)
)
)
)
)
)
)
)
)
)
)
)

A. GSK'S KNOWLEDGE OF THE ASSOCIATION BETWEEN PAXIL AND AN INCREASED RISK OF SUICIDALITY IN ADULTS

1. GSK has known about Paxil's association with suicidality for over 15 years, but concealed the risk and, instead, promoted Paxil as Safe and Effective

	ADDITIONAL PROPOSED FINDINGS OF FACTS
1.	In November 1989, GSK submitted its "Integrated Summary of Safety Information" to obtain approval of Paxil to treat adult depression. Amongst other adverse event statistics, the Safety Summary reported the number of suicides and suicide attempts experienced by patients who took Paxil, a placebo or a comparator drug during GSK's initial clinical trials. Exh. 1, Paxil Integrated Summary of Safety.

2.	In its presentation of the suicide attempts, GSK included in its analysis suicide attempts of placebo patients that had taken place in the placebo run-in (or wash-out) phase, before the clinical trial actually began, as though they had occurred after the start of the study.[1] This skewed the statistical analysis of the data presented and obscured the true risk. *Id.* *See also* Glenmullen Decl., Adult Report, p. 2.
3.	Adverse events that occur during run-in periods *cannot* be included when calculating adverse event ratios for clinical trials. This principle has been confirmed by both the FDA and, ultimately, GSK itself. Exhs. 2-5.
4.	To wit, FDA's Dr. Robert Temple, a senior figure within the FDA[2], and Dr. Martin Brecher, the FDA reviewer who analyzed Paxil's safety as part of the FDA approval process, confirmed that it is inappropriate to count run-in events. Exh. 2, 361:16-362:1 and Exh. 3, p. 210-211.
5.	Dr. Brecher specifically testified that it is "scientifically illegitimate" to count placebo run-in/washout events. Exh. 3, p. 210-211.
6.	Michael Seika, another FDA medical reviewer, explained why run-in adverse events should not be counted. According to a December 8, 1999 GSK memo of a conversation with the FDA: > Specifically, I [Thomas Kline, Assistant Director of Regulatory Affairs at GSK] asked [Michael Seika] if a patient were to die during placebo run-in, i.e. prior to randomization, should that patient be included in the calculation for placebo deaths. He clearly stated that such a patient should not be counted in our analyses, since such a patient would not comprise the "controlled" portion of a trial. Exh. 4.
7.	GSK understood that counting adverse events during placebo run-in was improper as reflected by GSK employee Daniel Burnham's email to other GSK employees: "However, we cannot combine these placebo run-in deaths with the randomized placebo death rate for the 3 reasons above." Exh. 5.
8.	GSK's Chief Executive Officer testified that adverse side effects should only be counted after the wash-out phase is complete and the official study has begun. Exh. 6, Garnier deposition at p. 172-174.

[1] During the placebo run-in period (which is also called wash-out), patients participating in a clinical trial are taken off of any medications they may be taking and given a placebo (inert substance) instead. In this way, a person's system is "washed out" of other drugs and all patients start the trial on a drug-free basis at "baseline," i.e. at the actual beginning of the clinical trial. Because people who are stopping medications during this wash-out period may be experiencing adverse events associated with withdrawing from the medication they were on, adverse events experienced during this period are not properly counted as occurring during the clinical trial.

[2] Dr. Temple holds two positions within the FDA. He is the Director of the Office of Medical Policy as well as Acting Director of the Office of Drug Evaluation I, that part of the FDA responsible for approving new drug applications.

9.	An accurate reading of GSK's original safety submission to the FDA, excluding placebo run-in events, comparing the on-Paxil and on-placebo event rates to each other, **patients taking Paxil were at an 8.9 times greater risk of experiencing a suicide event than those on placebo**. Exh. 1, Paxil Integrated Summary of Safety Information; Glenmullen Decl., Adult Report, pp. 2-7; Exh. 7, Drug-Demographic and Drug-Disease Interactions; and Grimson Decl., Report, pp. 30.

2. GSK Continued the Subterfuge in a 1991 Submission to FDA Analyzing Suicidality Data from its Clinical Trials

	ADDITIONAL PROPOSED FINDINGS OF FACTS
10.	In response to a request from the FDA, GSK prepared a report entitled, "Suicidal Ideation and Behavior: An Analysis of the Paroxetine Worldwide Clinical Database," which was sent to the FDA by cover letter dated May 10, 1991. Exh. 8.
11.	When GSK reported the number of suicide attempts, it increased the number of suicide attempts by double and failed to disclose how many occurred during the run-in phase. *Id.* *See also* Glenmullen Decl., Adult Report, p. 11.
12.	In fact, 5 of the 6 placebo suicide attempts identified in the May 10, 1991 report were placebo run-in events. (See Exh. 9, GSK Admissions).
13.	Additionally, GSK reduced the number of patients on Paxil who attempted suicide from 42 to 40[3]. Glenmullen Decl., Adult Report, pp. 9-11.
14.	By increasing the number of suicide attempts of patients taking placebo and reducing the number of Paxil patients attempting suicide, the percentages between Paxil and placebo became approximately the same, indicating a nominal increased risk for Paxil patients. *Id.*, Exh. 8. (The percentage of Paxil patients attempting suicide went down from the original submission because GSK reduced the number of Paxil suicide attempts from 42 to 40.) *Id.*, pp. 9-13.
15.	By taking out the run-in suicide attempt events, the correct number was 40 suicide attempts while on Paxil versus 1 attempt on placebo, an approximately 7.5 fold increase of suicide attempt risk for Paxil patients. *Id.*, p. 12, Table 9; Grimson Decl., Report.
16.	This does not include the number of completed suicide ratios which would provide a more complete picture of Paxil-induced suicidal behavior. Adding suicide deaths and suicide attempts together, there was an over 8 fold greater rate of suicidal acts on Paxil than on placebo. Glenmullen Decl., Adult Report, p. 13; Grimson Decl., Report.

[3] In discovery, GSK claims that it made an error in the original number of 42 suicide attempts in the Safety Summary. Exh. 10, GSK's Objectives and Responses to Plaintiffs' Fifth Set of Interrogatories in *Steinberg v. GSK*.

17.	According to Plaintiffs' expert, Dr. Richard Kapit (who was a safety reviewer at the FDA for 16 years and specialized in SSRI antidepressants), the non-manipulated data was sufficient to justify a suicidal behavior warning in Paxil's initial prescribing information when it was first introduced into the U.S. market in 1992. See Decl. Kapit, Report ¶ 2.1.

3. GSK "Bamboozled" FDA

	ADDITIONAL PROPOSED FINDINGS OF FACTS
18.	Paxil was approved in 1992. Exh. 11.
19.	The 1992 Summary Basis for Approval of Paxil shows that the FDA itself relied upon and reiterated the May 10, 1991 Suicide Report's false placebo numbers and the incorrect conclusions based on them. Exh. 12, p. 29, Table 55.
20.	On June 11, 2008, U.S. Senator Chuck Grassely (R-Iowa), Chairman of the Senate Committee on Finance noted in a speech to the Senate that GSK has engaged in deliberate concealment of safety risks and requested an investigation into GSK's conduct. See Exh. 13 (Exhibit includes statement from the Office of Senator Grassley; transcript of Senator Grassley's Floor Statement; letter from Senator Grassley to the FDA; and letter from Senator Grassley to GSK).
21.	In his floor statement, Sen. Grassley stated that "[e]ssentially, **it looks like GlaxoSmithKline bamboozled the FDA.**" *Id.*
22.	Senator Grassley stated that the true data "demonstrates a causal link between the antidepressant and suicidal behavior. This has been true since 1989 although the 'bad' Paxil numbers obscured the risk for a decade-and-a-half." *Id.*
23.	In public, GSK continues to defend its actions. GSK spokeswoman Mary Anne Rhyne told the New Scientist in a February 2008 article that inclusion of the run-in/washout data "was intended to present the full picture of events that occurred in all phases of the clinical trials - starting from the time patients were enrolled, before they were randomised." Exh. 14.
24.	But, the New Scientist reported, "[i]ndependent researchers say it was wrong to use washout data as GSK did. '**I can't imagine circumstances in which it would be appropriate**,' says Bruce Psaty of the University of Washington in Seattle." *Id.*

4. GSK's Promotion Perpetuates False Suicidality Figures

	ADDITIONAL PROPOSED FINDINGS OF FACTS
25.	Both prior to and following Paxil's approval, GSK conducted a substantial marketing campaign regarding the benefits and safety of Paxil, reiterating in multiple arenas the false placebo numbers from its May 10, 1991 report and the conclusions based on those false numbers. Exhs. 1, 12 and 15-18.

26.	For example, in September 1991, a year prior to Paxil's approval, SKB employees Dr. Geoffrey Dunbar and Sarah Mewett presented a paper entitled "Evaluation of Suicidal Thoughts and Acts with Paroxetine" at a medical conference in order to address the then-recent concerns linking suicidality to SSRI antidepressants. Exh. 15.
27.	The presentation repeated the false figures from the May 10, 1991 report. Exh. 8.
28.	Dr. Dunbar presented a paper entitled, "Reduced suicidal thoughts and behavior (suicidality) with paroxetine" to the December 1991 meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico. (Exh. 16 is a summary of that report.)
29.	The report asserts that "Suicides and suicide attempts occurred less frequently with paroxetine than with either placebo or active controls." However, the actual Paxil Safety Summary showed the opposite, that Paxil-treated patients attempted or committed suicide over 7 times more often than placebo-treated patients. See Exh. 1 and Grimson Decl., Report, pp.34-35.
30.	The paper falsely concluded, "This analysis shows that suicidality is inherent in depressive illness and that paroxetine is appropriate for the integrity of depressed patients." Exh. 1.
31.	After approval, GSK's promotional campaign continued and, in 1995, GSK's employee Dr. Geoffrey Dunbar and two other psychiatrists (relying upon the manipulated data) published another article in the medical journal of *European Neuropsychopharmacology*. Exh. 17, p. 10, Table 8).
32.	The article, titled, "Reduction of Suicidal Thoughts with Paxil in Comparison with Reference Antidepressants and Placebo" concluded that Paxil actually *reduced* suicides and suicides attempts. *Id.*
33.	Armed with the new "peer reviewed" article, GSK instructed its sales force to use the article with "your physicians to **alleviate any concerns they may have regarding suicidal ideation."** Exh.18, GSK's July 5, 1995 Marketing Memo.
34.	GSK did nothing to correct the flawed suicide data it had promulgated to the medical community. Declaration of Roger Grimson, Report; Declaration of Dr. Joseph Glenmullen, Report.
35.	In 2002, GSK reported $3.1 billion in annual sales for Paxil becoming the most profitable pharmaceutical product in GSK's inventory. Exh. 19, GSK's 2002 Annual Report, pp. 14-15.

5. Regulatory Analyses of Clinical Trials in Children/Adolescents Blow Lid Off Previously Hidden Paxil Suicide Risks

	ADDITIONAL PROPOSED FINDINGS OF FACTS

36.	On April 11, 2002, GSK submitted a Supplemental New Drug Application ("sNDA") to FDA "proposing the use of Paxil to treat children and adolescents with major depressive disorder and obsessive compulsive disorder." Exh. 20, Pediatric Supplemental Application, PAR001217065; See also Exh. 21, Letter from FDA to GSK dated April 22, 2002, PAR001216923 - 926. This Application was never approved by the FDA.
37.	On October 7, 2002, Dr. Andrew Mosholder, the FDA reviewer of the pediatric sNDA for Paxil completed his review and noted that the most prominent adverse reactions in the Paxil clinical trials were "behavioral effects," but he stated "these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients ... Further assessment of the safety profile will have to await the sponsor's reply to requests for additional information ..." Exh. 22, Mosholder Clinical Review, p. 6.
38.	On October 21, 2002, the FDA issued a letter to GSK on its adolescent sNDA requesting additional information and clarification including "an expanded version of [a table of adverse events coded under the terms hostility, emotional lability or agitation], including all psychiatric and behavioral adverse events, and also those that occurred among placebo patients" and GSK's "rationale for coding suicide attempts and other forms of self-injurious behavior under the [] term 'emotional lability.'" Exh. 23, Letter from FDA to GSK received by GSK on October 21, 2002. PAR001216928-931.
39.	On October 25, 2002, John Davies of GSK's Biomedical Data Sciences department completed two analyses of the pediatric studies adverse event data. The results of the first analysis showed a statistically significant difference between those children and adolescents taking Paxil (3.4%) compared to those taking placebo (1.2%). Paxil demonstrated a relative risk 2.83 times greater than placebo. Exh. 24. The second analysis showed a statistically signficant difference between children and adolescents taking Paxil (2.4%) compared to those taking placebo (0.8%). Paxil demonstrated a relative risk 3.0 times greater than placebo. Exh. 25.
40.	Neither of these analyses were submitted to the FDA prior to suicide attempt. *Id.*
41.	On May 21, 2003, seven months after the FDA requested additional data from GSK concerning events coded as hostility, emotional lability or agitation and seeking an explanation from GSK concerning its "rationale for coding suicide attempts and other forms of self-injurious behavior under the [ ] term 'emotional lability,'"GSK submitted a briefing document to UK regulators summarizing its pediatric clinical trial data. Exhs. 26 and 27.
42.	On June 2, 2003, Dr. Russell Katz of the FDA informed FDA reviewer, Dr. Andrew Mosholder that the FDA had been contacted approximately one week earlier by British regulators who informed FDA that data submitted in the UK by GSK "demonstrated that use of Paxil in kids was associated with increased suicidality compared to placebo, and that the company proposed labeling changes." Exh. 28, Congressional Record, Tab 1, p. 135.
43.	According to this same email, GSK "had not informed [FDA] of any of this ..." *Id.*

44.	The email also states that the FDA received a "partial response" from GSK to the FDA's request for further elaboration on events subsumed under the term "Emotional Lability" and that "**almost all of these events related to suicidality**." *Id.*, p. 136, emphasis added.
45.	Dr. Katz also pointed out in this email that GSK "**has not proposed labeling changes**, and makes a feeble attempt to dismiss the finding." He also stated FDA's intention to review other SSRIs to see whether or not "similar events are being **hidden by various inappropriate coding maneuvers.**" *Id.*, emphasis added.
46.	As with children and adolescents, GSK coded suicide events that occurred in the adult clinical trials of Paxil as "emotional lability" as well. See Kapit Decl., Report.
47.	On February 2, 2004, the FDA convened an advisory committee to discuss the relationship between Paxil and other antidepressants and suicidality in pediatric patients. Exh. 78.
48.	During the February 2, 2004 advisory committee meeting, Dr. Thomas Laughren of the FDA confirmed that a drug manufacturer can, without prior approval of the FDA, change its label to provide stronger warnings regarding risks associated with the drug and noted that the antidepressant manufacturer Wyeth had, in fact, done just that in August 2003. He stated: In August, Wyeth, the manufacturer of Effexor, having respnded to our July request and having looked at theri data, decided tht they did have a signal and they made labeling changes which they are allowed to do under changes being effected without our prior approval, so they changed their labeling, adding information about that percieved signal, and they also sent a Dear Doctor letter which essentially recommended agains thte use of Effexor in pediatrics." *Id.*, p. 237-238, emphasis added.
49.	During the February 2, 2004 advisory committee meeting, Dr. Katz noted: It is the controlled trial data that we believe is best able to help us provide an adequate answer to this question, but as you have heard, and you will hear throughout today's presentations, **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 (emphasis added).
50.	The February 2, 2004 FDA advisory committee ultimately recommended that the FDA issue an immediate warning concerning the potential risk of suicidality Exh. 51, p. 9-10.
51.	**On March 4, 2004, was prescribed Paxil. Exh. 44.**
52.	**On March 17, 2004, attempted suicide. Exh 44.**

53.	Five days following suicide attempt, on March 22, 2004, the FDA issued a Public Health Advisory, in which it asked antidepressant manufacturers to warn about a potential suicidality risk for **both children/adolescents and adults**. Exh. 29. Even though the FDA had not yet analyzed the adult data, the FDA asked for this added precautionary warning as to *both adult* and pediatric patients.
54.	In May 2004, GSK sent a "Dear Healthcare Professional" letter to doctors in the United States alerting them of the FDA's March 22, 2004 Public Health Advisory. The letter described new revised labeling that explained "patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and (suicidality) ..." Exh. 30. The new warning recommended "close observation" of patients taking Paxil "for worsening depression or the emergence of suicidality, particularly at the beginning of treatment or at the time of dose increases or decreases." *Id.* The May 2004 GSK warning provided: Patients with major depressive disorder, *both adult* and pediatric, may experience worsening of their depression and/or emergence of suicidal ideation and behavior (suicidality)...**patients being treated with antidepressants should be observed closely for clinical worsening and suicidality especially at the beginning of a course of drug therapy**... *** **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications...should be altered about the need to monitor patients for the emergence of agitation...as well as the emergence of suicidality...** Exh. 30, (italics added; bolding in original label).
55.	In June of 2004, the State of New York sued GSK for fraud for allegedly withholding negative information and misrepresenting data related to the use of Paxil. *The People of the State of New York v. GlaxoSmithKline*, in the Supreme Court of the State of New York, County of New York. Exh. 31.
56.	The lawsuit asserted that "GSK embarked on a campaign both to suppress and conceal negative information concerning the drug and to misrepresent the data it did reveal concerning the drug's efficacy and safety." *Id.*
57.	In addition, the lawsuit stated that in all of the studies that were the subject of the complaint, "GSK coded suicidal thinking and acts, as well as mood swings, crying and similar behaviors, as 'emotional lability.'" *Id.*
58.	The case was settled in August 2004. As part of the settlement, GSK agreed to disclose data on the safety and effectiveness of Paxil by posting on its website clinical trial data related to the drug. *The People of the State of New York v. GlaxoSmithKline*, United States District Court, Southern District of New York, Consent Order and Judgment. Exh. 32.

59.	On September 13 and 14, 2004, an FDA advisory committee was convened, and at the conclusion of the meeting, 25 of the experts on the FDA advisory panel voted that the data presented to them from antidepressant clinical trials in children/adolescents demonstrated a causal relationship between the antidepressants and increased suicidality. (One voted to abstain and one voted against.) Exh. 33, Summary Minutes of the CDER Psychopharmacologic Drugs Advisory Committee and the FDA Pediatric Advisory Committee of September 13-14, 2004.
60.	The advisory committee recommended that a black box warning be added to antidepressant labels. *Id.*
61.	In January 2005, GSK updated the Paxil label to add the black box warning concerning antidepressants and the increased risk of suicidality. That warning also urged practitioners to observe their patients for signs of drug-induced suicidal behavior, including "anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania . . . ." Exh. 34.

6. GSK's May 2006 analysis of adult clinical trials re-confirms risk

	ADDITIONAL PROPOSED FINDINGS OF FACTS
62.	Following the child/adolescent analyses and new warnings concerning the heightened suicide risk for children and adolescents taking antidepressants, the FDA next sought data from manufacturers for their adult clinical trials of antidepressants. The FDA requested specific studies including those that lasted less than 17 weeks and studies involving patients with major depressive disorder. (See Glenmullen Decl., Adult Report, pp. 48-53).
63.	GSK recognized that if it complied with the FDA requests, then the studies would show that patients on Paxil had a statistically significant increased risk of suicide attempts when compared to placebo. *Id.*
64.	GSK lobbied the FDA to allow it to include other studies it knew were clinically different and would dilute the data and obscure the findings. *Id.* at 55.
65.	GSK finally accepted the FDA's requests and, in late 2005, GSK began an internal analysis of the suicide data, following the FDA guidelines. *Id.*
66.	GSK looked specifically at all age groups of patients taking Paxil compared to patients taking placebo. GSK found that adults with Major Depressive Disorder treated with Paxil compared to placebo were at a significant increased risk of attempting suicide. Exh. 35
67.	The results showed that the odds ratio for suicide attempt on Paxil was 6.7, a statistically significant result (meaning a patient on Paxil was about 7 times more likely to attempt suicide than a patient on placebo). Exh. 35.
68.	GSK issued a "Briefing Document" on April 5, 2006, which stated: "The results provide evidence of an increase in suicide attempts in adults with MDD treated with paroxetine compared to placebo" with an "odds ratio [of] 6.7 ...") Exh. 35.

69.	This analysis resulted in GSK changing Paxil's label in May 2006, which 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 suicide attempts." Exh. 36, p. 12.
70.	The FDA did not object to GSK's label change.
71.	In its new proposed label, GSK proposed taking language out of the label that stated: "It is unknown whether the suicidality risk extends to adults" because of its adult analysis demonstrating a risk in adults. Exh. 37, Krall depo, p. 108:11-18.
72.	GSK also sent a "Dear Doctor" letter to U.S. physicians in May 2006, which included this same language. Exh. 38.
73.	Although GSK stated in this Briefing Document that the "evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo" was "new ..." *id.* that is not true.
74.	The studies analyzed by GSK, which resulted in its 2006 warning were not new and were in GSK's possession prior to suicide attempt. Exh. 35.
75.	In 2006, GSK's Paxil patent fully expired. Exh. 39.

7. FDA's December 2006 adult analysis provides further evidence of Paxil Risk

	ADDITIONAL PROPOSED FINDINGS OF FACTS
76.	In November 2006, the FDA conducted a pooled analysis of select clinical trials (e.g., lasting less than 17 weeks) of a number of antidepressants to determine whether the suicidal risk found in the pediatric population extended to adults. Grimson Decl., Report.
77.	The data behind the FDA dult analyses involved 372 trials with 99,839 subjects (Grimson Decl., Report) and involved 18 different kinds of antidepressants of which Paxil was but one. Of the 52,960 subjects receiving the primary antidepressants (not active control or placebo), Paxil subjects comprised 16.5% of them. *Id.*
78.	The 18 kinds of antidepressants are classified by FDA into 5 neurological classes: SSRIs, SNRIs, Other modern antidepressants, Tricyclic antidepressants and Other antidepressants (Grimson Decl., Report). The various SSRI drugs, of which Paxil is one, comprise 8 of the 18 types of antidepressants (44.4%). *Id.*
79.	SSRI drugs in general, including Paxil, are mixed with larger numbers of different kinds of drugs with different medical properties and which may produce different effects regarding suicidality. *Id.*
80.	The FDA's graph (See Grimson Decl., Report) indicating reduced suicidality with increasing age is extremely general and is not indicative of an age suicidality trend for Paxil itself. *Id.*

81.	The table presents odds ratios for suicidal behavior (preparation or worse) and for the 45-64 age group, the analysis shows an elevated risk (1.75) in age group with regard to *antidepressants in general.* was 60 years old at the time of his suicide attempt. *Id*.
82.	Looking at Paxil alone, the FDA found an odds ratio of 2.76 for suicidal behavior with a 95% Confidence Interval of 1.16-6.60 and a p-value of 0.02. Exh. 40, p. 26, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class." Exh. 40.
83.	What this means is that 1) the positive association between Paxil and these suicidal events did not likely happen by chance. *See* Declaration of Dr. Roger Grimson, Report.
84.	The FDA's Dr. Russell Katz explained at an advisory committee meeting that, if a signal of an adverse drug reaction is found in controlled clinical trials and "it is statistically significantly different from placebo, that is operationally defined as causality." Exh. 41, p. 275.
85.	Dr. Katz reiterated that FDA "interpret[s] [a statistically significant increase in episodes of suicidality] as causality." Id., p. 276.
86.	Dr. Katz stated: "We are unequivocally comfortable with using the word, the 'c' word with saying that this establishes causality. Again, we have talked about this a fair amount. This is how we determine causality, this is how we base our findings of effectiveness for drugs. We do randomized trials, we analyze them prospectively, we have an outcome measure, and if it's statistically significantly different from placebo, we say the drug caused it, you know, once you rule out chance and fraud and bias and that sort of thing, which we think we have done here. So, yes, we are quite comfortable with saying there is causality." *Id.*, p. 285.
87.	A study published in the Journal of the Canadian Medical Association stated: > 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.

8. GSK Failed to Warn Doctor About Paxil's Risks

	ADDITIONAL PROPOSED FINDINGS OF FACTS

88.	In 2004, when was prescribed Paxil, the label for Paxil contained the following statement in the "PRECAUTIONS" section regarding 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. Exh. 43, p. 10.
89.	The 2003 label also included, in a section titled "Other events Observed During the Premarketing Evaluation of Paxil" (under the sub-heading "Nervous System") the adverse reaction of "emotional lability," which was identified as a "frequent" event. There is no mention in this section of the label that any suicidal events occurred in the premarketing evaluation of Paxil. *Id.*, p. 26.
90.	Physicians seeing "emotional lability" would have no way of knowing that the majority of these events involved suicidality.
91.	Intentionally left blank.
92.	GSK's use of emotional lability completely obscured the fact that suicidal events occurred *at all* during the clinical trials of Paxil. Doctors seeing that "emotional lability" was a frequent event in the clinical trials would have no way of knowing that this included *any* cases of suicidality in the clinical trials.[4]

B. THE HISTORY OF PAXIL'S LABELING SHOWS THAT THE FDA HAS NEVER REJECTED A REQUEST BY GSK TO ADD A SUICIDALITY WARNING IN ADULTS

	ADDITIONAL PROPOSED FINDINGS OF FACTS
93.	When GSK submitted the initial proposed label for Paxil to the FDA in the late 1980s, GSK proposed a "precaution" in the label for "suicide" identical to the precaution contained in the label for Prozac, another SSRI antidepressant that had been approved before Paxil. Exh. 45 at 64:5-65:3, 126:11-127:3.

[4] Emotional lability is generally defined as frequent changes or wide fluctuations (as in blood pressure or glucose tolerance), emotional instability, such as mood swings, with fluctuations between crying and laughing, not suicidality.

94.	That language stated: > The possibility of a suicide attempt is inherent in major depressive disorder 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. Exh. 46.
95.	Ultimately, the FDA approved this language without change in 1992. *Id.*, Exh. 45 at 129:12-17.
96.	Between 1992 and 2001, GSK never sought, and by extension the FDA never rejected, any different suicide or suicidality language for Paxil's label. *Id.*, at 127:6-129:9.
97.	During that time period, GSK sought, and received, approval for at least 5 different formulations and/or indications for Paxil. Exh. 47.
98.	Between 1995 and 2001, GSK never sought approval for any suicide or suicidality language in Paxil's label different than what was approved in 1992. *Id.*, at 45:10-13, 74:23-75:11, 86:7-14, 88:22-89:4, 93:12-18, 95:7-96:18, 96:22-97:13, 119:16-121:15, 126:8-15, 128:3-129:1, 153:19-155:2.
99.	Accordingly, the FDA never rejected any different suicide or suicidality language from GSK between 1995 and 2001.
100.	In 2001, GSK added the following language to the precaution section regarding suicide: > Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders. Exh.48.
101.	Thereafter, the suicide language in Paxil's label did not change until 2004. During that time period, GSK sought, and received, approval for a number of additional indications for Paxil. In connection with all of the approved indications, GSK never sought approval for new or additional suicide or suicidality language. Exh. 49 at 69:24-70:4; Exh. 47 at 158:25-159:19, 161:2-162:23, 247:12-249:2.
102.	Accordingly, between 2001 and 2004, the FDA never rejected any new or additional suicide or suicidality language for Paxil's label.
103.	In 2004, Paxil's label was changed to include a warning regarding the association between Paxil and suicidality in pediatric patients. Exh. 30.
104.	GSK sought a label change in 2006 concerning suicidal risk in adults, which the FDA accepted. Exh. 50.

105.	This analysis resulted in GSK changing Paxil's label in May 2006. (Exh. 38.) 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 suicide attempts." (*Id.*) GSK also sent a "Dear Doctor" letter to U.S. physicians in May 2006, which included this same language. Exh. 36.
106.	GSK proposed this label change through a Changes Being Effected ("CBE") supplement. Exh. 52, Deposition of Barbara Arning, GSK's current FDA liaison, p. 108:12-17.
107.	The FDA neither requested the reanalysis nor did it request the label change. *Id.*, p. 112:5-113:17, 115:21-117:12.
108.	FDA did not object to GSK's May 2006 label change, which was based on a reanalysis of clinical trial data dating back to the 1990s. *Id.*, p. 116:3-11; 165:2-8.
109.	In May 2007, the FDA requested that manufacturers of "all antidepressant medications update the existing black box 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." Exh. 53, "Press Release" at 1.
110.	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 12 of the primary antidepressants, not Paxil by itself. Paxil was shown, in the FDA's own analysis, to increase the risk of suicidality in adult patients.[5]
111.	While 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 Paxil-specific language that had been a part of Paxil's label for the previous year, should remain in the label. (Exh. 54.)
112.	On June 21, 2007, the FDA told GSK: "We also have noted that some sponsors [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.
113.	In a June 22, 2007 email to GSK, the FDA responded to GSK's request by telling GSK that it could request a formal meeting concerning GSK's ostensible desire to keep the Paxil-specific language in the label. (Exh. 56.)

[5] The FDA specifically found that Paxil had an odds ratio of 2.76 with a 95% Confidence Interval of 1.16-6.60 and a p-value of 0.02. *See*, Exh. 40, "Suicidal Behavior for Active Drug relative to Placebo - Preparation or Worse - Adults with Psychiatric Disorders - By Drug and Drug Class." What this means is that 1) the positive association between Paxil and these suicidal events did not likely happen by chance (i.e., it is probably real, P-value=.02) and (2) if a patient is treated with Paxil and experiences such a suicidal event, then more likely than not (69% to 89%) the suicidality is attributable to Paxil. *See* Declaration of Dr. Roger Grimson, Report.

114.	**However, GSK never asked for a formal meeting, did not contest the class-wide labeling, nor did it seek additional labeling regarding Paxil-specific data. Instead, it chose to go along with the class-wide labeling.** (Exh. 57.)
115.	Dr. Ronald Krall, GSK's Senior Vice President and Chief Medical Officer and the Co-Chairman of GSK's Global Safety Board, testified: 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.)
116.	Dr. Krall 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).
117.	Although the FDA declined to allow GSK to include Paxil-specific data in the class-wide black box labeling, GSK could have sought inclusion of this data elsewhere in the Paxil label. Exh.58, Deposition of Dr. Richard Kapit at 357-364.
118.	GSK was never prohibited from including a warning in another section of the label other than in the class labeling section. Kapit Decl. ¶ 16.
119.	When asked by GSK's counsel: "FDA decided that after looking at the Paxil-specific language ... it should not be included in the Paxil label, true?" Dr. Kapit responded, "Well, no, it didn't say that." (*Id..*, ¶ 17.)
120.	Dr. Kapit explained that the FDA was simply stating that the Paxil-specific language "should not be included in the class label. That doesn't mean you can't put it in other sections of the labeling." *Id.*
121.	According to the testimony of Dr. Robert Temple, Director of the Office of Medical Policy at the FDA: "It's [the drug manufacturer's] job to keep the labeling up to date, at least nominally the labeling is owned by the company." Exh. 2, Temple depo, pp. 130:8-15, 131:1-5, 132:3-6, 14-20.
122.	Dr. Temple responded to GSK's counsel's question, "if there were no scientific basis for a warning and it were included in the drug labeling, would that render the drug labeling false or misleading?" stating: **"That would be a very unusual thing for us to do. I mean, the fact is that the company strongly wants labeling. Even if we think it's a little flimsy, we would probably defer."** *Id.*, p. 499-501, emphasis added.

C. FDA REGULATIONS AND THE PAXIL PRESCRIBING INFORMATION (LABEL)

	ADDITIONAL PROPOSED FINDINGS OF FACTS
123.	A drug's label must identify safety hazards in the following descending order of severity: Contraindications, Warnings, Precautions, and Adverse Reactions. 21 C.F.R. §§ 201.56, 201.80.
124.	The FDA approves drugs based on clinical trials with the understanding that the labeling will evolve as the company learns more about how the drug performs in the broader population. As the FDA Commissioner put it: > The Commissioner recognizes that drug labeling does not always contain the most current information and opinion available to physicians about a drug because advances in medical knowledge and practice inevitably precede formal submission of proposed new labeling by the manufacturer and approval by the FDA. 44 Federal Register at 37435
125.	21 CFR § 201.57(e) mandates changes in warnings "as soon as there is reasonable evidence of an association of a serious hazard with a drug" and further admonishes that "a causal relationship need not have been proved." 21 CFR § 201.57(e) **[**effective January 2006, this CFR was re-numbered and it is now 21 CFR 201.80]
126.	When 21 CFR § 201.57(e) was originally promulgated in 1979, the Commissioner of the FDA observed that "the act requires labeling to include warnings about both potential and verified hazards." He also emphasized that "these labeling requirements **do not prohibit** a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drugs, or the issuance of letters directed to health care professionals (e.g. "Dear Doctor" letters containing such information) is **not prohibited by these regulations."** 44 Fed. Reg. at 37,447 (June 26, 1979), emphasis added.
127.	Since 1965, FDA regulations have specifically allowed drug companies, such as GSK, to add new or different warnings without prior FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A)
128.	Drug companies such as GSK have an independent duty to warn drug users of dangers as soon as they become aware of them. Companies should not "wait and react to an order from the FDA ... or [] wait for FDA to order the company to change its label." (S11832.) Companies "can and must immediately correct any existing warning that has been issued and cannot hide behind the Byzantine regulatory structure of the FDA to shield them from liability for causing serious injury." Exh. 59, S11834. Congressional Record – Senate, S11834, 832, September 20, 2007**.**
129.	Prior to suicide attempt, GSK never asked the FDA to add suicide or suicidality language to the Paxil label.

130.	Prior to suicide attempt, the FDA never rejected a request by GSK to include suicide or suicidality language in the Paxil label.
131.	There is no evidence that the FDA specifically looked into the causal relationship or association between Paxil and suicidal behavior each time Paxil was approved by the FDA for other indications between 1992 and 2003.

D. PROZAC AND ITS REGULATORY HISTORY RELATED TO SUICIDAL RISK

Plaintiffs do not believe evidence regarding Prozac is relevant for a number of reasons (e.g., it is a different drug and its historical review did not include Paxil), however, in the event the Court decides to consider evidence submitted by GSK concerning Prozac, Plaintiffs offer the following additional facts related to Prozac.

	ADDITIONAL PROPOSED FINDINGS OF FACTS
132.	German regulators expressed concerns about Prozac and an increased risk of suicidality in the early 1980's, before Prozac was approved for marketing.
133.	According to a May 25, 1984 internal memorandum from Eli Lilly and Company ("Lilly," the maker of Prozac) regarding Lilly's efforts to obtain registration of Prozac in Germany: "During the treatment with the preparation [fluoxetine/Prozac] 16 suicide attempts were made, 2 of these with success. As patients with a risk of suicide were excluded from the studies, it is probable that this high proportion can be attributed to an action of the preparation in the sence (sic) of an deterioration of the clinical condition, which reached its lowest point." Exh. 60.
134.	According to a June 26, 1984 Lilly memorandum, item # 10: "The BGA [German equivalent of FDA] suspects fluoxetine [Prozac] to be a stimulating/activating drug (side-effect profile, suicides, suicide attempts)." Item # 14 states: "This is a very serious issue in the opinion of the BGA. It might well be that we will have to recommend concomitant tranquilizer intake for the first 2 or 3 weeks in the package literature." Exh. 61.
135.	A January 29, 1985 memo states: "Two major concerns [regarding the Prozac application] seem to be the reason that the registration [in Germany] was not accepted," "efficacy questioned" and "suicidal risk." Exh. 62. (http://www.baumhedlundlaw.com/03.pdf)
136.	A February 26, 1985 memo states: "The use of [Prozac] seems objectionable, as the increase in agitating effect occurs earlier than the mood elevating effect and therefore an increased risk of suicide exists." Exh. 63.
137.	According to an April 1, 1986 memorandum, under a discussion of safety issues, it states: "Still not resolved is the fact that suicide attempts have been observed more frequently on fluoxetine as compared to imipramine . . . . According to the today's knowledge [fluoxetine's "favourable" side effect spectrum] is negatively affected by the increased suicidal risk." Exh. 64.

138.	According to another memo, dated August 30, 1989, Lilly received feedback regarding Prozac from the "Commission A" (an expert working/consultant group to BGA), stating that there should be a "counterindication [for Prozac] because of acute suicidality should become a warning whereby the physicians should be advised that in the absence of sedation, the risk of higher suicidality should be taken into account." Exh. 65.
139.	When Lilly submitted its application to the FDA for approval of Prozac to treat depression in adults, the FDA reviewer was Dr. Richard Kapit. Decl., Kapit Report, p.1.
140.	According to Dr. Kapit's March 1985 Safety Review of Prozac: "It is fluoxetine's particular profile of side effects which may perhaps, in the future, give rise to the greatest clinical liabilities in the use of this medication to treat depression." Exh. 66.
141.	Under "Catastrophic and Serious Events," Dr. Kapit noted: "... 52 cases were [] subjected to review of case reports on microfiche. Certain additional adverse events, not reported by the Company, which were revealed on microfiche, are also included in this tabulation. In most cases, these adverse events involved the onset of an unreported psychotic episode." Exh. 67.
142.	Dr. Kapit explained: "[F]luoxetine's profile of adverse effects more closely resembles that of a stimulant drug than one that causes sedation and gain of weight," therefore, "fluoxetine treatment might, at least temporarily, make their illness worse." Exh. 68.
143.	In 1990, two prominent Harvard psychiatrists, Drs. Martin Teicher and Jonathan Cole, published a study entitled "Emergence of Intense Suicidal Preoccupation During Fluoxetine [Prozac] Treatment." From their personal observations of patients taking Prozac, Drs. Teicher and Cole, after first noting that four of the six patients referenced in their study experienced akathisia (a condition marked by profound inner restlessness and agitation), found that "persistent, obsessive, and violent suicidal thoughts emerged in a small minority of patients treated with fluoxetine." Exh. 69.
144.	Following the Teicher article, Lilly submitted to the FDA an analysis of suicidal events from its clinical trials. In a September 1990 memorandum, an FDA safety reviewer, Dr. David Graham, made the following observations about Lilly's submission: In support of its contention that Prozac did not cause suicidality, Lilly relied on a study by Fava & Rosenbaum, which Lilly asserted showed "no statistically significant differences among rates of treatment-emergent suicidal ideation associated with five classes of antidepressant therapy." Exh. 70. When Dr. Graham re-analyzed Fava & Rosenbaum's data, he found that "[t]reatment-emergent suicidality was more frequent among 'fluoxetine alone' than 'tricyclics with or without lithium' patients. The relative risk of suicidality was 3.3. (95% CL 0.9, 12.2), p-0.07.") Dr. Graham noted that "the proportion of patients with treatment-emergent suicidality on fluoxetine in this study was similar to that reported by Teicher et al." *Id.*, p. 8. Dr. Graham concluded his report by stating: "[Lilly's] analysis of suicidality does not resolve the issue." *Id.*, p. 8.

145.	Lilly assigned Dr. Gary Tollefson to testify at the September 1991PDAC. According to his November 16, 1994 testimony in the Prozac case, *Fentress v. Shea* et al., Case No. 90-CI-06033, he did not disclose to the FDA the fact that the issue had been raised by the German government in 1984/1985. Dr. Tollefson testified: Q. . . . Doctor [Tollefson], to back up a little bit, earlier you said . . . that the first time the issue of using Prozac and the incidence of suicide was raised [was] in 1990 by Doctor Teicher's article; correct? A. It was the first time that I was aware of the issue having arisen at that time. Q. Okay. So let's make sure we're clear on this. That issue was raised by the German government back in 1984; correct? A. I have heard that indication, yes. * * * Q. Were you aware in 1991, when you testified before the PDAC, that Lilly had in fact hired experts back in 1985 and 1986 to look at [the suicide] issue with regards to the German government? A. I had heard that there were some individuals that have consulted previously with Lilly on those issues but did not know specifically whether it was related to the BGA or the issue in general. Q. Okay. Did you tell the PDAC in 1991, that Lilly had previously - and I'm talking about prior to Doctor Teicher raising the issue, that Lilly had previously hired experts to look at the issue of increased suicide and the use of Prozac? A. I think as part of the presentation it was made clear that a very thorough and comprehensive analysis of the worldwide data on suicide and Prozac had been made. * * * Q. Let's try it one more time. Specifically, did you tell the PDAC that prior to 1990, when the German government raised this issue, that Lilly hired experts to investigate the issue of increased suicide and the use of Prozac, yes or no? A. That was not a question I was asked by the PDAC, so I did not answer that question. Q. Did you volunteer it? A. No. * * * Q. Did you inform the committee that there was a package insert in use in Germany, on the day of the advisory committee, that recommended the use of sedatives in people who were suicidal or agitated on Prozac? . . . A. That was not one of the points of discussion. Q. The answer is you didn't; right? A. Again, I did not feel there would be any reason. Exh. 71, Testimony of Dr. Gary Tollefson, transcript, p. 111:9-25; 114:10-115:15; 118:2-119:2.
146.	According to a GSK memorandum dated October 3, 1990, the FDA believed the public controversy that had erupted concerning the potential for antidepressants to increase the risk of suicide in adults was not “a real issue,” but rather "a public relations problem.” The FDA’s Dr. Martin Brecher indicated to GSK that the FDA “does not think it is an issue, but it needs to be addressed.” Exh. 72.

147.	Although GSK submitted its analysis of suicidality data from its clinical trials to the FDA in May 1991, the FDA did not provide this data to its advisory committee members. The advisory committee was only provided data from the Prozac clinical trials. See Exh. 73.
148.	As set forth above, GSK improperly included placebo run-in patients in the analysis submitted to the FDA and, thus, the true risk was hidden. See Decl. Glenmullen, Report.
149.	Although the committee members ultimately voted that there was insufficient data to conclude that Prozac caused suicide (the question posed to the committee was: "Is there credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors?"), the FDA stated that it did "not dismiss the possibility that antidepressants in general or fluoxetine in particular may have the capacity to cause untoward injurious behaviors and acts, and/or to intensify them." The FDA concluded that "more research is needed" and "asked [Lilly] to develop plans to conduct new studies, including clinical trials and epidemiological studies, studies that could provide more direct answers to the questions that have been raised" in the advisory committee meeting. *Id.*, Exh. 73, September 1991 PDAC Transcript at 128:18-24.
150.	According to Lilly's answers to Interrogatories submitted in the lawsuit *Biffle v. Eli Lilly*: "Discussions were had between Lilly and the FDA regarding possible data analyses or clinical trial designs which would test whether the Teicher assertions are in fact real. The FDA did not request or require any action from Lilly nor suggest a particular analytical of study approach. The discussions and question as to whether additional studies be done were mooted by the findings of the FDA Psychopharmacological Drug Advisory Committee on September 20, 1991. No additional studies were conducted." Exh. 74.
151.	However, according to a letter the FDA sent to Public Citizen in June 1992: "There was a consensus [amongst the PDAC above] that more research is needed to further explore the relationship between suicidality and the use of not only Prozac, but other antidepressants as well." Exh. 75.
152.	The FDA also stated during the advisory committee meeting that it did "not dismiss the possibility that antidepressants in general or fluoxetine [Prozac] in particular may have the capacity to cause untoward injurious behaviors and acts, and/or to intensify them." *Id.*, Exh. 73, p. 126.
153.	The FDA further stated that it would "continue our careful evaluation of data in our spontaneous reporting system and encourage additional research on this matter." Exh. 75.
154.	During the advisory committee meeting, several members of the FDA advisory panel expressed concerns about the lack of data provided to them. For example, the chairperson, Dr. Daniel Casey, stated that "I don't feel I have all the data." Another member, Dr. Nina Schooler stated: "I felt we were working with half a deck in terms of data." Exh. 73, p. 334.

155.	In one of its Citizen Petition denials, 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.
156.	During congressional hearings in 2004, senior FDA official, Dr. Robert Temple testified that, although the FDA "had been systematically looking at the adult data for almost that entire decade," he stated that the FDA's analyses could have been far "better, more structured, [and] more careful, ... but we didn't know to do that." Exh. 77, p. 113, Committee on Energy and Commerce hearing, September 23, 2004.
157.	During his December 2004 deposition in the *In Re Paxil Product Liability Litigation* (a mass tort case involving Paxil withdrawal reactions and dependence, Case No. 01-07937, C.D. Cal.), Dr. Temple testified that, although the FDA had been "watching for suicidality in each application," he admitted that the way FDA had been assessing suicidality was "not optimal." *Id.*, Exh. 2, pp. 49-56.
158.	During the February 2, 2004, FDA advisory committee meeting regarding pediatric suicidality, the FDA's Dr. Thomas Laughren explained: "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," but, he admitted, the method being used "was not particularly productive." *Id.*, Exh. 78, p. 342-343, February 2, 2004, PDAC transcript.

E. FDA APPROVAL AND POST-APPROVAL PRETERMISSION SHOULD HAVE NO PREEMPTIVE EFFECT

	ADDITIONAL PROPOSED FINDINGS OF FACTS
159.	On November 18, 2004, The Associate Director for Science at the FDA, Dr. David Graham, testified before the U.S. Senate Committee on Finance at a hearing titled "FDA, Merck and Vioxx: Putting Patient Safety First?" wherein he offered the following testimony in a prepared statement: • "In my opinion, the FDA has let the American people down, and sadly, betrayed a public trust." Exh. 79, p. 2. • Dr. Graham was "pressured to change [his] conclusions and recommendations [re Vioxx], and basically threatened that if [he] did not change them, [he] would not be permitted to present [his paper on Vioxx at an upcoming conference]." *Id.*, p. 3. • "[A] mere 6 weeks before Merck pulled Vioxx from the market [FDA] management did not believe there was an outstanding safety concern with Vioxx. At the same time, 2-4 jumbo jetliners were dropping from the sky every week and no one else at FDA was concerned." *Id.* p. 3. • "My experience with Vioxx is typical of how CDER responds to serious drug safety

	issues in general. This is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRIs should not be used by children." Id., p. 3. • "The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. ... FDA and its Center for Drug Evaluation and Research are broken" *Id.*, p. 4. • The FDA "views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety." *Id.*, p. 4-5. • "[T]he scientific standards CDER applies to drug safety guarantee that unsafe and deadly drugs will remain on the US market." *Id.*, p. 5.
160.	According to a March 2006 General Accounting Office (GAO) Report titled "Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process": "FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. ... GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them. ... There are weaknesses in the different types of data available to FDA, and FDA lacks authority to require certain studies and has resource limitations for obtaining data." Exh. 80. The report noted that "at congressional hearings in September 2004, FDA was criticized for taking too long to tell physicians and patients about studies linking the use of antidepressants among children to an increased risk of suicidal behavior." *Id.*, p. 1. The GAO pointed out that "FDA has the authority to withdraw the approval of a drug on the market for safety-related and other reasons, although it rarely does so. ... FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action. For example, if FDA determines that an approved drug may produce adverse events not previously identified, FDA and sponsor may negotiate on revised labeling for the drug." *Id.*, p. 10, emphasis added.

F. THE ROLE OF LITIGATION IN PROMOTING DRUG SAFETY

	ADDITIONAL PROPOSED FINDINGS OF FACTS
161.	An article titled "The Role of Litigation in Defining Drug Risks," published in *Journal of the American Medication Association* by Jerry Avorn, M.D., Professor of Medicine at Harvard Medical School and Aaron S. Kesselheim, J.D., M.D., explains that lawsuits have "help[ed] uncover previously unavailable data on adverse effects, questionable practices

	by manufacturers, and flaws in drug regulatory systems." Exh. 81, JAMA, January 17, 2007 – Vol. 297, No. 3, p. 308. The authors also stated that: a) The sources available to doctors for drug information "provide a limited perspective on a drug's benefits and risks" and "lawsuits have helped uncover important and previously unavailable data about major adverse events." *Id.*, p. 308; b) "Litigation has also helped the medical community reassess drugs by bringing to light new information about adverse effects." *Id.*; c) Litigation has also uncovered companies that have "downplayed and kept secret research." *Id.* 309; d) Lawsuits have "exposed important limitations in the FDA information collection and dissemination procedures." *Id.*; e) Of the drug safety issues highlighted in the article, "the legal system played an important role in spurring change in regulatory or corporate procedures, as well as extending knowledge about drug risks by adding to the evidence available for evaluation by physicians, patients and regulators." *Id.*; f) "[L]imiting legal involvement in the prescription drug arena is likely to increase the nation's problem of poorly defined and inadequately presented drug risk information." *Id.* p., 311; and, g) "Clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products." *Id.*
162.	The FDA's MedWatch campaign provides: "*When a drug goes to market, we know everything about its safety. Wrong*." See Exh. 82
163.	An article titled "Prescription Drugs, Products Liability, and Preemption of Tort Litigation," published in the Journal of the American Medical Association (JAMA) by Catherine DeAngelis, M.D. and Phil Fontanarosa, M.D. stated: "[U]nless and until the FDA drug approval process and postmarketing surveillance system imporve significantly, patients must have a means to seek recourse throught tort litigation against product manufacturers. Antying less may well preempt the well-being and safety of the public." Exh. 83, JAMA, October 22/29, 2008–Vol 300, No. 16, 1939, 1941.

164.	In January and February 2008, Members from both the Senate and the House of Representatives wrote letters to Andrew C. von Eschenbach, Commissioner of the FDA, voicing concerns over the FDA's Proposed Rule to amend the regulations that permit companies to promptly update their drug and device labels with new safety information. The House letter pointed out that the Proposed Rule "seeks to substantively amend current regulations." See Exhs. 84 & 85.
165.	The House of Representatives' letter stated, inter alia: "We included language in the FDAA to preserve the status quo, allowing the FDA and state remedies to remain complementary and necessary safeguards to protect American families. However, we believe the FDA's proposed rule directly contradicts this language by reversing a drug manufacturer's obligation to warn of new risks and hazards and, instead, allowing these companies to claim immunity from liability because they had no duty to warn. This is contrary to congressional intent and to the FDA's mission to protect the public health." *Id.*, Exh. 84.
166.	The Senate letter stated, inter alia: "[The] proposal has no purpose other than to shore up the industry's legal arguments for avoiding liability. Indeed, the proposal fails to identify a single problem associated with these regulations that would warrant a modification much less a public health threat of such magnitude as to put issuing the proposal at the top of the FDA's priority list." *Id.*, Exh. 85.

G. MANUFACTURERS HAVE A RIGHT TO DISSEMINATE TRUTHFUL AND NON-MISLEADING INFORMATION ABOUT THEIR DRUGS

	ADDITIONAL PROPOSED FINDINGS OF FACTS
167.	According to GSK's own public policy position, GSK "publicly discloses the results of GSK-sponsored clinical trials that are relevant for patient care irrespective of whether the results are positive or negative for GSK prescription medicines and vaccines." Exh. 86.
168.	GSK's recently hired Vice President and General Counsel, Daniel Troy, Esq., wrote in a recent opinion article for the New England Journal of Medicine that pharmaceutical companies have a First Amendment right to publish truthful information regarding drug uses the FDA has yet to approve. Exh. 87, Pharmaceutical Promotion and First Amendment Rights, 359 N. Engl. J. Med. 445, 536 (July 31, 2008).
169.	In June 2006, when the FDA questioned GSK's marketing of one of its drugs (not Paxil), the Washington Legal Foundation responded on behalf of GSK and told the FDA that: "GSK has a First Amendment right to disseminate information about clinical investigations, whether or not they meet FDA's definition of 'substantial evidence or substantial clinical experience.'" Exh. 88.
170.	In a March 19, 2001 letter from the FDA to the Washington Legal Foundation, Associate Director for Policy, Jane Axelrad wrote: "[T]he FDA's regulations at 21 CFR 312.7(a) do not ... operate as a bar to disclosure of study results relating to investigational new drugs in reports with the SEC and in press releases, and public companies make such disclosures on a routine basis." Exh. 89. See also, Exh. 90, FDA letter to Washington Legal Foundation, dated December 10, 1997).