with the circumstances discussed in *Levine*. This case is not one in which FDA's "limited resources" prevented it from monitoring Seroquel or other atypical antipsychotics, or where state tort lawsuits were needed to "uncover *unknown* drug hazards." 2009 WL 529172, at *12 (emphasis added). Rather, even before this litigation, FDA was examining the very same risks about which Plaintiffs complain here. *See* pp. 6-9, *supra*. Indeed, this also is not even a case where the regulated entity had "superior access to information" about the risks than FDA did. *Levine*, 2009 WL 529172, at *12. To the contrary, FDA had superior access, because FDA was accumulating data on a classwide basis that was otherwise unavailable to AstraZeneca regarding the effects of other drugs, and so FDA had, by far, the best information to use in determining how to regulate the labeling for these medications in a manner that would protect patients while also not unduly discouraging beneficial use.

This extensive record of agency consideration contrasts sharply with that in *Levine*, where the Supreme Court found that there was no evidence FDA ever gave serious consideration to the risk-benefit tradeoffs of the particular method of drug administration at issue, and could not see how the benefits outweighed the risks. Here, FDA carefully considered the importance of having treatment options for serious and debilitating mental illnesses; evaluated the underlying science about a possible association with diabetes and glucose regulation – a complicated endeavor given the background risks of diabetes from other causes; determined that classwide labeling (on the very risks about which Plaintiffs complain) was the best approach; and

crafted the classwide warning itself. In short, the *Levine* Court left open that a future case could involve a preempting frustration of federal interests; this is such a case.

Moreover, allowing Plaintiffs' claims to proceed also would frustrate FDA's purposes and objectives in creating and enforcing its classwide warning here. It would effectively require companies to pursue the empty formality of going to FDA immediately upon receiving the Agency's classwide warning mandate to urge a different drug-specific warning approach that FDA necessarily considered but rejected. This would burden FDA and serve no purpose other than to reaffirm the obvious, *i.e.*, that the Agency considered the issue in the exercise of its administrative expertise and reached its judgment. Preemption should thus apply at least where, as here, FDA exercised its discretion to create and impose a classwide warning.

In sum, the evidence demonstrates that allowing Plaintiffs' state-law claims to go forward would obstruct FDA's efforts to resolve the issue of what warning physicians should receive concerning Seroquel and diabetes and hyperglycemia through a classwide warning that reflected FDA's own evaluation. After FDA engaged in a detailed study of the risks of Seroquel and other atypical antipsychotics – including taking action “to create a drug label containing a specific set of cautions and instructions” that could be supported by its expert review of all the then-“currently available information” – state-law claims that would have overridden those determinations present an unacceptable obstacle to FDA's regulation of Seroquel's labeling. Accordingly, Plaintiffs' warning claims conflict with federal law and are preempted.

3. Plaintiffs' Claims Are Preempted At Least Through June 2007, When AstraZeneca Implemented Additional Labeling On Glucose Results From Trials 126 And 127

Plaintiffs cannot credibly contend that AstraZeneca had a duty to reject FDA's classwide warning at the outset, or to abandon it *the day after* it went into effect. Under either or both the “impossibility” or “obstacle” strains of preemption discussed and applied in *Wyeth v. Levine*, any

such contention is squarely preempted. The real question before the Court, therefore, is the length of time in which FDA's classwide diabetes and hyperglycemia warning has preemptive effect, not whether it does at all.

Where, as here, FDA has comprehensively obtained and reviewed the available data concerning the risk at issue (across all the drugs in the class of atypical antipsychotic medications, not just Seroquel), and issued an express and considered judgment as to what should be said to physicians on this risk, that decision should preempt contrary state law duties to provide physicians a different message at least until there is some evidence that could reasonably support a change. Without such evidence, there is simply no basis on which to conclude that FDA would have approved a materially different warning; without an evidentiary foundation, any such approval would be arbitrary.

Plaintiffs have no competent admissible evidence that, between 2004 and 2007, AstraZeneca was in possession of "newly acquired information" – either "new data" or "new analyses of previously submitted data" – that was not provided to FDA and that reasonably could have supported a CBE Supplement materially altering FDA's views of the relationship between Seroquel and diabetes. *Levine*, 2009 WL 529172, at *7. Absent such evidence, it is sheer speculation on Plaintiffs' part that FDA would have approved a materially different statement of glucose-related risk for Seroquel than the statement that FDA – after years of active and exhaustive investigation – itself prepared. *See id.*; *see also, e.g., O'Bannon v. Union Pac. R.R. Co.*, 169 F.3d 1088, 1091 (8th Cir. 1999) ("theoretical issue of fact" insufficient to defeat summary judgment based on preemption); *Cordoba v. Dillard's, Inc.*, 419 F.3d 1169, 1181 (11th Cir. 2005) ("Speculation does not create a *genuine* issue of fact" sufficient to defeat "summary

judgment”) (emphasis in original; quotations omitted); *Border Collie Rescue, Inc. v. Ryan*, 418 F. Supp. 2d 1330, 1339 (M.D. Fla. 2006) (same).

The only new evidence during this period relevant to the diabetes/glucose warning to which Plaintiffs could reasonably point is the data generated by Trials 126 and 127. As described above, these two trials were undertaken to support AstraZeneca’s decision to seek approval for a new indication for Seroquel, for maintenance of treatment of bipolar disorder. The results of these trials provided data relevant to the relationship between Seroquel and diabetes/glucose regulation. AstraZeneca therefore evaluated the data with this purpose, and reported the results to FDA, along with a proposed change to the Seroquel labeling to account for the glucose results.

AstraZeneca is not seeking in this motion a judgment of preemption for the time period *after* it provided this data to FDA. But AstraZeneca does contend that these trials do provide a clear and logical endpoint for preemption based on FDA’s mandate in 2003 of a classwide warning.

B. Federal Law Preempts Plaintiffs’ State-Law Claims Premised On AstraZeneca’s Failure To Include The Japanese Contraindication In Its Seroquel Labeling In The United States, Including Florida.

Plaintiffs next advance an even more extreme warnings claim, asserting that state law imposed a duty on AstraZeneca to amend its label to “contraindicate” Seroquel for “persons who already have high blood sugar or suffer from diabetes.” Pls.’ Omnibus Resp. at 35; *see also id.* at 25-27. In support of their contention, Plaintiffs cite a Japanese Dear Doctor letter sent to Japanese physicians in November 2002, which reflects the Japanese Government’s regulatory determination that, in Japan, Seroquel “must not be administered to patients with diabetes or a history of diabetes.” *Id.* at 26 (quoting Japanese Dear Doctor letter). This warning claim

likewise is preempted, and, in all events, is not cognizable in light of this Court's *in limine* rulings to date.

First, Plaintiffs' duty to contraindicate claim is preempted by federal law because "FDA would not have approved a change to [Seroquel's] label" mandating that the drug not be prescribed to such patients. *Levine*, 2009 WL 529172, at *9. Seroquel has never been contraindicated for any class of patients in the United States. *See, e.g.*, January 2009 labeling (Ex. 24) at 1 ("Contraindications . . . none"). Moreover, in connection with its classwide warning, FDA explicitly affirmed that Seroquel *was approved* in the United States for use by those persons with diabetes and/or elevated blood glucose. *See* Sept. 11, 2003 FDA Ltr. (Ex. 1) at 1-2. Instead of contraindicating the drug for diabetics, FDA affirmatively chose to approve prescription of the drug to such persons while dictating that the label warn that "[p]atients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control." *Id.* at 1. Similarly, instead of contraindicating the drug for patients with elevated glucose, FDA wrote and required a warning that "patients with risk factors for diabetes" undergo baseline glucose testing and subsequent monitoring while using the drug, and that "[p]atients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing." *Id.* Furthermore, despite having since imposed additional glucose-related warnings, FDA continues to adhere to these views on contraindication today as expressed in the classwide warning. *See* January 2009 labeling (Ex. 24) at 3 ¶ 5.3; *see also id.* at 1, 2 ¶ 4 (no contraindications).

Given that FDA issued a warning making clear that Seroquel could be prescribed to such patients during the period relevant to the preemption defense asserted here, there is no question that FDA would not have approved a labeling change that contraindicated the very same use. As

such, Plaintiffs' claims are preempted. *See Levine*, 2009 WL 529172, at *9. Indeed, in light of *Levine*, it is especially significant that Plaintiffs' theory here is that state laws required a contraindication in Seroquel's labeling. There, the Court suggested that, if plaintiff were pursuing a state-law "duty to contraindicate claim" that conflicted with FDA's approach, conflict preemption may apply but the Court did not need to resolve that question. *Id.* at *5. Here, Plaintiffs' admission that their state-law warnings claims rest on precisely such a duty confirms that they are preempted. Pls.' Omnibus Resp. at 35.

Second, Plaintiffs' claims that AstraZeneca had a duty to contraindicate these uses in its labeling are preempted because they stand as an obstacle to FDA's execution of the FDCA scheme with respect to Seroquel. As discussed, after careful study of the risks of atypical antipsychotic use among diabetic patients or patients with risk factors for diabetes, FDA "create[d] a drug label containing a specific set of cautions and instructions" that expressly authorized Seroquel prescriptions for such patients. *Levine*, 2009 WL 529172, at *13 (Breyer, J., concurring). Plaintiffs' state-law claims strike at the heart of the FDCA regulatory scheme by seeking to prohibit altogether the approval of a drug for a use that FDA specifically determined was proper under the standards set by federal law. At bottom, Congress established FDA and delegated to it the authority to establish and enforce the regulatory requirements for drug approval and labeling in the United States. Congress has not delegated any authority to overseas regulators applying different standards. For state law to impose a duty to contraindicate predicated on the requirements of foreign regulators is fundamentally at odds with the scheme Congress established in the FDCA and would "frustrate the achievement of congressional objectives." *Id.* at *13 (majority op.).

Finally, aside from the preemption-based grounds for summary judgment, Plaintiffs' claims that state laws required AstraZeneca to follow Japanese labeling standards are not cognizable in light of this Court's ruling that evidence concerning "foreign regulatory actions and foreign label changes" is inadmissible. *In re Seroquel Prods. Liab. Litig.*, ___ F. Supp. 2d ___, 2009 WL 614764, at *5 (M.D. Fla. Mar. 11, 2009) (emphasis added), *affirming*, 2009 WL 223140, at *5-6 (M.D. Fla. Jan. 30, 2009). As this Court explained, "the probative value [of evidence of foreign regulatory actions and foreign label changes] is greatly overmatched by the jury confusion, waste of time, and unfair prejudice that would result." ___ F. Supp. 2d at ___, 2009 WL 614764, at *5. Similarly, Magistrate Judge Baker recognized that "allowing the evidence of foreign regulations and dispositions as to Seroquel – which the Court views as akin to evidence of foreign legal standards" – creates an unreasonable risk of jury confusion. 2009 WL 223140, at *6. Because Plaintiffs' warnings claims based on AstraZeneca's purported duty to contraindicate rest on evidence (*i.e.*, the Japanese regulatory experience with Seroquel) that is inadmissible in this litigation, those claims fail.

V. CONCLUSION

For the foregoing reasons, AstraZeneca respectfully requests that the Court enter partial summary judgment in AstraZeneca's favor ruling that, on the undisputed FDA regulatory record concerning Seroquel, the doctrine of implied conflict preemption operates to bar (1) Plaintiffs' claims that AstraZeneca violated state laws by failing to give a stronger warning on diabetes risk than the classwide warning mandated for all atypical antipsychotics by FDA for the time period ending June 2007, when AstraZeneca completed its analysis of glucose regulation data from two recent clinical studies, Trials 126 and 127; and (2) Plaintiffs' claims that AstraZeneca violated state laws by failing to include in its Seroquel labeling a contraindication, such as that mandated

by the Japanese Government for Japan, instructing that Seroquel should not be used by those with diabetes or a history of blood glucose problems. The preempted nature of these inadequate warning claims lends itself to MDL-wide determination by this Court at this time. The remaining aspects of AstraZeneca's preemption defense must await full consideration and resolution in the context of individual cases at a later time, on a full record tailored to facilitate determination of the particular aspect of the preemption defense where it actually arises.

DATED: March 23, 2009

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, on March 23, 2009, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system through which all participating parties are deemed served. I further certify that, by using the CM/ECF, the foregoing has been served on plaintiffs' liaison counsel, who is charged with serving any non-CM/ECF participants on the attached Service List.

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