IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

WENDY DOLIN, Individually and as Independent Executor of the ESTATE OF STEWART DOLIN, deceased, Plaintiff, v. SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE, a Pennsylvania Corporation, Defendant.	)	Case No. 12-CV-06403 Judge James B. Zagel

PLAINTIFF'S STATEMENT OF GENUINE ISSUES OF MATERIAL FACT IN OPPOSITION TO DEFENDANT GSK'S MOTION FOR SUMMARY JUDGMENT (FEDERAL PREEMPTION)

Plaintiff Wendy Dolin respectfully submits this Statement of Genuine Issues of Material Fact in Opposition to Defendant's Motion for Summary Judgment, pursuant to Federal Rule of Civil Procedure 56 and Local Rule 56-2:

Defendant's Uncontroverted Facts and Conclusions of Law	Plaintiffs' Response in Opposition And Supporting Evidence
A. Plaintiff's Allegations	
1. On July 10, 2010, Stewart Dolin allegedly began taking generic paroxetine (10 mg/day dose) manufactured by Mylan Pharmaceuticals Inc. (See Compl. ¶¶ 15-16.)	**Admit.**
2. On July 15, 2010, Mr. Dolin committed suicide at the age of 57. (Id. ¶¶ 14, 16, 17.)	**Admit.**
3. Plaintiff alleges that "[t]he paroxetine label in existence at the time of Stewart Dolin's death did not warn of the drug's association with an increased risk of suicidal behavior in adults despite GSK's knowledge of a statistically significant 6.7 times greater risk in adults of all ages. In fact, the label stated	**Admit.**

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the opposite – that the suicidality risk did not extend beyond the age of 24." (Id. ¶ 22.)	
4. Venue lies in this Court, pursuant to 28 U.S.C. § 1441(a), because the original action was filed in the Circuit Court of Cook County, Illinois, a state court located within this District. Further, the Northern District of Illinois is the "judicial district in which a substantial part of the events or omissions giving rise to the claim occurred" based on the allegations in Plaintiff's Complaint. 28 U.S.C. § 1391(b)(2).	**Admit.**
5. GSK is a pharmaceutical company and citizen of the State of Delaware and Plaintiff is a citizen of the State of Illinois.	**Admit.**
B. FDA's Review and Approval of Original NDA for Paxil, 1991 **Panel Meeting on Prozac, and Denial of Citizen Petitions (1989-1992)**	
6. The prescription medication Paxil® (paroxetine hydrochloride or "Paxil") is one of the class of medications known as selective serotonin reuptake inhibitors, or SSRIs. (See Declaration of John E. Kraus, M.D., Ph.D. in Support of Defendant GlaxoSmithKline LLC's Motion for Summary Judgment on Federal Preemption ("Kraus Decl.") ¶ 5, which is attached hereto as Exhibit A.)	**Admit.**
7. On November 20, 1989, SmithKline Beecham Pharmaceuticals ("SB") filed a NDA for paroxetine (Paxil) seeking FDA approval for the treatment of depression in adults. (Id. ¶ 15.)	**Objection.** Dr. John E. Kraus, the GSK employee who has submitted a declaration and on whom GSK relies for evidentiary support in its motion for summary judgment in this case, has no personal knowledge of the statements contained in paragraph 15 of his declaration. See Exh. 44, May 20, 2015 deposition of John E. Kraus, pp. 17:25-18:1 (Dr. Kraus did not begin working for GSK until 2005) and he does not properly authenticate the documents cited in his declaration. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding nor waiving this objection, **Admit**.
8. SB submitted extensive data to FDA,	**Objection.** Dr. Kraus has no personal

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including data describing any incidents of suicidality (i.e., suicidal thinking or behavior). (Id. ¶¶ 15-18, Exs. 1,3, attached to Kraus Decl.)	knowledge of statements contained in paragraphs 15-18 of his declaration and does not properly authenticate the documents cited in his declaration. **DISPUTED**. Plaintiff disputes that GSK submitted extensive data concerning suicidality to the FDA and further disputes that GSK described "any incidents of suicidality." In fact, GSK obscured the data concerning incidents of suicidality in its presentations to the FDA. See Plaintiff's Additional Proposed Findings of Fact ("PFF"), filed concurrently herewith at 1-23; 91-106.
9. In 1990, before FDA completed its review of Paxil, the press widely reported on public concerns about a possible relationship between suicidality and Prozac, another SSRI, stemming from an article published in February 1990 hypothesizing that antidepressants (particularly Prozac) might induce suicidal ideation in some patients. See M.H. Teicher, et al., "Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment," 147 Am. J. Psychiatry 207 (1990), attached as Ex. 1 to Declaration of Todd P. Davis in Support of Defendant's Submission Regarding Federal Preemption ("Davis Decl."), which is attached hereto as Exhibit B.	**Objection.** GSK has not properly authenticated the document cited in this paragraph. Notwithstanding nor waiving this objection, **Admit.**
10. In response to the Teicher article, in 1990 and 1991, two groups filed "Citizen Petitions," seeking the withdrawal of NDA approval for Prozac, the only FDA-approved SSRI at the time. These petitions alternatively sought warning statements in SSRI labeling regarding an increased risk of suicide. (Petitions attached as Ex. 2 & 3 to Davis Decl.)	**Objection**. **Irrelevant**. The document cited in this paragraph is not properly authenticated. Without waiving the foregoing objections, Plaintiff **does not dispute** that two groups submitted Citizen Petitions to the FDA concerning Prozac (one was to warn about the risk of suicide associated with Prozac and the other was to remove Prozac from the market.) Davis Decl., Exhs. 2 and 3 filed in support of GSK's motion for summary judgment (Federal Preemption).
11. Because of the questions raised about an increased risk of suicidality with Prozac, FDA requested a supplemental analysis of data on suicidality from SB while the Paxil NDA was under review. (Kraus Decl. ¶ 19, Ex. 2, attached to Kraus Decl.)	**Objection. Irrelevant. DISPUTED.** Dr. Kraus has no personal knowledge of the statements contained in paragraph 19 of his declaration (particularly the reasons for the FDA's actions) and does not properly authenticate the document cited. Plaintiff also

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	disputes the veracity of GSK's statements in this paragraph. In fact, when GSK responded to the FDA's request in 1991, GSK obscured the risk, as set forth more fully in PFF 10-23; exhibits 1-10, 69, and 72, and the declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, Dr. David Ross and Dr. Roger Grimson. When analyzed correctly, the net result was that patients on Paxil had a statistically significant greater than eight-fold increase in suicidal behavior. *Id.* *See also* Exhibits 1-10, 69, 72. GSK has no personal knowledge concerning FDA's reasoning for requesting data from GSK. In fact, the memo GSK cites in support of this paragraph stated that the FDA "does not see it [suicidality induced by SSRIs] as a real issue, but rather as a public relations problem" and that "the [FDA] does not think it is an issue, but it needs to be [publicly] addressed." Kraus Exh. 2. The FDA's lack of serious attention to the suicide issue further supports a rejection of the preemption defense. See *Wyeth v. Levine*, 129 S.Ct. 1187, 1197-98, 173 L.Ed. 2d 51 (2009), (hereinafter referred to as "*Levine*"). Without waiving the foregoing objection, Plaintiff **does not dispute** that the FDA requested data on suicidality from GSK while the Paxil NDA was under review.
12. On May 10, 1991, SB submitted a supplemental analysis based on its worldwide clinical database that concluded that patients randomized to Paxil therapy were at no greater risk for suicidal ideation or behavior than patients who were randomized to placebo or other active medication. (See id. ¶ 20, Ex. 3, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 20 of his declaration and does not properly authenticate the document cited in this statement. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff also **DISPUTES** the veracity of GSK's statements in this paragraph. In fact, when GSK responded to the FDA's request in 1991, GSK obscured the risk, as set forth more fully in PFF 1-23, and the declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, Dr. David Ross and Dr. Roger Grimson. When analyzed correctly, the net result was that patients on Paxil had a statistically significant greater than eight-fold increase in suicidal behavior. *Id.* *See also*

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	Exhibits 1-10, 69, and 72.
13. On June 19, 1991, Dr. Martin Brecher, the lead safety reviewer for the Paxil NDA, issued his Safety Review report (which was reviewed and approved on October 5, 1992, by Thomas Laughren, M.D., then the Group Leader for the FDA's department within the Center for Drugs with responsibility for reviewing the Paxil NDA) and stated, "there is no signal in this large data base that paroxetine exposes a subset of depressed patients to additional risk for suicide, suicide attempts or suicidal ideation." (Id. ¶ 22, Ex. 5 at 25, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 22 of his declaration and does not properly authenticate the document cited in this statement. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff also **DISPUTES** the veracity of GSK's statements in this paragraph. In fact, when GSK responded to the FDA's request in 1991, GSK obscured the risk, as set forth more fully in PFF 1-23 and the declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, Dr. David Ross and Dr. Roger Grimson. When analyzed correctly, the net result was that patients on Paxil had a statistically significant greater than eight-fold increase in suicidal behavior. PFF 9. *See also* Exhibits 1-10, 69, and 72. The FDA (reviewer Martin Brecher) relied on GSK's faulty data in making this statement. PFF 19.
14. In September 1991, FDA convened a Psychopharmacological Drugs Advisory Committee ("PDAC") meeting to consider further whether there was an association between SSRIs and suicide. (Id. ¶ 23.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 23 of his declaration and does not properly authenticate the document cited in this statement. Plaintiff also objects to this paragraph in its entirety because it is irrelevant. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment on federal preemption grounds, filed concurrently herewith. Plaintiff also objects to this paragraph in that GSK has no personal knowledge concerning FDA's reasoning for convening the 1991 PDAC. In fact, the memo GSK cited in paragraph No. 11 above stated that the FDA "does not see it [suicidality induced by SSRIs] as a real issue, but rather as a public relations problem" and that "the [FDA] does not think it is an issue, but it needs to be [publicly] addressed." Kraus Exh. 2. The FDA's lack of serious attention to the suicide issue further

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	supports a rejection of the preemption defense. *Levine* at 1197-98. Notwithstanding these objections, Plaintiff **does not dispute** that the FDA convened an advisory committee meeting in September 1991 to discuss "an association between the use of certain antidepressants, in particular Prozac, and suicidal thoughts and acts (suicidality) or other violent behavior." See Kraus Exh. 6.
15. In charging the Committee, FDA noted that "evaluation by FDA scientists, outside consultants, and by [FDA] physicians, have not led us to conclude that there is a differential rate of risk for Prozac related to suicidal thoughts, acts, or other violent behaviors." (Sept. 20, 1991 Transcript of the Proceedings of the PDAC, at 126, excerpts attached as Ex. 4 to Davis Decl.)	**Objection. DISPUTED.** The document cited in this paragraph is not properly authenticated, in fact, it is misquoted. Plaintiff also objects to this paragraph in its entirety because it is irrelevant. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment, filed concurrently herewith. This paragraph fails to demonstrate that GSK and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidality prior to Stewart Dolin's suicide. GSK has misrepresented the quote. The actual quote is: [A]n evaluation of such [clinical] sources, at least to date, evaluation by FDA scientists, outside consultants, and by our physicians, have not led us to conclude that there is a differential rate of risk for Prozac related to suicidal thoughts, acts, or other violent behaviors.
16. The PDAC unanimously agreed that no credible evidence existed to conclude that antidepressants cause the "emergence and/or intensification of suicidality and/or other violent behaviors." (Id. at 294.)	**Objection. DISPUTED. Misleading.** The document cited in this paragraph is not properly authenticated. Plaintiff also objects to this paragraph in its entirety because it is irrelevant. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment on federal preemption grounds, filed concurrently herewith.

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	While FDA found that the Prozac data it examined in 1991 were not sufficient to **require** a warning, comments from the committee members confirm that there was no authoritative determination prohibiting such a warning: "We agree the data are not great quality data" Exh. 73, PDAC transcript, p. 185; "I don't feel I have all the data," *id.*, p. 269; "I felt we were working with half a deck in terms of data ... we had very, very few data regarding other drugs" *Id.*, p. 334; "[N]obody in the agency dismisses the possibility that antidepressants in general or fluoxetine [Prozac] in particular may have ... the capacity to cause untoward injurious behaviors, acts, and/or intensify them." *Id.*, p. 126. The panel and FDA also concluded that further research was needed. (See PFF 121-148, Exhibits 66, 70, 74-75 and 97.) Moreover, the FDA has in recent years repeatedly admitted that it had not been appropriately evaluating the adult suicide data in earlier years. See PFF 121-148. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
17. Shortly after the meeting, FDA issued a statement providing the results of Eli Lilly's "analyses [relating to Prozac that] did not reveal any evidence to support the hypothesis that Prozac induces suicidality," and reflecting the conclusions of the PDAC that "there is no credible evidence of a causal link between the use of antidepressant drugs, including Prozac, and suicidality or violent behavior," and that no labeling changes were warranted. (Kraus Decl. ¶ 24, Ex. 6, attached to Kraus Decl.)	**Objection. Irrelevant. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 24 of his declaration and does not properly authenticate the document cited in this statement. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. See No. 16 above. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment, filed concurrently herewith.
18. In 1991 and 1992, FDA denied the	**Objection.** The document cited in this

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pending citizen petitions. In its denial of the Public Citizen petition, FDA concluded that "Upon analyzing the case reports, clinical trials, conclusions of the PDAC, and other relevant evidence, we have concluded that a change in labeling is not warranted at this time. There is no reasonable evidence of an association between the use of Prozac and suicidality." (Letter from FDA to Public Citizen Health Research Group (June 3, 1992), at 15, attached as Ex. 5 to Davis Decl.)	paragraph is not properly authenticated. Plaintiff objects to this paragraph in its entirety because it is irrelevant. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. See No. 16 above. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment. Without waiving the above objections, Plaintiff **does not dispute** that the FDA denied the citizen petitions seeking to either add suicide warnings to Prozac's label or to remove Prozac from the market. However, while FDA found that the Prozac data it examined in 1991 were not sufficient to **require** a warning, comments from the committee members confirm that there was no authoritative determination prohibiting such a warning: "We agree the data are not great quality data" Exh. 73, PDAC transcript, p. 185; "I don't feel I have all the data," *id.*, p. 269; "I felt we were working with half a deck in terms of data ... we had very, very few data regarding other drugs" *id.*, p. 334; "[N]obody in the agency dismisses the possibility that antidepressants in general or fluoxetine [Prozac] in particular may have ... the capacity to cause untoward injurious behaviors, acts, and/or intensify them." *Id.*, p. 126. The panel and FDA also concluded that further research was needed. See PFF 139, Exhibits 66, 70, 74-75 and 97. In one of the letters denying one of the citizen petitions, the FDA stated: "[A]n actual court finding of a causal relationship between Prozac and violent behavior would be relevant. In that event, the agency would be able to evaluate the scientific basis for the court's conclusion and consider whether [the] court's conclusion warranted a modification of its own position." Exh. 76. Moreover, the FDA has in recent years repeatedly admitted that it had not been

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	appropriately evaluating the adult suicide data in earlier years. See PFF 121-148. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
19. In denying the other petition, FDA concluded that "[t]he data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." (Letter from FDA to Citizens Commission on Human Rights (July 26, 1991), at 1, attached as Ex. 6 to Davis Decl.)	**Objection.** The document cited in this paragraph is not properly authenticated. Plaintiff also objects to this paragraph in its entirety because it is irrelevant. GSK cites no evidence which ties these purported actions by the FDA regarding another drug, Prozac, to Paxil. In fact, there is no evidence that the FDA panel considered any Paxil data. *See also* Plaintiff's motion to strike evidence in support of GSK's motion for summary judgment on federal preemption grounds. Notwithstanding these objections, Plaintiff **does not dispute** that the letter states: "The data and information available at this time do not indicate that Prozac causes suicidality or violent behavior." Davis Decl. Exh. 6, p. 1. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
20. As part of its review of the Paxil NDA, FDA asked the PDAC, an independent panel of outside experts, to evaluate the data on Paxil. (Kraus Decl. ¶ 25.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 25 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Without waiving the above objections, Plaintiff **does not dispute** that the FDA asked a panel of experts outside of the FDA to review Paxil data.
21. On October 5, 1992, during the PDAC panel meeting on Paxil, FDA officials presented their analysis of the Paxil NDA,	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 25-27 of his declaration and does

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including clinical trial data on safety and efficacy. (Id. at ¶¶ 25-27.)	not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Without waiving the above objections, Plaintiff **does not dispute** that data was presented to the advisory committee regarding paroxetine's efficacy and safety.
22. Dr. Paul Leber, Director of FDA's Division of Neuropharmacological Drug Products, reported: "the Division's clinical review team and its statistical consultants have concluded that the evidence submitted by SmithKline Beecham's NDA for paroxetine convincingly documents that paroxetine, a selective serotonin reuptake inhibitor, is both a safe and effective antidepressant." (Id. ¶ 25, Ex. 7 at 8, attached to Kraus Decl.)	**Objection. Irrelevant.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 25 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Without waiving the above objections, Plaintiff **does not dispute** that Dr. Paul Leber stated that, under FDA standards, paroxetine was considered "safe and effective." However, Plaintiff **DISPUTES** the veracity of this paragraph because the PDAC based its decision on GSK's faulty data. See PFF 1-23. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
23. During its deliberations, the panel specifically considered data relating to "the possible emergence of suicidal thinking and behavior." (Id. ¶ 26.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 26 of his declaration nor what the panel "specifically considered" and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **does not dispute** that data concerning "the possible emergence of suicidal thinking and behavior" was presented, however, when GSK responded to the FDA's request in 1991, GSK obscured the risk, as set forth more fully in PFFs 10-17 and the declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, Dr. David Ross and Dr. Roger Grimson. When analyzed correctly, the net result was that patients on Paxil had a statistically significant greater than eight-fold increase in suicidal behavior. PFF 9. The FDA relied on

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	GSK's faulty data in making this statement. PFF 19. The suicidal behavior risk rates in the NDA clinical trials only showed Paxil outperforming placebo when **false** placebo events were added by counting run-in events as post-baseline events.
24. One FDA official, Dr. Thomas Laughren, who at the time was the Group Leader for FDA's Psychopharmacology Unit and the Team Leader for the review of Paxil, specifically reported to the panel on suicidality: Ever since the concern was raised about fluoxetine [Prozac] being associated with suicidality, we have always looked at the other serotonin reuptake blockers with regard to [the] question of the possible emergence of suicidal thinking and behavior. This was the search strategy with paroxetine . . . . The bottom line here is that none of [the investigations] suggested any greater risk of suicidality for paroxetine than for the other comparator groups and, in fact, paroxetine actually beat the other groups on a number of these variables. So there was no suggestion here of emergence of suicidality with paroxetine. (Id. ¶ 26, Ex. 7 at 29-30, attached to Kraus Decl.)	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 29-30 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff disputes the veracity of Dr. Laughren's statement because, when GSK responded to the FDA's request in 1991, GSK obscured the risk, as set forth more fully in PFFs 10-17 and the declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, Dr. David Ross and Dr. Roger Grimson. When analyzed correctly, the net result was that patients on Paxil had a statistically significant greater than eight-fold increase in suicidal behavior. PFF 9. The FDA relied on GSK's faulty data in making this statement. PFF 19. The suicidal behavior risk rates in the NDA clinical trials only showed Paxil outperforming placebo when **false** placebo events were added by counting run-in events as post-baseline events. Dr. Laughren's statement actually proves the FDA's reliance on the false placebo data and the effect of that reliance on the FDA's labeling decisions in 1992. See declarations of Plaintiff's experts, Drs. Glenmullen, Healy, Grimson, and Ross.
25. The PDAC found Paxil safe and effective for use in the treatment of adult depression and voted unanimously in favor of approval. (Id. ¶ 27, Ex. 7 at 153-54, attached to Kraus Decl.)	**Objection. Irrelevant. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 27 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **disputes** the veracity of this paragraph because the PDAC based its decision on GSK's faulty data. See PFF 1-23. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding

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	Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
26. On December 29, 1992, having concluded that Paxil was safe and effective for its intended use, FDA issued an approval letter for Paxil. (Id. ¶ 28, Ex. 8, attached to Kraus Decl.)	**Objection. DISPUTED in part.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 28 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, Plaintiff **does not dispute** that the FDA sent an approval letter to GSK for Paxil in December 1992. However, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98. In fact, GSK's FDA liaison at the time, testified that GSK only proposed, for the "suicide" section of Paxil's label, the same language that already appeared in Prozac's label. Exh. 45 at 126:11-127:3.
27. FDA made clear that approval was conditioned on the verbatim use of the FDA approved prescribing information, which accompanied the letter. In pertinent part, FDA's approval letter stated: We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling attached. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter. Accompanying this letter (ATTACHMENT 1) is the labeling, including the revisions agreed to, that	**Objection. DISPUTED in part. Misleading.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 28 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, Plaintiff **does not dispute** that the FDA sent an approval letter to GSK for Paxil in December 1992, which included labeling GSK and FDA had agreed upon. However, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98. In fact, GSK's FDA liaison at the time, testified that GSK only proposed, for the "suicide" section of

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should be used for marketing this drug product. The attached labeling is identical to the draft that we mutually agreed to in our teleconference on December 29, 1992. These [labeling] revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug. (Id. ¶ 28, Ex. 8 at 1, attached to Kraus Decl.)	Paxil's label, the same language that already appeared in Prozac's label. Exh. 45 at 126:11-127:3.
28. The original FDA-approved labeling did not include any warning or other statement indicating that there was an increased risk of suicide or suicidality from Paxil. The FDA-required class labeling for antidepressants, including Paxil, contained the following precaution about suicide: Suicide - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. (Id. ¶ 29, Ex. 8, Attachment 1, at 5, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 29 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, Plaintiff **does not dispute** that the original FDA approved labeling did not include a warning concerning suicide. However, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98. In fact, GSK's FDA liaison at the time, testified that GSK only proposed, for the "suicide" section of Paxil's label, the same language that already appeared in Prozac's label. Exh. 45 at 126:11-127:3.
C. FDA Approval of New Indications and Formulations of Paxil (1995-2004)	
29. Since Paxil's original approval in 1992, FDA has reviewed and approved at least 12 supplemental NDAs for new therapeutic indications for Paxil, and two additional NDAs. (See Kraus Decl. ¶ 44.)	**Objection. Irrelevant. DISPUTED in part.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 44 of his declaration or what FDA actually reviewed and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, Plaintiff **does**

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	not dispute that the FDA has approved several supplemental sNDAs and NDA's for Paxil. However, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
30. With the exception of three supplemental NDAs that consisted of a single pivotal study, for each of the supplemental NDAs, before granting approval, FDA conducted a comprehensive scientific review of the cumulative safety and efficacy data (including data related to suicidality) and proposed labeling. (Id. ¶¶ 44-45, Exs. 10, 23, attached to Kraus Decl.)	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 44-45 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **DISPUTES** that "FDA conducted a comprehensive scientific review." Not only does GSK lack personal knowledge of this "fact," but there is evidence to the contrary. See, PFF 1-23; 35-62; 91-120 and declarations of Plaintiff's experts, Dr. Joseph Glenmullen, Dr. David Healy, and Dr. David Ross and Exhibits 1-10, 66, 69, 70, 72-75, 78-79 and 95-97.
31. Each approval was conditioned on the verbatim use of the FDA-approved prescribing information and warnings. In some cases, FDA mandated changes to Paxil's prescribing information, including information related to adverse events (but not suicidality). (Id. ¶ 33, 44, Ex. 10, attached to Kraus Decl.)	**Objection. DISPUTED in part.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 33 and 44 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff also **DISPUTES** this paragraph because GSK employees working as liaisons between GSK and the FDA regarding Paxil during this time period specifically testified that GSK did not propose additional or different language concerning suicidality for Paxil's label during this time period. Thus, there was nothing for the FDA to reject. See Exhibits 45, 47, 49. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.

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32. With each NDA submission, SB (and later GSK) submitted the required information demonstrating the safety and effectiveness of the drug. In every submission where it was required, SB and GSK submitted to FDA an Integrated Safety Summary ("ISS"), which included all available information about the safety of the drug product, including adverse events involving suicidality. (Id. ¶ 45.) Each ISS summarized all available information about the safety of the drug product, including adverse events involving suicidality. (Id.)	**Objection. DISPUTED in part.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 45 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff also **DISPUTES** this paragraph because GSK employees working as liaisons between GSK and the FDA regarding Paxil during this time period specifically testified that GSK did not propose additional or different language concerning suicidality for Paxil's label during this time period. Thus, there was nothing for the FDA to reject. See Exhibits 45, 47, 49. In addition, GSK has not shown that it submitted to the FDA all the necessary data to make a valid conclusion, one way or the other, as to whether Paxil is associated with a higher risk of suicidality. In fact, the evidence demonstrates that GSK actually submitted misleading data that obscured the risk. See PFF 1-23 and declarations of Plaintiff's experts, Drs. Glenmullen, Healy, Ross and Grimson, and Exhibits 1-10, 69, and 72. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
33. In the case of Paxil, FDA used the opportunities presented by the 12 additional NDA submissions to review updated safety information, including information concerning suicidality, and to require various changes to the product's labeling. None of these reviews required labeling changes related to an association between Paxil and suicide or suicidality in adult or pediatric patients. (Id. ¶¶ 45-46, Exs. 10, 23, attached to Kraus Decl.)	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 45-46 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Dr. Kraus could not possibly have any personal knowledge regarding what the FDA actually reviewed and what it did not review or what "opportunities" the FDA took concerning GSK's NDA submissions. Further, Plaintiff **DISPUTES** GSK's assertion because GSK never proposed with these NDA submissions any labeling concerning Paxil's association with suicidality. In 2001, GSK proposed

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	language that simply indicated that certain psychiatric conditions are associated with suicidality. (See Exhibits 45, 47, 49 and 95.) Plaintiff also **DISPUTES** this paragraph because GSK employees working as liaisons between GSK and the FDA regarding Paxil during this time period specifically testified that GSK did not propose additional or different language concerning suicidality for Paxil's label during this time period. Thus, there was nothing for the FDA to reject. See Exhibits 45, 47, 49. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
D. FDA's Monitoring and Evaluation of Suicide Risk with Paxil (1995-2005)	
34. For several years, FDA approved Paxil's labeling without any changes to the medication's warnings relating to suicide or suicidality. (Id. ¶ 43.)	**Objection. Irrelevant. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 43 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff also **DISPUTES** this paragraph because GSK employees working as liaisons between GSK and the FDA regarding Paxil during this time period specifically testified that GSK did not propose additional or different language concerning suicidality for Paxil's label during this time period. Thus, there was nothing for the FDA to reject. See Exhibits 45, 47, 49. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
35. From 1995 to 2003, GSK submitted extensive data for FDA's review, evaluation, and consequent regulation of Paxil, including information relating to the	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements in paragraph 32, 34, 35, 36, 37 and 40 and does not properly authenticate the documents cited.

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risk of suicide and suicidality. (Id. ¶ 32, Ex. 9; id. ¶ 34, Ex. 11; id. ¶ 35, Ex. 12; id. ¶ 36, Exs. 15,17; id. ¶ 37, Ex. 18; id. ¶ 40, Ex. 20, attached to Kraus Decl.)	GSK has offered no evidence the FDA considered and evaluated or critically reviewed and analyzed the data submitted. In addition, GSK has not shown that it submitted to the FDA all the necessary data to make a valid conclusion, one way or the other, as to whether Paxil is associated with a higher risk of suicidality. In fact, the evidence demonstrates that GSK actually submitted misleading data that obscured the risk. See PFF 1-23 and declarations of Plaintiff's experts, Drs. Glenmullen, Healy, Ross and Grimson, and Exhibits 1-10, 69, and 72. Significantly, GSK's May 2006 analysis of clinical trials encompassed studies dating back to the 1980s and this analysis concluded that a higher risk did, in fact, exist. (See Exhibits 7-9). Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. Because GSK **"bears the responsibility for the content of its label at all times,"** GSK's submissions to the FDA are irrelevant because none of these submissions included a proposed warning concerning the increased risk of suicidal behavior in adults of all ages. In fact, both times GSK sought to add additional language to Paxil's label regarding suicide or suicidality, the FDA approved GSK's request. Exh. 52 at 116:3-11; Exh. 47 at 150:4-20.
36. [redacted]	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 32 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.

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[redacted]	
37. [redacted]	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraphs 34-35 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. There is no evidence the FDA considered and evaluated or critically reviewed and analyzed the data submitted. In addition, GSK has not shown that it submitted to the FDA all the necessary data to make a valid conclusion, one way or the other, as to whether Paxil is associated with a higher risk of suicidal behavior. In fact, the evidence demonstrates that GSK actually submitted misleading data that obscured the risk. See PFF 1-23 and declarations of Plaintiff's experts, Drs. Glenmulen, Healy, Ross and Grimson and Exhibits 1-10, 69, and 72. Significantly, GSK's May 2006 analysis of clinical trials encompassed studies dating back to the 1980s and this analysis concluded that a higher risk did, in fact, exist. See Exhibits 7-9. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
38. [redacted]	**Objection. Irrelevant.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 36 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. Because GSK **"bears the responsibility for**

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	the content of its label at all times," the FDA's approval of Paxil's labeling without a suicide warning is irrelevant. FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Mr. Dolin's death.
39. In 2002, FDA conducted an internal review of SSRIs to evaluate the state of scientific knowledge regarding a possible connection between the use of SSRIs and suicide. FDA concluded that "[t]here were no significant differences in suicide rates between active treatments and placebo in any diagnostic category." (Kraus Decl. ¶ 42, Ex. 21, attached to Kraus Decl.)	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 42 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant. Misleading.** GSK's unsolicited re-analyses of the 1991 data without the run-ins – after the FDA told the company in 1999 that it was inappropriate to do so (Exh. 4); [redacted] and; after a jury verdict against the company in 2001 (Tobin) (Exh. 106; *see* also Exh. 107) – did not use the same data set as in 1989, 1991 and 1999 (and published in the 1995 Montgomery/ Dunbar article, which article GSK used to "alleviate any concerns" doctors might have about suicidality, (Exh. 18; *See* also Exh. 112 and Glenmullen Decl., Report, p. 42-46). In its 1991 report, on the other hand, GSK stated that, "rather than **introducing any selection bias**, the data for **all trials** has been pooled." (Exh. 8, 1991 Adult Report, p. ii). Instead of including all trials in its 2002 and 2003 analyses to avoid selection bias, the company excluded a number of studies (*See* Glenmullen Decl., Report, p. 44-46). In its 2003 report, GSK also added studies from anomalous patient populations (i.e., Studies 057 and 106) who were at high risk for suicide, which obscured the risk. (*See* GSK Exh. 16; Glenmullen Decl., Report; Healy Decl., Report; Ross Decl., Report, Grimson Decl., Report. See also Exhs. 1, 4, 5, 8 and 107). GSK's own expert consultants later told the

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	company that including studies 057 and 106 was inappropriate and "skewed" the results. (Exhs. 108 and 109. *See* also Exh. 111). According to two FDA epidemiologists in memos dated September 11, 1990 regarding the exclusion of suicide events that took place in non-placebo controlled trials, Dr. Stadel stated "… In the analyses of suicidality 76 of the total of 97 cases were excluded because they occurred in compassionate use studies or other studies which did not have controls. **It is inappropriate in a safety analysis to exclude such a large proportion of cases."** The FDA's Dr. David Graham explained in a memo: "In the meta-analysis of suicidality from IND trials, 76 fluoxetine cases were excluded from analysis because the patients were in studies or other trials lacking comparative controls. It can be argued that these exclusions are not justified or appropriate in a meta-analysis." Exh. 70. Even if GSK had submitted a legitimate analysis to the FDA that did not obscure the risk, GSK misses the point. As *Levine* makes clear, the duty to warn rests with the manufacturer, not the FDA. *Levine*, 129 S.Ct. at 1198.
40. On May 2, 2002, GSK submitted to FDA additional analyses of results from a review of data originally submitted to FDA on May 10, 1991, regarding the original Paxil NDA. (Id. ¶ 37, Ex. 18, attached to Kraus Decl.) This May 2, 2002 submission included an analysis of data regarding "suicide attempts" that was originally submitted to FDA on May 10, 1991, which analyzed data only from randomized double-blind placebo-controlled trials. This analysis found no statistically significant difference between patients on Paxil and patients on placebo. (Id.)	See No. 39 above.
41. Prior to making the May 2, 2002 submission, Dr. David Wheadon, an employee of GSK, contacted FDA and informed FDA about the additional analysis as well as the counting of placebo run-in events in the May 10, 1991 submission.	See No. 39 above.

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(Kraus Decl. ¶ 38, Ex. 19, attached to Kraus Decl.)	
42. Following this conversation and GSK's May 2, 2002 submission, at no time did FDA state to GSK or find that (a) it believed that either the May 10, 1991 submission or the May 2, 2002 submission reflected reasonable evidence of an association between Paxil and suicide attempts, suicide or suicidality; (b) there was a scientific or other basis for changing Paxil's labeling and warnings to suggest that there was an increased risk of suicide attempts, suicide or suicidality from Paxil; or (c) that Paxil's labeling should be changed to reflected the information in the submissions. (Kraus Decl. ¶ 39.)	See No. 39 above. GSK **"bears the responsibility for the content of its label at all times,"** *Levine*, and FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Mr. Dolin's death.
43. On February 6, 2003, GSK submitted to FDA, among other things, additional analyses of results from a review of data originally submitted to FDA on May 10, 1991, regarding the original Paxil NDA (NDA 20-031). In the submission on February 6, 2003, GSK included the following: (1) an analysis of "suicide attempts" by narrow definition algorithm from the datasets submitted to FDA on February 9, 2001; (2) an analysis of "possibly suicide-related" events by broad definition algorithm from the datasets submitted to FDA on February 9, 2001; (3) an analysis of suicides from the datasets submitted to FDA on February 9, 2001; and (4) an additional analysis of data regarding suicides that was originally submitted to FDA on May 10, 1991. This latter analysis demonstrated that no suicides occurred in any patient in either the Paxil or placebo arms of the double-blind, randomized placebo controlled portions of the trials that were part of the original NDA for Paxil. (Id. ¶ 40, Ex. 20, attached to Kraus Decl.) None of these analyses showed a statistically significant difference in the risk of suicide	See No. 39 above.

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or suicide attempt between patients taking Paxil and those taking placebo. (Id. ¶¶ 37, 40 Exs. 18, 20, attached to Kraus Decl.)	
44. On May 22, 2003, GSK submitted to FDA analyses of the reports of possible "suicide attempts" and "possibly suicide-related" events from the pediatric-only Paxil clinical trials. The analyses of possible "suicide attempts" and "possibly suicide-related" events did not show a statistically significant difference between paroxetine and placebo during the "ontherapy" period. During the "on-therapy plus 30 days post-therapy period," however, there was a statistically significant difference between paroxetine and placebo when the data from all pediatric studies included in the analyses were pooled together. For all of the submitted analyses, there was no statistically significant difference between paroxetine and placebo for any of the specific individual pediatric indications. (Id. ¶ 48, Ex. 24, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 48 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Misleading.** Plaintiff **does not dispute** that GSK submitted analyses on suicidality to the FDA on May 22, 2003, but **DISPUTES** the veracity of these analyses. As GSK acknowledged to the FDA over the next several months (references to which are conspicuously absent from GSK's Statement of Undisputed Facts) corrected analyses of possible "suicide attempts" and "possibly suicide-related" events DID show a statistically significant difference between paroxetine and placebo during the "on-therapy" period. (Exh. 103). Additionally, on June 30, 2003, GSK acknowledged for the first time that adolescents taking Paxil in Study 329 had a statistically significant eight times increased risk of experiencing a possible suicide related event compared to those taking placebo. (Exh. 104. *See* also Exh. 105).
45. On June 19, 2003, following its review of GSK's submissions, FDA issued a Talk Paper, reporting that it was "reviewing reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents under the age of 18 treated with the drug Paxil for major depressive disorder (MDD)." (Id. ¶ 50, Ex. 27, attached to Kraus Decl.)	**See No.** 46 below.
46. Regarding adult patients, FDA stated in the Talk Paper that: (1) "[t]here is no evidence that Paxil is associated with an increased risk of suicidal thinking in adults" (id. ¶ 50, Ex. 27 at 1, attached to Kraus Decl.), and (2) "[e]xtensive analyses of the data from studies of Paxil in adults and from postmarketing adverse event reports have not revealed an increase in the rate of suicidal thoughts or suicide attempts	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 51 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant. Misleading.** While Plaintiff **does not dispute** that the FDA Talk Paper included such statement, Plaintiff **DISPUTES** the veracity of the statement. The FDA's statement was

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compared to placebo" (id. ¶ 51, Ex. 28 at 2, attached to Kraus Decl.).	simply wrong and made prior to later analyses that clearly demonstrate the risk in adults. See PFF 63-90. Notwithstanding, the FDA has repeatedly admitted that it had not appropriately evaluated the data in earlier years. For instance: • When the FDA's advisory committee convened in February 2004 to examine antidepressants and suicide risk in children and adolescents, the chairman observed that "we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully." Exh. 78, p. 24. • Dr. Thomas Laughren (former head of the FDA's Neuropharm division) explained, also during this meeting: "Just one follow up on a suggestion that has come up from several committee members now about looking at items from the rating scales. That was actually done here, and it turned out not to be very helpful. Now, this was a similar analysis that had been done with the adult data years ago ..." He explained that this method "did not detect a signal in these trials ..." and admitted that the method was "was not particularly productive." Exh 78, pp. 342-343. • During his December 2004 deposition in *In Re Paxil Product Liability Litigation* (involving Paxil withdrawal reactions and dependence, Case No. 01-07937, C.D. Cal.), the FDA's Dr. Robert Temple testified that, although the FDA had been "watching for suicidality in each [new drug] application," he admitted that the way FDA had been assessing suicidality was "not optimal." Exh. 2, pp. 49-56. • In testimony before Congress, Dr. Temple stated that the FDA's analyses of data concerning suicidality could have been far "better, more structured, [and] more careful ... but we didn't know to do that." Exh. 77, p. 113.

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	When GSK actually did conduct a comprehensive analysis of its clinical trials, it determined that there was, in fact, an increased risk. Exhs. 35-36, 38.
47. FDA did not take any action with respect to Paxil's labeling and warnings at this time. (Ex. 32 at 8, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 32 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Plaintiff does not dispute** the fact that the FDA did not take any action with respect to Paxil's labeling and warnings at this time, however, GSK misunderstands its responsibility. **"[T]he manufacturer bears the responsibility for the content of its label at all times."** GSK did not propose and, by extension, FDA did not reject a warning regarding Paxil's association with an increased risk of suicidality during this time. Both times GSK sought to add additional language to Paxil's label regarding suicide or suicidality, the FDA approved GSK's request. Exh. 52 at 116:3-11; Exh. 47 at 150:4-20.
48. On October 27, 2003, FDA issued a Public Health Advisory and corresponding Talk Paper, and noted, as of that date, "the data do not clearly establish an association between the use of these drugs and increased suicidal thoughts or actions by pediatric patients." (Id. ¶ 52, Ex. 29, Talk Paper, at 1, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 52 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** The FDA later went on to conclude there is an increased suicidality risk in pediatric patients. See Exh. 110. Nevertheless, because GSK **"bears the responsibility for the content of its label at all times,"** FDA's inaction is immaterial. FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Stewart Dolin's death.
49. In October 2003, FDA reaffirmed the language in the Paxil labeling that had been in place since 1992 stating that there is an inherent risk of suicide in patients with depression. (Id., Public Health Advisory, at 2, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 52 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.**

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	GSK **"bears the responsibility for the content of its label at all times,"** thus, FDA's inaction is immaterial. FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Stewart Dolin's death.
50. At no time prior to 2004 did FDA require that Paxil's labeling be revised to warn about an increased risk of suicide, suicide attempts or suicidality in adult or pediatric patients from use of the drug. (Id. ¶¶ 47-64.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 47-64 of his declaration and does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** GSK **"bears the responsibility for the content of its label at all times,"** thus, FDA's inaction is immaterial. FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Stewart Dolin's death.
51. On January 5, 2004, FDA's Dr. Laughren issued a Memorandum to the members of the PDAC and the Pediatric Subcommittee in advance of a scheduled advisory committee meeting on February 2, 2004. Dr. Laughren's Memorandum provided background and FDA's assessments on the issue of whether suicidality is associated with antidepressant drug treatment in both adult and pediatric patients. (Id. ¶ 54, Ex. 32, attached to Kraus Decl.) In the Memorandum, FDA advised that determining whether there is an association between suicidality and a drug must be done in a "careful thoughtful manner. Erring in either direction would have adverse consequences." (Id. at 2.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 54 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **does not dispute** that Dr. Laughren issued a memorandum on January 5, 2004 prior to the referenced PDAC and the memo as quoted states what it states. **Irrelevant.** GSK **"bears the responsibility for the content of its label at all times,"** thus, FDA's inaction is immaterial. FDA *inaction* cannot form the basis of preemption. *Spreitsma v. Mercury Marine*, 537 U.S. 51, 67 (2002). This paragraph does not constitute "clear evidence" that the FDA would have rejected a suicide warning prior to Stewart Dolin's death.
52. Dr. Laughren's Memorandum stated that FDA had sought assistance from an expert group of independent suicide researchers at Columbia University to develop a new methodology for classifying data on suicide and suicidality. (Id. at 13-15.)	See No. 51 above.

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53. Dr. Laughren also specifically addressed the question of suicidality in adults and described FDA's assessment of the issue: FDA has done several analyses on completed suicides for adult data sets provided to us in response to a request for patient level data sets for all relevant studies involving 20 antidepressant drugs studied in 234 randomized controlled trials with [Major Depressive Disorder ("MDD")]. Based on our initial analyses of these data, we have reached a similar conclusion, i.e., that there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD. (Id. at 4 (footnote and citations omitted).)	**Objection. DISPUTED.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 54 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Misleading.** Dr. Laughren's statement was not Paxil-specific and was limited to completed suicides. The memo does not purport to suggest that Paxil is free from any suicidality risk. In fact, the evidence demonstrates that GSK actually submitted misleading data that obscured the risk. See PFF 1-23 and declarations of Plaintiff's experts, Drs. Glenmulen, Healy, Ross and Grimson and Exhibits 1-10, 69, and 72. Moreover, the hypothesis of whether Paxil causes suicidality has *never* been prospectively studied. GSK has never conducted a single safety oriented clinical trial specifically designed to answer the question of whether or not Paxil can cause suicide or suicidality, or to measure the strength of such association. Healy Decl., Report. Indeed, one would not expect to find a rare event such as completed suicides to a statistically significant degree in ordinary clinical trials. *Id.* The fact that patients who are suicidal are excluded from entering most studies and a significant percentage of patients quit clinical trials due to side effects, including emergent suicidality, makes it even less likely. *Id.* According to epidemiologists Gunnell and Ashby (*BMJ* 1995), "[s]uicide is rare, even among people with depression. [Cite omitted.] Thus, most clinical trials have insufficient power to provide clear evidence on the effect of antidepressants on suicide." Exh. 100. The fact that a statistically significant increased risk of suicidal behavior was revealed in GSK's clinical trials dating back to the 1989 Integrated Safety Summary is, thus, significant. Healy Decl, Report. Ultimately, Dr. Laughren's statement is contradicted by GSK's May 2006 Dear Healthcare Professional Letter and labeling changes disclosing the greater than six times

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	risk of suicidal behavior for Paxil versus placebo. (Exhibits 35-36 and 38). See declarations of Plaintiff's experts, Drs. Glenmullen, Healy, Grimson and Ross. As set forth in Plaintiff's PFFs 1-23, GSK had knowledge of a risk long before this time and should have sought additional warnings. Dr. Laughren's statement also shows the effect of his having been provided false and misleading information regarding suicidal behavior in the Paxil clinical trials.In addition, the FDA has repeatedly admitted that it had not appropriately evaluated the data in earlier years. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's death. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
54. On February 2, 2004, an FDA Advisory Committee convened to discuss the possible relationship between antidepressants and suicidal thinking (focusing on the pediatric population). (Kraus Decl. ¶ 56.)	**Admit.**
55. Dr. Laughren explained that the Agency had reviewed NDA supplements submitted by SSRI manufacturers during the preceding years and "suicidality did not emerge as a matter of concern based on those reviews." (Id. ¶ 56, Ex. 33 at 235, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 56 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff does not dispute that Dr. Laughren issued a memorandum on January 5, 2004 prior to the referenced PDAC and the memo states what it states. **Irrelevant. Misleading. DISPUTED.** The panel was convened "to address concerns about reports of suicidal ideas and behavior developing in some children and adolescents during treatment of depression with an SSRI or similar newer antidepressant." Exh. 78, pp. 12-13. Plaintiff **does not dispute** the data pertained to patients 18 and under. Dr. Laughren's statement that "suicidality did not emerge as a matter of concern" based on its

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	past reviews of the pediatric supplements from various antidepressant manufacturers **is not** applicable to Paxil and is **misleading.** See PFF 35-69. In fact, Dr. Laughren stated, immediately following GSK's selective quote: "However, the Paxil review did raise a question about data management in that events suggestive of suicidality were coded under... 'emotional lability.' This struck the reviewer as odd, and so in responding to GSK, we asked them to separate out the verbatim terms suggestive of suicidality" and, when GSK responded, the FDA found the data "indeed suggested an increased risk of suicidality associated with paroxetine use in particular in one of the three studies done in pediatric depression." Exh. 78, pp. 235-236**.**
56. In terms of making a decision as to whether a warning should be included in a medication's labeling, FDA stated: "It is absolutely critical, in [FDA's] view, that we make every effort to provide the best answer possible to [the question of whether a drug is associated with increased suicidality]. The wrong answer in either direction, prematurely arrived at, could have profound negative consequences for the public health." (Ex. 33 at 22, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 54 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **DISPUTES** that the memo says anything about "in terms of making a decision as to whether a warning should be included in a medication's label." It does not. Plaintiff **does not dispute** that page 22 of the February 2, 2004 transcript contains the quoted section of this paragraph.
57. During the meeting, Dr. Kelly Posner from Columbia University presented a summary of the new methodology to be applied to the data from the antidepressant clinical trials called Columbia-Classification Algorithm for Suicide Assessment ("C-CASA") The goal of the reanalysis was to "look at the data consistently and logically across trial in order to make some clinically meaningful sense of it" and to determine if there was a signal of increased suicidality in pediatric patients taking antidepressants. (Id. at 265-73.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 54 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Plaintiff **DISPUTES** that the methodology GSK used was "new." In fact, the reason the methodology was developed was for purposes of having a standardized approach to *classifying* suicide events. A standardized classification was deemed necessary due to the inappropriate and varying classification techniques that manufacturers had utilized – particularly GSK's improper classification of suicide events under the term "emotional lability." See PFF 37-43. Accordingly, the

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	Columbia "methodology" is not some newly invented mathematical methodology, rather it is simply a standardized "*classification*" system.[3]
58. The Committee ultimately recommended that FDA reanalyze the data on pediatric use of antidepressants using this newly developed C-CASA methodology, warn the public and physicians of the possibility of suicidality in the pediatric population, and change the labeling for antidepressants. The Committee did not find evidence of an increased risk of suicidality in adult patients being treated with antidepressants. (Kraus Decl. ¶ 57, Ex. 34, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 54 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. See No. 57 above. Plaintiff **does not dispute** that the committee recommended that the FDA reanalyze the data on pediatric use of antidepressants, but **DISPUTES** that the committee did not find evidence of an increased risk of suicidality in adult patients. Data concerning adults was not the subject of the meeting. An FDA advisory committee was convened in 2006 to examine the adult data, which analysis (for Paxil) showed a statistically significant 2.76 increased risk of suicidal behavior in adults. See Exh. 40.
59. On March 19, 2004, FDA issued a letter to GSK requesting revision of its product labeling "in order to caution practitioners and patients about the need for close observation of patients being treated with antidepressants for clinical worsening, for the emergence of suicidality, and for the emergence of a variety of other symptoms that may represent a precursor to suicidality." The labeling revision requested the addition of a new subsection entitled "Clinical Worsening and Suicide." (Kraus Decl. ¶ 58, Ex. 35, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 59 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**
60. FDA requested that GSK add to the WARNINGS section, under the bolded heading "Clinical Worsening and Suicide Risk": Patients with major depressive disorder,	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 58 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements

[3] For a more detailed discussion of the Columbia University classification *see* Posner K. et. al., *Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants*, 164 Am. J. Psychiatry 1035-1043 (July 2007). A free copy of this article is available for download at http://ajp.psychiatryonline.org/cgi/reprint/164/7/1035

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both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. * * * (Kraus Decl. ¶ 59, Ex. 35, attached to Kraus Decl.)	in this paragraph in their entirety. Notwithstanding, **Admit.**
61. FDA also included additional language for the "Precautions-Information for Patients" section: Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe,	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 60 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**

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abrupt in onset, or were not part of the patient's presenting symptoms. The "Suicide" section of the "Precautions-General" section was deleted. FDA requested that GSK incorporate the specific labeling revisions in the labeling for Paxil and Paxil CR and submit the changes through a CBE labeling supplement within 30 days. (Kraus Decl. ¶ 60, Ex. 35, attached to Kraus Decl.)	
62. Then, on March 22, 2004, FDA issued a Talk Paper and Public Health Advisory stating that it was further evaluating the initial reports of the possibility of an increased risk of suicidal thinking in pediatric patients given antidepressants. (Id. ¶ 61, Ex. 36, attached to Kraus Decl.) FDA emphasized that "it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior." (Id. ¶ 62, Talk Paper, at 1.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 62 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Objection. Irrelevant.** Plaintiff **does not dispute** that the FDA issued the referenced Talk Paper and Public Health Advisory. While Plaintiff **does not dispute** that the FDA stated that "it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior," this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. The evidence, however, demonstrates that GSK actually submitted misleading data that obscured the risk. See PFF 1-23 and declarations of Plaintiff's experts, Drs. Glenmulen, Healy, Ross and Grimson and Exhibits 1-10, 69, and 72. This paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's death. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
63. In this Talk Paper, FDA "advis[ed] clinicians, patients, families and caregivers of adults and children that they should closely monitor all patients being placed on therapy with these drugs [antidepressants]	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 62 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety.

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for worsening depression and suicidal thinking, which can occur during the early period of treatment…. FDA is asking manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening." (Id.)	Notwithstanding, Plaintiff **does not dispute** that the Talk Paper states what it states.
64. In its March 22, 2004 Talk Paper and Public Health Advisory, FDA outlined that it "asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality." (Kraus Decl. ¶¶ 61- 62, Ex. 36, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 62 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit**.
65. FDA also stated that it was "asking manufacturers to change the labels of ten [antidepressants] to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening." (Kraus Decl. ¶¶ 61-62, Ex. 36, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 61-62 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit**.
66. On April 28, 2004, GSK submitted a Changes Being Effected ("CBE") labeling supplement for Paxil and Paxil CR to reflect changes in the prescribing information pursuant to FDA's March 2004 letter. This included language stating: The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications,	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 63 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**

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both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.** Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. (Kraus Decl. ¶ 63; Ex. 37, attached to Kraus Decl.)	
67. In May 2004, FDA approved GSK's April 2004 CBE labeling supplement without a warning regarding an increased risk of suicide or suicidality in any patient population. The approved labeling stated that, "a causal link . . . has not been established" between adverse events reported in patients using antidepressants and "the worsening of depression and/or the emergence of suicidal impulses." (Id. ¶ 64, attached to Kraus Decl. (emphasis added).)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 64 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Misleading. DSIPUTED.** The cited exhibit does not contain the referenced label. However, GSK has taken the quote from the label out of context, thus distorting its meaning. The complete quote is: "The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor

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	restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality." See Kraus Exhibit 37, p. 2 of the label. Nevertheless, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
68. On September 13-14, 2004, the PDAC and Pediatric Advisory Committees convened again to review the available data and information collected following the February 2004 meeting related to reports of an increased risk of suicidality associated with the use of certain antidepressants in pediatric patients. (Id. ¶ 67, Ex. 40, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 67 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**
69. The committee concluded that, in the aggregate, the data reflected an increased risk of suicidality (there were no suicides in any of the trials) in pediatric patients and recommended that FDA consider new class labeling changes. The FDA's analysis did not find a statistically significant increased risk of suicidality in any of the individual Paxil pediatric trials or when all of those Paxil pediatric trials were combined. (Id. ¶ 67, Ex. 40, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 67 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Misleading. DISPUTED.** The initial FDA reviewer of the Paxil pediatric clinical trials, Dr. Andrew Mosholder, found a statistically significant excess risk for Paxil over placebo (8.65% vs. 1.1%) for one study alone (study 329) and (3.4% vs. 1.1%) across all six of GSK's pediatric Paxil trials. See Exh. 105, Mosholder September 2003 Report, Table 2. Furthermore, GSK ignores its own later analysis of its clinical trials, which found a significant risk ratio using a virtually identical methodology to Columbia except (1) the

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	Columbia review used "relative risk" numbers in their significance equations instead of "odds ratios,"[4] and (2) "The GSK reviewers were furnished all case materials, i.e. the CRF's [Patient Case Report Forms] and SAE [Serious Adverse Event] reports; the Columbia reviewers were not." (Exh. 118, Comparing the Columbia/FDA and GSK Analyses). As a result, GSK's reviewers were provided more data than the Columbia reviewers, found a statistically significant 3.86 times more suicidality events for Paxil over placebo, and the Columbia group did not. See Exh. 117, Apter et al. study. Using virtually the same methodology as the Columbia reviewers, but with more data and using odds ratios instead of relative risks, GSK found a statistically significant risk. *Id.*
70. Regarding adult suicidality, Dr. Laughren stated that, "subsequent to the Prozac experience [in 1991], all subsequent NDAs for all antidepressants were looked at in the same way. The companies did an item analysis and they looked at their own event data, using their own approaches to classification. With all these subsequent NDAs, we have never seen a signal for excess suicidality, either looking at event data or looking at item data." (See Sept. 13-14, 2004 Transcript of Joint Meeting of PDAC and the FDA Pediatric Advisory Committee, at 188, excerpts attached as Ex. 7 to Davis Decl.)	**Objection.** The cited document is not properly authenticated. Plaintiff **DISPUTES** the veracity of FDA's statement because, with respect to Paxil, the FDA relied on GSK's faulty data. PFF 19. Notwithstanding, the FDA has repeatedly admitted that it had not appropriately evaluated the data in earlier years. For instance: • When the FDA's advisory committee convened in February 2004 to examine antidepressants and suicide risk in children and adolescents, the chairman observed that "we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully." Exh. 78, p. 24. • The FDA's Dr. Thomas Laughren explained, also during this meeting: "Just one follow up on a suggestion that has come up

[4] Using "odd ratios" is the more appropriate methodology for retrospective analyses. See Grimson Decl., Report, p.37, citing Sutton et al. GSK's biostatistician, John Davies agreed, stating "you can do some rather more powerful and more appropriate statistical analysis if you interpret the results using odds ratios than you can with a relative risk. So you are quite restricted in what you can do with a relative risk compared to what you can do with an odds ratio." *Id.*, citing Davies' testimony. See also Reference Manual on Scientific Evidence, Second (2005-2006), glossary of terms, pp. 549-551, definitions for "relative risk" and "odds ratio."

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	from several committee members now about looking at items from the rating scales. That was actually done here, and it turned out not to be very helpful. Now, this was a similar analysis that had been done with the adult data years ago ..." He explained that this method "did not detect a signal in these trials ..." and admitted that the method was "was not particularly productive." Exh 78, pp. 342-343. In an interview following the advisory committee meeting, the Director of the FDA's Division of Neuropharma-cological Drug Products, Dr. Russell Katz, underscored that "there's more or less standard approaches to various things. And there hasn't been one for suicidality to date." Exh. 99, transcript of interview with Drs. Russell Katz and Robert Temple of the FDA (February 2, 2004), bates page 000028. • During his December 2004 deposition in *In Re Paxil Product Liability Litigation* (involving Paxil withdrawal reactions and dependence, Case No. 01-07937, C.D. Cal.), the FDA's Dr. Robert Temple testified that, although the FDA had been "watching for suicidality in each [new drug] application," he admitted that the way FDA had been assessing suicidality was "not optimal." Exh. 2, pp. 49-56. • In testimony before Congress, Dr. Temple stated that the FDA's analyses of data concerning suicidality could have been far "better, more structured, [and] more careful ... but we didn't know to do that." Exh. 77, p. 113. When GSK actually did conduct a comprehensive analysis of its clinical trials that had been conducted prior to Stewart Dolin's suicide, it determined that there was, in fact, an increased risk which required a label modification. Exhs. 35-36 and 38. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding

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	Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
71. During the September 2004 hearing, various attendees advocated for revisions to antidepressant labeling that reflected a warning of increased suicide and suicidality in all patients, not just pediatric patients. (Id. at 336-37, 348-49, 354-55, 373-74, 378-79, 383-85, 417-19.)	**Objection**. The cited document has not been properly authenticated. Notwithstanding, Plaintiff **does not dispute** the factual assertions in this paragraph.
72. On September 23, 2004, Dr. Robert Temple of FDA testified before Congress about suicidality and antidepressants and explained, "[i]n recent years, several groups have conducted pooled analyses of data on completed or attempted suicides [in adults] in an effort to identify a possible signal of risk from active treatment." (Hearing of the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce of the U.S. House of Representatives (Sept. 23, 2004), at 70, excerpts attached as Ex. 8 to Davis Decl.) Dr. Temple testified that these researchers evaluating "adult data obtained from FDA review" found no increase in suicide for patients on SSRIs as compared with those on placebo (i.e., a sugar pill). (Id.)	**Objection.** The cited document has not been properly authenticated. Notwithstanding, Plaintiff **does not dispute that** Dr. Temple made this statement, however, his statement was not Paxil-specific and was limited to completed suicides. The statement does not purport to suggest that Paxil is free from any suicidality risk. The hypothesis of whether Paxil causes suicidality has *never* been prospectively studied. GSK has never conducted a single safety oriented clinical trial specifically designed to answer the question of whether or not Paxil can cause suicide or suicidality, or to measure the strength of such association. Healy Decl., Report. Indeed, one would not expect to find a rare event such as completed suicides to a statistically significant degree in ordinary clinical trials. *Id.* The fact that patients who are suicidal are excluded from entering most studies and a significant percentage of patients quit clinical trials due to side effects, including emergent suicidality, makes it even less likely. *Id.* According to epidemiologists Gunnell and Ashby (*BMJ* 1995), "[s]uicide is rare, even among people with depression. [Cite omitted.] Thus, most clinical trials have insufficient power to provide clear evidence on the effect of antidepressants on suicide." Exh. 100. The fact that a statistically significant increased risk of suicidal behavior was revealed in GSK's clinical trials dating back to the 1989 Integrated Safety Summary is, thus, significant. Healy Decl, Report. Ultimately, Dr. Temple's statement is contradicted by

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	GSK's May 2006 Dear Healthcare Professional Letter and labeling changes disclosing the greater than 6 times risk of suicidal behavior for Paxil versus placebo. (Exhibits 35-36 and 38). See declarations of Plaintiff's experts, Drs. Glenmullen, Healy, Grimson and Ross. As set forth in Plaintiff's PFFs 1-23, GSK had knowledge of a risk long before this time and should have sought additional warnings. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidality. GSK **"bears the responsibility for the content of its label at all times"** *Levine* at 1197-98.
73. At the same hearing, Dr. Laughren testified that "[FDA] had been systematically looking at the adult data for almost that entire decade, you know, looking at both suicide item scores, looking at event data, and more recently had begun to accumulate the completed suicides in adults, had not seen a signal." (Id. at 113 (emphasis added).)	**Objection.** The cited document has not been properly authenticated. Plaintiff **DISPUTES** the veracity of Dr. Laughren's statement because, with respect to Paxil, the FDA relied on GSK's faulty data. PFF 19. Notwithstanding, the FDA has repeatedly admitted that it had not appropriately evaluated the data in earlier years. See No. 46 above. When GSK actually did conduct a comprehensive analysis of its clinical trials, which pre-dated Stewart Dolin's suicide, determined that there was, in fact, an increased risk. Exhs. 35-36 and 38. Moreover, the hypothesis of whether Paxil causes suicidality has *never* been prospectively studied. GSK has never conducted a single safety oriented clinical trial specifically designed to answer the question of whether or not Paxil can cause suicide or suicidality, or to measure the strength of such association. Healy Decl., Report. Indeed, one would not expect to find a rare event such as completed suicides to a statistically significant degree in ordinary clinical trials. Id. The fact that patients who are suicidal are excluded from entering most studies and a significant percentage of patients quit clinical trials due to side effects, including emergent suicidality, makes it even less likely. Id. According to

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	epidemiologists Gunnell and Ashby (*BMJ* 1995), "[s]uicide is rare, even among people with depression. [Cite omitted.] Thus, most clinical trials have insufficient power to provide clear evidence on the effect of antidepressants on suicide." Exh. 100. The fact that a statistically significant increased risk of suicidal behavior was revealed in GSK's clinical trials dating back to the 1989 Integrated Safety Summary is, thus, significant. Healy Decl., Report.
74. On October 15, 2004, FDA issued a Public Health Advisory and a letter directing all manufacturers to add a boxed warning and expanded warning statements to the labeling of all antidepressant medications describing an increased risk of suicidality in children and adolescents. (Kraus Decl. ¶ 68, Ex. 41, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 68 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**
75. FDA specifically requested additional changes to the Warnings section of the labeling concerning "Clinical Worsening and Suicide Risk." Among the statements that FDA asked GSK and other antidepressant manufacturers to include were the following: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressants medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. A causal role for antidepressants in inducing suicidality has been established in pediatric patients. (Kraus Decl. ¶ 68, Ex. 42, attached to Kraus Decl.)	**Objection.** Dr. Kraus has no personal knowledge concerning the statements made in paragraph 68 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**

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76. On January 26, 2005, FDA notified GSK that it had decided "to modify the new PI [package insert] slightly so that the language in the 'Warnings Section' of the PI more precisely mirrors the language set forth in the black box warning." Specifically, it stated: **[T]he sentence in the current 'Warnings Section' of the PI that reads, 'A causal role of antidepressants in inducing suicidality has been established in pediatric patients' should be excised and replaced with the following:** 'Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.' The final PI, which reflects this change, is enclosed with this letter. The final Medication Guide is also enclosed. It remains identical, except for some minor revisions, to the final Medication Guide we enclosed with the approval letter we sent you January 12, 2005. (Id. ¶ 73, Ex. 48 (emphasis added), attached to Kraus Decl.) FDA did not remove – and again approved – the following statement from Paxil's labeling: "It is also unknown whether the suicidality risk extends to adults" and "a causal link between the emergence of such symptoms [including akathisia] and either the worsening of depression and/or the emergence of suicidal impulses has not been established."	**Objection.** There is no indication that Dr. Kraus has personal knowledge concerning the statements made in paragraph 73 of his declaration and he does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** While Plaintiff **does not dispute** that the FDA sent GSK a letter on January 26, 2005, which included the language quoted, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.
77. The Paxil prescribing information starting in January 2005 included the following language in the PRECAUTION section: **Akathisia:** The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 75 of his declaration and he does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**

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such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment. This PRECAUTION has remained in the Paxil labeling since that time. (Kraus Decl. ¶ 75, Ex. 49, attached to Kraus Decl.)	
78. On January 26, 2005, FDA approved the labeling supplements for Paxil (and other antidepressants), submitted by GSK on November 12, 2004. (Id. ¶¶ 69, 73, Exs. 43, 48, attached to Kraus Decl.)	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 69 and 73 of his declaration and he does not properly authenticate the documents cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** Notwithstanding, Plaintiff **does not dispute** that the FDA, in its January 26, 2005 letter to GSK, set forth the final approved labeling for Paxil and other antidepressants reflecting that "antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders."
E. FDA's and GSK's Analyses of Adult Suicidality and Regulatory Activities Concerning Paxil's Labeling and Warnings (2004-2007)	
79. On December 24, 2004, FDA requested data from antidepressant manufacturers, including GSK, regarding adult suicidality for purposes of reevaluating the adult data based on Columbia University's C-CASA methodology to determine whether an increased risk of suicidality existed in that population. [redacted]	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 70 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.** However, GSK appears to imply, by mentioning the Columbia *methodology* that, prior to the 2004 Columbia classification system, it did not know how to classify a suicide event and that it should be entitled to preemption until the FDA informed it of its illegitimate classification (i.e., its use of "emotional lability" to describe suicide events). In the *Fall of 2002*, the FDA uncovered GSK's improper classification and asked GSK for an explanation as to why it had coded adverse events under the inappropriate term "emotional

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[redacted]	lability." See PFF Nos. 35-43. Thus, GSK was on notice that it had used an inappropriate method to code suicide events. Moreover, by claiming it did not know how to properly classify suicide events until the Columbia system was implemented, GSK forgets that, as a drug manufacturer, it is held to the standard of an expert in the field and is charged with the knowledge of an expert.
80. FDA here applied the same methodology it had utilized in conducting its earlier suicidality analysis of clinical studies involving pediatric patients. Specifically, FDA analyzed and reviewed data from randomized, double-blind placebo-controlled trials; FDA excluded "events that occurred in the post-blind period" as it "avoids the uncontrollable confounding stemming from the array of scenarios that could have happened after the end of a given trial." (Id. ¶ 71, Ex. 45, attached to Kraus Decl.) And as a later article co-authored by FDA officials Tarek A. Hammad, MD and Thomas Laughren, MD, explained: "Rates based on the pooling of data from both randomized controlled trials (RCTs) and open-label extension trials are subject to bias and could lead to misleading conclusions." (Kraus Decl. ¶ 71, Ex. 46, attached to Kraus Decl.)	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 71 of his declaration and he does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** Notwithstanding, Plaintiff **does not dispute** that the FDA analyzed data from randomized double-blind placebo controlled trials.
81. FDA's reliance on double-blind, randomized placebo-controlled data (and not open-label or uncontrolled data) was consistent with FDA's requests to GSK and other manufacturers. In FDA's November 17, 2006 analysis entitled "Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults," FDA explained the type of trials it wanted to assess the issue of adult suicidality:	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 72 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Irrelevant.** Notwithstanding, Plaintiff **does not dispute** that the FDA analyzed data from randomized double-blind placebo controlled trials.

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Data Submission In order to perform additional analyses investigating the relationship between exposure to the drug of interest and PSRAEs2 among the subjects of interest, we would appreciate your submitting the following various as outlined in the next table. As noted, ***we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies, or combination drug studies.*** (Kraus Decl. ¶ 72, Ex. 47, Clinical Review at 50, attached to Kraus Decl.) FDA again explained: "The FDA's data request to sponsors [] asked that the trials included in the dataset be limited to completed, double-blind, randomized, placebo-controlled trials." (Id., Ex. 47 at 8.)	
82. On June 30, 2005, FDA issued a Public Health Advisory notifying patients and health care providers that FDA had commenced "the process of reviewing available data to determine whether there is an increased risk of suicidal behavior in adults taking antidepressants." In its Advisory, FDA made some recommendations, including close monitoring of adult patients "for worsening of depression and for increased suicidal thinking or behavior." (Id. ¶ 76, Ex. 50, Talk Paper, attached to Kraus Decl.)	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 72 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. Notwithstanding, **Admit.**
83. At this time, FDA reaffirmed the appropriateness of the substance of the warnings "already present in approved labeling for antidepressants used by adults." (Id.)	**Objection. DISPUTED.** There is no indication that Dr. Kraus has any personal knowledge concerning the statements made in paragraph 72 of his declaration and does not properly authenticate the document cited. Accordingly, Plaintiff objects to the statements in this paragraph in their entirety. **Vague. Misleading.** The Warnings section of the label included: "Patients with major depressive disorder (MDD), **both adult and pediatric,**

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	may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior ..." Exh. 34, attached labeling, p. 10 and that: "**Adults** with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly [as with pediatric patients] for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases." Id., attachment, p. 11. Emphasis added. Notwithstanding, this paragraph fails to demonstrate that GSK proposed and, by extension, FDA rejected a warning regarding Paxil's association with an increased risk of suicidal behavior in adults of all ages prior to Stewart Dolin's suicide. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98
84. The following day, July 1, 2005, FDA issued a Talk Paper, "FDA Reviews Data for Antidepressant Use in Adults," in which FDA noted its "process of reviewing available data to determine whether there is an increased risk of suicidal behavior in adults taking antidepressants." FDA noted its recommendations, which "are consistent with warnings already present in approved labeling for antidepressants used by adults." (Id.)	See No. 83 above.
85. While FDA was reviewing the adult data, GSK performed its own meta-analysis of its adult clinical trial data based on the new methodology developed by FDA and Columbia University in 2004. In March and April 2006, GSK submitted to FDA the results of GSK's meta-analysis of Paxil placebo-controlled studies in adult patients with MDD and a similar metaanalysis of Paxil placebo-controlled studies in adult patients with non-MDD disorders. (The placebo-controlled studies included in both meta-analyses had been the subject of previous correspondence with FDA.) (Id. ¶	See Nos. 79 and 57 above.

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78.)	
86. GSK's "Update April 5, 2006 Briefing Document," submitted to FDA in April2006, included the following findings: • "On the primary endpoint of definitive suicidal behavior or ideation, there was no statistically significant difference between adults with MDD treated with paroxetine compared to placebo (31/3455 (0.90%) vs. 11/1978 (0.56%); odds ratio = 1.3 (95% CI 0.7, 2.8); p=0.493)"; • "The results provide evidence of an increase in suicide attempts in adults with MDD treated with paroxetine compared to placebo; however, as the absolute number and incidence of events are very small (11/3455 (0.32%) for paroxetine, vs. 1/1978 (0.05%) for placebo; odds ratio = 6.7 (95% CI 1.1, 149.4); p=0.058), these data should be interpreted with caution"; • "There were proportionally slightly more events (suicidal behavior with or without ideation) in young adults between 18-24 years of age with MDD treated with paroxetine (5/230 (2.17%)) compared to placebo (0/104 (0%) than in older adults, however these data are not conclusive due to the relatively small size of the 18-24 age group and the small number of events. These trends are consistent with findings from previous analyses in pediatric and adolescents, and while it appears that the risk seen in pediatrics seems to extend beyond age 18, the extent to which this occurs is less clear"; • "In placebo-controlled clinical trials in psychiatric disorders other than MDD, there was no evidence of an	Plaintiff **does not dispute** that GSK's letter to the FDA made these statements, however, they are taken out of context: (1) with respect to completed suicides, see No. 53 above; (2) with respect to suicidal behavior combined with ideation, see Healy Decl., Report in which he points out that he did "not include suicidal ideation in my analyses because suicidal ideation is far too common and nebulous and dilutes the data to the point that it obscures the serious risk of actual suicidal behavior"); (3) Plaintiff **does not dispute** that there was a statistically significant association between Paxil and suicide attempts in adult patients (all ages) with Major Depressive Disorder ("MDD"); (4) with respect to suicidality in pediatric patients, this is inconsistent with a number of GSK's analyses of its pediatric clinical trials. For instance, at the conclusion of the September 13 and 14, 2004 advisory committee (PDAC) meeting, 25 of the experts on the FDA advisory panel voted that the data demonstrated a causal relationship between the antidepressants and increased suicidality. (One voted to abstain and one voted against.) Exh. 33, Summary Minutes of the Pediatric Advisory Committee of September 13-14, 2004. In his November 16, 2006 memo, Dr. Laughren stated: **"The pediatric data presented at the September, 2004 PDAC meeting represented the first systematic demonstration of a causal link [between antidepressants and suicidality].**" Exh. 110.

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increased risk of suicidal behavior or ideation (primary endpoint) in patients treated with paroxetine"; • In placebo-controlled clinical trials in psychiatric disorders other than MDD, "[t]here was no evidence of treatment differences in suicidal behavior alone (secondary endpoint) in any overall population grouping"; • "Although not statistically significant, there were proportionally slightly more events (suicidal behavior with or without ideation) in young adults between 18-24 years of age with psychiatric disorders other than MDD treated with paroxetine (0.99% for paroxetine versus 0.25% for placebo). This finding was consistent across the non-MDD indications"; and • "Suicidal behavior alone was slightly higher in young adults treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant." (Kraus Decl. ¶ 79, Ex. 52, attached to Kraus Decl.)	
87. GSK informed FDA that these analyses showed (1) no statistically significant association between Paxil and completed suicide; (2) no statistically significant association between Paxil and definitive suicidal behavior or ideation (the primary endpoint of the analyses); (3) what appeared to be a statistically significant association between Paxil and suicide attempts in adult patients with MDD on the secondary endpoint of the analyses; and (4) no statistically significant association between Paxil and suicidal behavior in young adults aged 18 to 24. (Ex. 52 at 2-3, attached to Kraus Decl.) GSK noted that "[i]t is difficult	See No. 86 above.

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to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute numbers of events, the retrospective nature of this meta-analysis, and the potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves," and requested a conference with FDA to discuss possible label changes. (Id. at 3.)	
88. On April 20, 2006, GSK had a telephone conference with FDA in which GSK advised of its plans to implement, following the submission of a CBE labeling supplement, a change in the Warnings section of the Paxil labeling to describe additional information from GSK's recently completed meta-analyses on the adult MDD and non-MDD data sets. (See Kraus Decl. ¶ 81, Ex. 54, attached to Kraus Decl.)	**Admit.**
89. FDA did not object at the time to the implementation of GSK's proposed CBE labeling supplement for Paxil, but FDA (a) stated that it had not completed its evaluations of GSK's analyses in adult patients; (b) advised GSK to remove any reference to FDA agreement to GSK's DHCP letter; and (c) advised GSK that it had not completed its review of the data on adult suicidality received from other antidepressant manufacturers. (See id. ¶ 81.)	**Admit.**
90. On April 27, 2006, following this consultation with FDA, GSK submitted a CBE labeling supplement, proposing to include language in the Paxil labeling the following statement to the Clinical Worsening and Suicide Risk subsection of the Warnings section: Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo-controlled trials of adults with psychiatric	**Admit.**

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disorders showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24. (Id. ¶ 82, Ex. 55, labeling at 12, attached to Kraus Decl.) The statement "[i]t is also unknown whether the suicidality risk extends to adults" was deleted, but the statement "a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulse has not been established" remained. (Id.)	
91. The Paxil prescribing information included the following statement to the Information for Patients subsection of the Precautions section: Information from clinical trials has suggested that young adults, particularly those with depression, may be at an increased risk of suicidal behavior (including suicide attempts) when treated with PAXIL. The majority of attempted suicides in clinical trials in depression involved patients aged 18-30 years.	**Admit.**

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(Id. at 17.)	
92. After discussing the changes with FDA, GSK implemented these changes to Paxil's labeling, understanding that they were subject to FDA's further review and approval. (Kraus Decl. ¶ 84.)	**Objection. DISPUTED.** There is no indication that Dr. Kraus has personal knowledge that GSK understood the changes were subject to FDA's further review and approval.
93. Also in April 2006, an article co-authored by FDA employees, including Dr. Laughren, was published entitled "Suicide Rates in Short-term Randomized Controlled Trials of Newer Antidepressants." In this article, these FDA scientists discussed the results of FDA's analysis of suicide rates in placebo-controlled studies (up to year 2000), and concluded that "[n]either use of placebo nor of antidepressants in short-term [randomized controlled trials] was associated with an increased risk of completed suicide among patients with MDD or various anxiety disorders." (Kraus Decl. ¶ 85, Ex. 56, attached to Kraus Decl.)	**Objection. Irrelevant.** See No. 53 and 86 above.
94. In an August 22, 2006 letter to GSK, FDA approved GSK's supplemental labeling applications relating to Paxil (unrelated to the suicidality issue). FDA noted, however, that approval of those supplemental applications did not constitute an approval of GSK's April 2006 CBE labeling supplement and that the CBE was still pending. FDA advised that it was "currently evaluating the pending applications and will comment on the changes in a separate letter." (Id. ¶ 88, Ex. 57, attached to Kraus Decl.)	Plaintiff **does not dispute** that the FDA sent this letter to GSK. Plaintiff further notes that the FDA did not reject GSK's labeling changes and permitted GSK to make the labeling changes as discussed in GSK's Paragraph 92 above.
95. In November 2006, FDA released a memorandum from Dr. Thomas Laughren providing the conclusions from its study involving over 372 clinical trials and almost 100,000 patients. (Id. ¶ 89, Ex. 47 at 1, attached to Kraus Decl.)	**Objection.** Plaintiff does not dispute that Thomas Laughren issued such memo, but points out that this was a pooled analysis of a number of different antidepressants, not Paxil by itself. The data specific to Paxil showed an increased risk of suicidal behavior in patients of all ages. The FDA specifically found, based on a selection of clinical trials, that patients taking Paxil were nearly three times as likely to experience suicidal behavior compared to

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	placebo and the difference was statistically significant. Paxil had an odds ratio of 2.76 with a 95% Confidence Interval of 1.16-6.60 and a low p-value of 0.02. Exh. 40, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class," p. 26, Table 16. What this means is that the positive association between Paxil and these suicidal events did not likely happen by chance. See Grimson Decl., Exhibit 1, p. 31. A study published in the Journal of the Canadian Medical Association confirms this: The present analysis, which suggests that paroxetine is associated with a statistically significant increase in the risk of suicidal tendencies, expands the results of previous re-analyses of GlaxoSmithKline's data [citing GSK's 2006 analysis finding a 6.7 times increased risk] ... **The recently released re-analysis by the US food and Drug Administration ... confirmed these figures by showing that, among the selective serotonin reuptake inhibitors and newer antitdepressants, only paroxetine was significantly associated with an excess risk of suicidal behavior** ... (OR 2.76, 95% CI 1.16-6.60)." Exh. 42, Barbui et al., "Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials," CMAJ, January 29, 2008, emphasis added. GSK's own 2006 analysis, which looked specifically at all age groups of patients taking Paxil compared to patients taking placebo, found that adults with Major Depressive Disorder treated with Paxil compared to placebo were at a significant increased risk of attempting suicide. The results showed that the odds ratio for suicide attempt on Paxil was 6.7, a statistically significant result. (Exh. 35.) This means a patient on Paxil was nearly seven times more likely to attempt suicide than a patient on placebo.
96. Regarding paroxetine specifically, on the primary outcome endpoint, there was no increased risk of suicidal thoughts or	**Objection. DISPUTED in part.** Plaintiff **does not dispute** that the FDA analysis found a statistically significant increased risk of

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behavior for patients taking paroxetine. See Ex. 47 at 24, Table 15, attached to Kraus Decl. Instead, the analysis instead showed a slight decrease in risk (which was not statistically significant). For the secondary outcome, suicidal behavior, there was a statistically significant (at the 0.05 level) increased risk observed for paroxetine. See id. at 26, Table 16. Regarding findings such as these, however, FDA stated: "Although the values for some individual drugs are statistically significant at the 0.05 level, the significance of those findings must be discounted for the large number of comparisons being made." Id. at 23.	suicidal behavior for Paxil (see No. 95 above). With respect the finding of no increased risk in the data comprising suicidal ideation and behavior *combined*, that is likely because "suicidal ideation is far too common and nebulous and dilutes the data to the point that it obscures the serious risk of actual suicidal behavior." See Healy Decl., Report. With respect to the statement concerning discounting due to the "large number of comparisons," this refers to "multiple comparisons." Plaintiff **DISPUTES** the veracity of the statement. If many comparisons are being made in a study, statisticians may suggest that the investigators adjust the significance level downward to account for the likelihood that the more comparisons being made, the more likely it is that a result will be significant by chance. Many experts argue that a concern with multiple comparisons is unwarranted. See Grimson Decl., Report, p. 51-53. Indeed, GSK's own expert explained during his deposition that "in drug safety, we rarely use adjustments for multiplicity because we don't want to miss anything. We don't want to miss a potential signal that could be a safety signal that could actually be harmful to human life or the quality of life." Exh. 58, Gibbons depo, p. 92:3-8.
97. In this memorandum, Dr. Laughren addressed PDAC's upcoming meeting "to consider new information on the occurrence of suicidality in the course of treatment of adult patients with various antidepressants." (See id. at 1.) Dr. Laughren noted the meeting was intended to "discuss our plans for labeling modifications based on" findings from FDA's metaanalysis "involving 372 placebo-controlled antidepressant trials and almost 100,000 patients." (Id.)	**Objection. Irrelevant. Misleading. DISPUTED in part.** Dr. Laughren's memo stated: "The purpose of the December 13th meeting is to update the committee with our findings from this meta-analysis. We will present our findings and our interpretations of the data, and we will generally discuss our plans for labeling modifications based on these findings."
98. In December 2006, FDA held a public hearing to discuss the data from FDA's recent analyses of suicidal thoughts and behavior in adult clinical trials involving antidepressants, including Paxil. At the	Objection. **DISPUTED in part.** Plaintiff **does not dispute** that a public advisory committee meeting took place in December 2006 concerning analyses of adult clinical trials involving a number of different

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hearing, Dr. Laughren noted that the review of the pooled data relating to the risk of suicidality in adults taking antidepressants revealed a possible increased risk of suicidality in adults up to age 25, but that "the expected protected effect for suicidality with antidepressant appears to emerge beyond age 30 and particularly beyond age 65." (Kraus Decl. ¶ 92, Ex. 60, at 313, attached to Kraus Decl.)	antidepressants, but **DISPUTES** that the FDA's statement concerning a protective effect beyond age 30 applies to Paxil. Dr. Laughren's statement was based on a pooled analysis of a number of different antidepressants, not Paxil by itself. An examination of the data on which the FDA relied reveals that the supposed decreased risk in older adults, even if true for other antidepressants, is not true for Paxil. In fact, according to the FDA's analysis, Paxil *does* increase the risk of suicidal behavior in patients of all ages. The FDA specifically found, based on a selection of clinical trials, that patients taking Paxil were nearly three times as likely to experience suicidality compared to placebo and the difference was statistically significant. Paxil had an odds ratio of 2.76 with a 95% Confidence Interval of 1.16-6.60 and a low p-value of 0.02. Exh. 40, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class," p. 26, Table 16. What this means is that the positive association between Paxil and these suicidal events did not likely happen by chance. See Grimson Decl., Exhibit 1, p. 31. A study recently published in the Journal of the Canadian Medical Association confirms this: The present analysis, which suggests that paroxetine is associated with a statistically significant increase in the risk of suicidal tendencies, expands the results of previous re-analyses of GlaxoSmithKline's data [citing GSK's 2006 analysis finding a 6.7 times increased risk] ... **The recently released re-analysis by the US food and Drug Administration ... confirmed these figures by showing that, among the selective serotonin reuptake inhibitors and newer antitdepressants, only paroxetine was significantly associated with an excess risk of suicidal behavior**

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	... (OR 2.76, 95% CI 1.16-6.60)." Exh. 42, Barbui et al., "Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials," CMAJ, January 29, 2008, emphasis added. GSK's own 2006 analysis, which looked specifically at all age groups of patients taking Paxil compared to patients taking placebo, found that adults with Major Depressive Disorder treated with Paxil compared to placebo were at a significant increased risk of attempting suicide. The results showed that the odds ratio for suicide attempt on Paxil was 6.7, a statistically significant result. (Exh. 35.) This means a patient on Paxil was nearly seven 7 times more likely to attempt suicide than a patient on placebo. *See* Ross Decl., Report. See also No. 95 above.
99. During the hearing, some attendees advocated for a warning of increased suicidality without reference to age groups. (Id. at 100-01, 104, 130-34, 264-65.)	**Objection. Irrelevant.** Notwithstanding, Plaintiff **does not dispute** that some attendees advocated for warnings notwithstanding age.
100. At the December 13, 2006 public hearing, FDA presented its findings, which included that the "net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64 and to reduce the risk of both suicidality and suicidal behavior in subjects aged 65 years and older." As FDA's Dr. Laughren testified: I think that what we are seeing here is an extension of the suicidality risk finding that we were seeing in pediatric patients and young adults up to age 25, but we are not seeing it beyond that. In fact, there appears to be a beginning of a reversal of the effect in adults beyond age 30 with the suggestion of a protective [e]ffect. That [e]ffect appears to be even	**Objection. Irrelevant. Misleading. DISPUTED.** See No. 95 and 98 above. Also, this was a public advisory committee meeting and Dr. Laughren's statements do not constitute sworn testimony as this "statement of fact" suggests.

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more clear-cut in the elderly. (Id. at 307.)	
101. At the same hearing, Plaintiff's experts, Dr. Joseph Glenmullen and Dr. David Healy, requested that FDA extend the warning of an increased risk of suicidality to all age groups. (Id. at 158-60; 215-18.) An attorney from Plaintiff's counsel's law firm also made a statement to FDA and insisted that the warnings be extended to patients of all ages. (Id. at 165- 68.)	**Objection. Irrelevant.** Notwithstanding, Plaintiff **does not dispute** that Dr. Glenmullen, Dr. Healy and a former attorney from Plaintiff's counsel's firm individually attended the FDA Advisory Committee meeting and advocated for stronger suicidality warnings for all ages.
102. On May 1, 2007, following its independent analysis of adult suicidality data for a variety of antidepressants, including paroxetine, and on the recommendation of its expert advisory committee, FDA notified GSK that it had completed its review of the April 2006 CBE labeling supplement, and that it was "approvable." (Kraus Decl. ¶ 93, Ex. 61, attached to Kraus Decl.) FDA emphasized, however, that "[b]efore these applications may be approved, [GSK] will need to make revisions to [the Paxil] labeling, as outlined below, so as to ensure standardized labeling pertaining to adult suicidality with all of the drugs to treat major depressive disorder (MDD)." The letter specifically referenced the December 13, 200 Psychopharmacologic Drugs Advisory Committee (PDAC) meeting and recommended GSK revise its labeling and antidepressant Medication Guides to include the specific language provided by FDA. FDA's letter also instructed that "[c]hanges are also needed to inform practitioners about an apparent favorable effect of antidepressants on suicidality in older adults and to remind them that the disorders being treated with antidepressants are themselves associated with an increased risk of suicidality." The letter noted that FDA had issued a press release and updated its website to include the revised Medication Guides. FDA noted	**Objection. Irrelevant. Misleading.** Plaintiff **does not dispute** that the FDA sent this letter to GSK, but **DISPUTES** GSK's characterization of the letter and its inferred meaning. The FDA's decision to enact class wide labeling changes for all antidepressants, including Paxil, regarding suicidality in the adult population was based on a pooled analysis of a number of different antidepressants, not Paxil by itself. An examination of the data on which the FDA relies reveals that the supposed decreased risk in older adults, even if true for other antidepressants, is not true for Paxil. In fact, according to the FDA's analysis, Paxil *does* increase the risk of suicidal behavior in patients of all ages. The FDA specifically found, based on a selection of clinical trials, that patients taking Paxil were nearly three times as likely to experience suicidality compared to placebo and the difference was statistically significant. Paxil had an odds ratio of 2.76 with a 95% Confidence Interval of 1.16-6.60 and a low p-value of 0.02. Exh. 40, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class," p. 26, Table 16. What this means is that the positive association between Paxil and these suicidal events did not likely happen by chance. See Grimson Decl., Exhibit 1, p. 31. A study recently published in the Journal of the Canadian Medical Association confirms this:

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that these public announcements "are a better way to alert the community than individual Dear Health Care Professional (DHCP) letters for each of [the] products." Accordingly, FDA did not request sponsors disseminate individual DHCP letters. (Id.)	The present analysis, which suggests that paroxetine is associated with a statistically significant increase in the risk of suicidal tendencies, expands the results of previous re-analyses of GlaxoSmithKline's data [citing GSK's 2006 analysis finding a 6.7 times increased risk] ... **The recently released re-analysis by the US food and Drug Administration ... confirmed these figures by showing that, among the selective serotonin reuptake inhibitors and newer antitdepressants, only paroxetine was significantly associated with an excess risk of suicidal behavior** ... (OR 2.76, 95% CI 1.16-6.60)." Exh. 42, Barbui et al., "Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials," CMAJ, January 29, 2008, emphasis added. GSK's own 2006 analysis, which looked specifically at all age groups of patients taking Paxil compared to patients taking placebo, found that adults with Major Depressive Disorder treated with Paxil compared to placebo were at a significant increased risk of attempting suicide. The results showed that the odds ratio for suicide attempt on Paxil was 6.7, a statistically significant result. (Exh. 35.) This means a patient on Paxil was nearly seven times more likely to attempt suicide than a patient on placebo. *See* Ross Decl., Report. This analysis resulted in GSK changing Paxil's label in May 2006. (Exh. 36.) Thus, from May to August 2007, the Paxil label included Paxil-specific language that stated: "In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were

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	suicide attempts." (*Id.*) GSK also sent a "Dear Doctor" letter to U.S. physicians in May 2006, which included this same language. (Exh. 38.) The FDA nowhere has stated that **Paxil** does not increase the risk of suicidality in patients over 24 or in Stewart Dolin's age range.
103. The new labeling stated "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in the risk with antidepressants compared to placebo in adults aged 65 and older." (Kraus Decl. ¶¶ 94-95, Ex. 62, "Revisions to Product Labeling" at 1, attached to Kraus Decl.)	**See No. 102 above. Objection. Misleading. Irrelevant. DISPUTED** as to Paxil specifically. According to the FDA's analysis, Paxil *does* increase the risk of suicidal behavior in patients of all ages. The FDA specifically found, based on a selection of clinical trials, that patients taking Paxil were nearly three times as likely to experience suicidality compared to placebo and the difference was statistically significant. GSK could have supplemented its label with the Paxil specific risks, but chose not to do so. See PFF Nos. 102-114. GSK declined the FDA's invitations to discuss and/or propose Paxil-specific adult warnings even though it knew that the Paxil-specific data justified additional warnings. *Id.* When GSK included suicide warnings in 2006, the FDA did not indicate that such warnings were false or misleading. The FDA did not initiate any sort of an enforcement action against GSK. And, the FDA did not request any substantive changes in the proposed labeling submitted by GSK. GSK was never prohibited from including a warning in another section of the label other than in the class labeling section. Ross Decl., Report.
104. The new labeling also stated "[s]uicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide," (id. at 1), and that, while a few suicides occurred during the adult trials, "the number [of completed suicides] was not sufficient to reach any conclusion about drug effect on suicide" (id. at 2).	See Nos. 102 and 103 above.
105. On May 2, 2007, FDA issued a press release entitled "FDA Proposes New Warnings About Suicidal Thinking,	See Nos. 102 and 103 above.

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Behavior in Young Adults Who Take Antidepressant Medications." In this release, FDA announced that it had requested that manufacturers of "all antidepressant medications update the existing boxed warning on their products' labeling to include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment." FDA further explained that its labeling changes, however, also included language stating that "scientific data did not show this increased risk in adults older than 24, and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality." (Id. ¶ 94, Ex. 62, "FDA News" at 1, attached to Kraus Decl.) FDA's warning statements also emphasized that "depression and certain other serious psychiatric disorders are themselves the most important causes of suicide." (Id.)	
106. FDA explained that the basis for its decision was "a comprehensive review of 295 individual antidepressant trials that included over 77,000 adult patients with major depressive disorder (MDD) and other psychiatric disorders." (Id., Ex. 62, "Revisions to Product Labeling" at 2, attached to Kraus Decl.)	While Plaintiff **does not dispute** that the FDA made such a statement, the FDA's review encompassed a number of different antidepressants, not Paxil by itself. See Declaration of Grimson Decl, Report.
107. In an accompanying Question & Answer document, FDA stated: "The labeling also will point out that scientific data did not show this increased risk in adults older than 24 and that adults ages 65 and older taking antidepressants actually have a decreased risk of suicidality." (Id., "Question & Answer" at 1, attached to Kraus Decl.)	**Objection. Misleading. Irrelevant. DISPUTED.** FDA's statement was based on a pooled analysis of a number of different antidepressants, not Paxil by itself. An examination of the data reveals that the supposed decreased risk in older adults, even if true for other antidepressants, is not true for Paxil. In fact, according to the FDA's analysis, Paxil *does* increase the risk of suicidal behavior in patients of all ages. The FDA specifically found, based on a selection of clinical trials, that patients taking Paxil were nearly three times as likely to experience suicidality compared to placebo and the difference was statistically significant. Paxil had an odds ratio of 2.76 with a 95%

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	Confidence Interval of 1.16-6.60 and a low p-value of 0.02. Exh. 40, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class," p. 26, Table 16. What this means is that the positive association between Paxil and these suicidal events did not likely happen by chance. See Grimson Decl., Exhibit 1, p. 31. A study published in the Journal of the Canadian Medical Association confirms this: The present analysis, which suggests that paroxetine is associated with a statistically significant increase in the risk of suicidal tendencies, expands the results of previous re-analyses of GlaxoSmithKline's data [citing GSK's 2006 analysis finding a 6.7 times increased risk] ... **The recently released re-analysis by the US food and Drug Administration ... confirmed these figures by showing that, among the selective serotonin reuptake inhibitors and newer antitdepressants, only paroxetine was significantly associated with an excess risk of suicidal behavior** ... (OR 2.76, 95% CI 1.16-6.60)." Exh. 42, Barbui et al., "Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials," CMAJ, January 29, 2008, emphasis added. GSK's own 2006 analysis, which looked specifically at all age groups of patients taking Paxil compared to patients taking placebo, found that adults with Major Depressive Disorder treated with Paxil compared to placebo were at a significant increased risk of attempting suicide. The results showed that the odds ratio for suicide attempt on Paxil was 6.7, a statistically significant result. (Exh. 35.) This means a patient on Paxil was nearly seven times more likely to attempt suicide than a patient on placebo. *See* Decl. of David Ross, Report.
108. On May 2, 2007, FDA emailed GSK, advising that drug manufacturers were to "submit revised prescriber labeling and [Medication Guides], verbatim, as outlined in" FDA's May 1, 2007 letter. (Kraus Decl.	Plaintiff **does not dispute** that Renmeet Grewel of the FDA sent an email to GSK's regulatory employee, Barbara Arning, concerning the FDA's request for class labeling.

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¶ 97, Ex. 63, attached to Kraus Decl.)	
109. On May 7, 2007, GSK asked FDA for clarification of its May 1, 2007 letter, asking whether it could keep the language in Paxil's labeling that had been the subject of GSK's April 2006 CBE labeling change or whether it should "replace the complete warning section on this topic [with] the new class labeling?" GSK specifically asked whether it could keep and maintain the following language in Paxil's labeling: *Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo-controlled trials of adults with psychiatric disorder showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.* (Kraus Decl. ¶ 98, Ex. 63, attached to Kraus Decl.)	Objection. There is no indication that Dr. Kraus has personal knowledge of the statements in this paragraph and he does not properly authenticate the cited document. Notwithstanding, Plaintiff **does not dispute** that GSK's employee, Barbara Arning, asked for clarification of the FDA's request for class labeling.
110. Later that same day, May 7, 2007, FDA responded to GSK's inquiry and rejected	**Objection**. There is no indication that Dr. Kraus has personal knowledge of the

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GSK's request to keep and maintain Paxil-specific language in the labeling about suicidality which had been added by way of GSK's April 2006 CBE labeling change. FDA directed GSK to "replace the previous warning section with the new language [FDA] provided to [the Company] in the Class labeling letter signed on May [1], 2007." 4 (Kraus Decl. ¶ 99, Ex. 63, attached to Kraus Decl.)	statements in this paragraph and he does not properly authenticate the cited document. Notwithstanding, Plaintiff **does not dispute** that Renmeet Grewel of the FDA sent an email to Barbara Arning telling her to replace GSK's "paragraph on young adults" with the class labeling. However, see also No. 113 below.
111. On May 11, 2007, GSK formally responded to FDA's May 1, 2007 letter, and proposed to retain the Paxil-specific language that had been added in May 2006 to Paxil's labeling. GSK again requested that it be allowed to keep and maintain the following Paxil specific language in Paxil's labeling: *A GlaxoSmithKline sponsored analysis of placebo-controlled trials of paroxetine found that ~~Y~~young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. ~~An~~ For all psychiatric disorders combined, this* analysis ~~of placebo-controlled trials of adults with psychiatric disorders~~ showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these	Plaintiff **does not dispute** that GSK sent such letter on the stated date. However, see No. 113 below.

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attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24. (Kraus Decl. ¶ 100, Ex. 64, attached to Kraus Decl.)	
112. GSK specifically asked whether FDA agreed that the Paxil-specific language added by GSK's April 2006 CBE labeling change could remain in Paxil's labeling to "complement" the class labeling: "Do you agree with complementing the class labeling with maintaining the Paxil specific paragraph?" (Kraus Decl. ¶ 101)	Plaintiff **does not dispute** this alleged fact. However, see also No. 113 below.
113. On May 15, 2007, FDA responded and advised GSK: "Please submit your CBE application with your requests. [FDA] will be discussing all the sponsor's proposals during the last week of May. After we discuss everyone's proposal [FDA] will have a response to your questions." (Id. ¶ 102, Ex. 65, attached to Kraus Decl.)	**Objection. Irrelevant. Misleading. DISPUTED in part.** At the point in time when the FDA was in the process of implementing class wide labeling in 2007, GSK suggested in its exchanges with the FDA that it believed the 2006 **Paxil-specific** adult language should become part of **class labeling**. (Exh. 56-57 and 101.) On June 22, 2007, the FDA told GSK "we do not believe that your **product specific** analysis should be included in the **class labeling** revisions **since the labeling is targeted at the class of drugs** [not Paxil specifically]. **If you would like to discuss this matter further, please submit a formal meeting request**." Exh. 56, June 22, 2007 email. According to a June 21, 2007 FDA correspondence, the FDA stated: "We also have noted that some [drug manufacturers] have taken this opportunity to include other revisions to their labeling which are **not applicable to the class labeling** revision requested in our 5-1-07 letter. *We are requesting that these changes be submitted as a separate supplement*." *See* Exh. 55 (emphasis added). **GSK never asked for a formal meeting, did not contest the class-wide labeling, nor did it seek additional labeling regarding Paxil-specific data.** Accordingly, GSK could have supplemented its label with the Paxil specific risks, but chose not to do so.

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	GSK declined the FDA's invitations to discuss and/or propose Paxil-specific adult warnings even though it knew that the Paxil-specific data justified additional warnings. Dr. Ronald Krall, GSK's Senior Vice President and Chief Medical Officer and the Co-Chairman of GSK's Global Safety Board, testified that it was his decision not to request the meeting because he "speculated" it would take a long time to get a meeting date and would not lead to a different result (Exh. 37, p. 126:16-127:15). Dr. Krall's decision not to push the issue was made notwithstanding his testimony that GSK's 2006 analysis resulting in revised labeling for Paxil and its dissemination of a "Dear Doctor" letter alerting doctors to the 6.7 times increased risk of suicidality in depressed adults of all ages was important to communicate to doctors: Q. ... [S]ir, would you agree that this new change to the warning section of the Paxil label GSK thought was important to get to prescribing physicians? A. Yes. Q. Okay. Now, in fact, the importance was such that GSK believed that it should notify physicians immediately through what we've described or what we've called the Dear Healthcare Professional letter? A. Correct. (Exh. 37, Krall depo, p. 32, -33, 107-113.) GSK was never prohibited from including a warning in another section of the label other than in the class labeling section. Ross Decl., Report.
114. Following FDA's directive, on May 23, 2007, GSK formally submitted a CBE labeling supplement that again proposed to retain Paxil-specific language that GSK had added through its CBE supplement filed in April 2006. (Id. ¶ 103, Ex. 66, attached to Kraus Decl.)	See No. 113 above.
115. FDA contacted GSK on June 21, 2007, advising that the class labeling for SSRIs	See No. 113 above. This June 21, 2007 FDA letter also stated: "We also have noted that

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needed some additional revision. Accordingly, FDA provided new language that all SSRI-sponsors (including GSK) were required to include in their product labeling. The new language did not include any of the Paxil-specific language included in either GSK's April 2006 labeling change or GSK's May 23, 2007 CBE labeling supplement. In its June 21 correspondence, FDA emphasized: "Please be reminded that it is critical that the labeling is consistent for all of these products." (Kraus Decl. ¶ 104, Ex. 67, attached to Kraus Decl.)	some [drug manufacturers] have taken this opportunity to include other revisions to their labeling which are **not applicable to the class labeling** revision requested in our 5-1-07 letter. *We are requesting that these changes be submitted as a separate supplement*." *See* Exh. 55 (emphasis added). **GSK never asked for a formal meeting, did not contest the class-wide labeling, nor did it seek additional labeling regarding Paxil-specific data.**
116. On June 22, 2007, GSK again contacted FDA to confirm whether FDA was directing GSK to remove the Paxil-specific language and analyses added to Paxil's labeling in April 2006. (Kraus Decl. ¶ 105.)	See No. 113 above.
117. FDA responded by e-mail on June 22, stating in part: As for your first question, the Agency has reviewed your proposed changes, and we do not believe that your product specific analysis should be included in class labeling revisions since the labeling is targeted at the class of drugs. If you would like to discuss this matter further, please submit a formal meeting request. As for your second question, please respond by email that you accept the changes and also send in a word version of the labeling via email. We will then send an approval letter since you have accepted the changes. (Kraus Decl. ¶ 105, Ex. 68, attached to Kraus Decl.)	See No. 113 above.
118. GSK made all FDA-mandated changes that same day. (Kraus Decl. ¶ 108.)	**Objection.** There is no indication that Dr. Kraus has personal knowledge of the statement in this paragraph and GSK has submitted no evidence indicating that GSK made the changes that same day.
119. GSK did not formally request a meeting to address this issue on yet another	**Objection**. There is no indication that Dr. Kraus has personal knowledge of the

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occasion, because doing so would have been futile. GSK believed that FDA's invitation to file a formal meeting request was a customary, regulatory process courtesy and clearly signaled that a final decision had been made by the FDA's review division and would not be reconsidered. FDA had been clear, on several prior occasions, that (a) FDA was not accepting either Paxil specific data for inclusion in Paxil's labeling or Paxil-specific data that had been included in GSK's prior CBE labeling supplements and other correspondence and (b) FDA wanted the labeling for medications in the class to be identical and consistent on the issue of adult suicidality. (Id. ¶ 106.)	statements in this paragraph or the state of mind of others within GSK on this matter, nor does Dr. Kraus cite any evidence to support this statement. **DISPUTED.** This statement is utterly lacking in foundation and constitutes nothing but self-serving speculation.
120. Moreover, for GSK to have made such a formal request to meet and ask again the FDA's Review Division to include the GSK-specific language in labeling, GSK would have been required to present new data, new analysis, or other newly-acquired information to FDA – as opposed to the various analyses and data described above, which GSK had already presented to FDA – and no such new data or analyses existed. Without new data, new analyses, or new information, it is a virtual certainty that any formal meeting request to reconsider the Paxil-specific language would have been either (a) rejected, or (b) if FDA had granted the meeting request, the FDA would have restated and reiterated its decision against including the Paxil-specific labeling because the issue had already been carefully reviewed, considered, and decided, and there was no new information to warrant reconsideration. (Id. ¶ 107.)	See No. 119 above.
121. On August 2, 2007, FDA approved GSK's revised labeling that included the verbatim language provided by FDA, including the statement that "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared	**Objection. Irrelevant. Misleading.** See Nos. 107 and 113 above.

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to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older." Kraus Decl. ¶ 109, Ex. 69, at Paxil labeling, p. 11, attached to Kraus Decl. The approved labeling added: "There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide." Id. at Paxil labeling, p.12. In its letter, FDA instructed GSK that its "[f]ailure to make these changes within the specified period of time could make your product misbranded under 21 USC 321(n) and 352(a)." The labeling with the class language was issued and posted on both FDA's and GSK's websites (Id. at ¶ 109; Exs. 69-70, attached to Kraus Decl.)	
122. In accordance with the FDA's instructions and directives described above, this revised labeling did not include the Paxil-specific language that was the subject of GSK's CBE submissions in April 2006 or May 23, 2007. (Kraus Decl. ¶ 110.)	**Objection. Irresponsible.** The fact that the revised label "did not include the Paxil-specific language" is the result of GSK's own actions/inaction. In fact, GSK "bears the responsibility for the content of its label at all times." *Levine* at 1197-98. GSK *knows* the class labeling which states the risk of suicidality with antidepressants compared to placebo does extend to adults beyond age 24 is *false* with respect to Paxil.
123. Since FDA's meta-analysis in December 2006, there have been no new randomized, double-blind placebo-controlled trials of paroxetine conducted by GSK that have provided data that would merit changes or additions to the Paxil labeling regarding adult suicidal thinking or behavior or completed suicide. Similarly, since FDA's meta-analysis in December 2006, there are no new randomized, double-blind placebo-controlled trials of paroxetine conducted by others that have provided data that would merit changes or additions to the Paxil labeling regarding adult suicidal thinking or behavior or completed suicide. (Kraus Decl. ¶ 111.)	**Objection.** There is no indication that Dr. Kraus has any personal knowledge concerning the statement in this paragraph (or whether or not there have been any new randomized, double-blind placebo-controlled trials of paroxetine since December 2006). **Irrelevant.** There is no requirement that a plaintiff must show newly acquired information after initial approval in order to defeat preemption. The FDA is exclusive judge of safety and efficacy based on information available *at the commencement of marketing*. If new information develops *post-approval*, the duty is triggered and a manufacturer is obligated to ensure the content of its label is not false or misleading in any particular. GSK **"bears the responsibility for the content of its label at all times."** *Levine* at 1197-98.

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	See also No. 113 above.
124. In May 2009, FDA officials published the meta-analysis that had been discussed at the December 2006 meeting, discussed supra. The article states: When we presented these results [including a neutral or possibly protective effect on suicidal behavior for adults between the ages of 25 and 64] at a [PDAC] meeting…the committee agreed with FDA's conclusion that the risk of suicidality associated with antidepressants in young adults (under 25) approached that seen in children and adolescents, that the net effect seemed to be neutral in adults aged 25-65, and that the effect on suicidality was favourable in adults older than 65. They recommended that the FDA should expand the suicidality warning language in labeling and in the medication guide with this new information, including the strong age relatedness of the findings….These changes to labeling and medication guides have now been implemented. Risk of Suicidality in Clinical Trials of Antidepressants in Adults: Analysis of Proprietary Data Submitted to US Food and Drug Administration, BMJ 2009; 339:b2880, attached as Ex. 9 to Davis Decl.	**Admit.**
125. The current FDA-approved paroxetine prescribing information reflects FDA's determinations. The paroxetine labeling today contains the same language regarding suicidality, akathisia, and adult patients as it did following the FDA's requested changes in August 2007, and the same language as it contained in 2010. That language includes the following: • In a boxed warning entitled "**Suicidality and Antidepressant Drugs**": "Short-term studies did not	**Objection. Irrelevant.** GSK "bears the responsibility for the content of its label at all times." *Levine* at 1197-98.

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show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber." • In the WARNINGS section, "**Clinical Worsening and Suicide Risk"**: … Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. * * * … There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. * * * **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose**	

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changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. * * * **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual**	

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changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include dailyobservation by families and caregivers…. • In a PRECAUTION regarding **"Clinical Worsening and Suicide Risk"**: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. • In a PRECAUTION entitled "**Akathisia**: The use of paroxetine or other SSRIs has been associated with	

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the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment." (Kraus Decl. ¶ 113, Exs. 70-72, attached to Kraus Decl.)	

Respectfully submitted,

BAUM HEDLUND ARISTEI & GOLDMAN, P.C.

Dated: September 14, 2015

By: /s/ R. Brent Wisner

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CERTIFICATE OF SERVICE

I, R. Brent Wisner, hereby certify that on September 14, 2015, I served a copy of the foregoing **PLAINTIFF'S STATEMENT OF GENUINE ISSUES OF MATERIAL FACT IN OPPOSITION TO DEFENDANT GSK'S MOTION FOR SUMMARY JUDGMENT (FEDERAL PREEMPTION)** on the following counsel via electronic mail:

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