UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA	)	Crim. No.
v.	)	Violations:
GLAXOSMITHKLINE LLC	)	21 U.S.C. §§ 331(a),333(a)(1), 352 (Misbranding)
Defendant	)	21 U.S.C. §§ 331(e),333(a)(1), 355(k)(1)(Failure to Report Data to FDA)

INFORMATION

The United States Attorney charges that:

GENERAL ALLEGATIONS

At all times material hereto, unless otherwise alleged:

1. From 1999 through 2003, **GLAXOSMITHKLINE LLC** or entities for which it is the corporate successor (hereinafter **"GSK"**) promoted the sale of its drugs Paxil and Wellbutrin for uses other than those approved as safe and effective by the Food and Drug Administration ("FDA"). Specifically, GSK

a. promoted Paxil for children and adolescents, and

b. promoted Wellbutrin for weight loss, the treatment of sexual dysfunction, substance addictions, Attention Deficit Hyperactivity Disorders, among other unapproved uses.

2. From 2001 through September 2007, **GSK** failed to report data relating to clinical experience and other data and information as required by law, regarding Avandia, a diabetes

medication, to the FDA.

The Defendant

3. Defendant **GSK** was a pharmaceutical company originally organized as a corporation under the laws of Pennsylvania, and later converted to a Delaware Limited Liability Company, GlaxoSmithKline LLC. **GSK's** operational headquarters were in Philadelphia, Pennsylvania, and Research Triangle Park, North Carolina. **GSK** manufactured, distributed, and sold pharmaceutical drugs for human use, including for sale and use in Massachusetts.

The FDA and the FDCA

4. The FDA was the federal agency of the United States responsible for protecting the health and safety of the public. The FDA was responsible for enforcing the Food, Drug, and Cosmetic Act ("FDCA") and ensuring, among other things, that drugs intended for use in humans were safe and effective for their intended uses and that the labeling of such drugs contained true and accurate information.

5. With certain limited exceptions not pertinent here, a drug could not be distributed in interstate commerce without FDA approval. To gain FDA approval, data from adequate and well-controlled clinical studies had to demonstrate that the drug would be safe and effective for a particular use. As part of the approval process, the FDA had to approve the drug's labeling,

which was required to set forth detailed information about the drug, including the approved medical conditions of use, dosages, and patient population(s).

6. Once the FDA found a drug to be safe and effective for a particular use and approved it for that use, doctors were free to exercise their medical judgment to prescribe the drug for other, unapproved (or "off-label") uses.

7. Under the FDCA, however, the manufacturer could not lawfully market and promote the drug for off-label uses.

8. The FDCA provided that a drug was misbranded if, among other things, "its labeling is false or misleading in any particular." 21 U.S.C. § 352(a). Labeling includes written, printed, or graphic information on or accompanying a drug, including information that explains the uses of the drug and is used in connection with the sale of the drug, whether or not it physically accompanies the drug when distributed. False and misleading safety and efficacy claims in a drug's labeling rendered the drug misbranded.

9. The FDCA also provided that a drug was misbranded if its labeling did not bear "adequate directions for use." 21 U.S.C. § 352(f)(1). As the phrase was used in the FDCA and its regulations, "adequate directions for use" meant directions under which a layperson could use a drug safely and effectively for the

purposes for which it was intended. 21 C.F.R. § 201.5. A prescription drug, by definition, could not bear adequate directions for use by a layperson, but an FDA-approved prescription drug, bearing the FDA-approved labeling, could be exempt from the adequate directions for use requirement if it met a number of conditions, including that it was sold only for an FDA-approved use. A prescription drug that was marketed for unapproved, off-label uses would not qualify for this exemption and therefore was misbranded. 21 C.F.R. § 201.100.

10. The FDCA prohibited causing the introduction or delivery for introduction into interstate commerce of, or introducing or delivering for introduction into interstate commerce, any drug that was misbranded. 21 U.S.C. § 331(a).

COUNT ONE - PAXIL

(Distribution of a Misbranded Drug: False and Misleading Labeling: 21 U.S.C. §§ 331(a), 333(a)(1), & 352(a))

11. The allegations contained in paragraphs 1 and 3 through 10 are realleged and incorporated herein as if set forth in full.

GSK'S OFF-LABEL PROMOTION OF PAXIL FOR CHILDREN AND ADOLESCENTS

12. **GSK** manufactured, distributed, and sold the prescription drug Paxil for human use. Paxil was **GSK**'s trade name for the drug paroxetine hydrochloride. Paxil was part of a class of drugs known as selective serotonin reuptake inhibitors ("SSRIs").

13. In December 1992, the FDA approved Paxil to treat depression in adults. The FDA subsequently approved Paxil for other uses in adults.

14. The FDA never approved Paxil for any purpose for patients under age 18 ("children and adolescents").

15. **GSK** promoted the use of Paxil to doctors through a sales force of approximately 1,900 sales representatives who made personal visits ("sales calls") to doctors to encourage those doctors to prescribe Paxil to their patients.

16. **GSK** sales representatives wrote "call notes" to document what happened during their sales calls with doctors.

Once sales representatives entered their call notes into **GSK**'s computer system, the call notes could be read by the sales representatives' colleagues and supervisors.

17. Paxil became one of the 10 top-selling drugs in the United States and for a time the most commonly prescribed SSRI. Paxil sales in the United States surpassed $1.8 billion per year in 2001 and 2002.

Placebo-Controlled Clinical Trials

18. The safety and efficacy of pharmaceutical drugs were tested in clinical trials or studies.

19. In a "placebo-controlled" clinical study, one group of patients was treated with the drug being studied and another group of patients received a placebo. A placebo looked like the drug that was being studied, but contained no active ingredient.

20. In a "double-blinded" clinical study, neither the patient nor the treating doctor knew whether the patient was receiving the drug being studied or a placebo.

21. In a placebo-controlled clinical study, the efficacy of a drug was measured by primary and secondary "endpoints" that typically were identified before the study began in a protocol prepared by the sponsor of the study. The primary endpoint or endpoints were the main measures of whether the drug worked. The secondary endpoints contained additional measures to assess the

drug's efficacy.

22. At the end of the study, the study was "unblinded" and the results on the endpoints of patients who had received the drug being studied were compared to the results on the endpoints of the patients who received a placebo.

23. In determining whether a study had demonstrated a drug's efficacy, the FDA typically looked at whether there was a statistically significant difference on the primary endpoints between the patients in the study who received the drug being studied and patients in the study who received a placebo.

Three Clinical Studies Failed to Establish Paxil's Efficacy for Treating Depression in Children and Adolescents

24. Between 1994 and 2001, **GSK** conducted three placebo-controlled clinical studies that studied Paxil's safety and efficacy in treating depression in children and adolescents. These studies were known as Study 329, Study 377, and Study 701.

25. Study 329 compared the efficacy of Paxil and a second drug, imipramine, to placebo in treating depression in patients age 12 to 18. Imipramine was part of a class of drugs known as tricyclic antidepressants ("TCAs"). The acute phase of Study 329 began in April 1994 and ended in May 1997. **GSK**'s internal clinical report summarizing the results of Study 329 was issued on November 24, 1998.

26. Paxil failed to demonstrate efficacy on Study 329's two primary endpoints. Paxil also failed to demonstrate efficacy on the five secondary endpoints identified in Study 329's protocol. Paxil demonstrated efficacy on four other secondary endpoints that were not identified in the protocol, but that were identified as secondary endpoints by the clinical investigators before Study 329's results were unblinded.

27. Study 377 compared the efficacy of Paxil to placebo in treating depression in patients age 13 to 18. Study 377 began in April 1995 and was completed in May 1998. **GSK**'s internal clinical report summarizing the results of Study 377 was issued on November 19, 1998.

28. Paxil failed to demonstrate efficacy on any of the primary or secondary endpoints in Study 377.

29. Study 701 compared the efficacy of Paxil to placebo in treating depression in patients age 7 to 17. Study 701 began in March 2000 and ended in January 2001. **GSK**'s internal clinical report summarizing the results of Study 701 was issued on July 30, 2001.

30. Paxil failed to demonstrate efficacy on any of the primary or secondary endpoints in Study 701.

GSK Helped Write and Approved a Medical Journal Article Which Stated that Study 329 Demonstrated that Paxil Was Effective in Treating Depression in Adolescents

31. **GSK** hired a contractor to help write an article about the results of Study 329. The contractor wrote the first draft of the article based on GSK's internal final clinical report on Study 329. The contractor then incorporated into subsequent drafts of the article revisions made by the clinical investigators and a **GSK** employee involved in the study.

32. The article about Study 329 was published in July 2001 in the Journal of the American Academy of Child and Adolescent Psychiatry ("JAACAP"). The article listed 22 authors, including 20 clinical investigators who were not **GSK** employees and two **GSK** employees. In addition, the contractor was identified as having provided "editorial assistance." **GSK** and the authors approved the article before it was submitted to JAACAP.

33. The JAACAP article identified Study 329's two primary endpoints. The JAACAP article also listed five secondary endpoints "that were declared a priori." Three of these five secondary endpoints were not identified before the study began, but had been identified as secondary endpoints by the clinical investigators before Study 329's results were unblinded. Elsewhere, the article contained a chart that showed the results of eight endpoints. The chart did not indicate which endpoints

were primary, which endpoints were identified as secondary in the protocol before the study began, and which endpoints had been added after the study had begun but before the results were unblinded.

34. The JAACAP article was false and misleading. Although the article's text identified the two primary endpoints and the article's chart reported the results on those endpoints, the article never explicitly stated that Study 329 failed to demonstrate efficacy on either of its two primary endpoints. The article at one point inaccurately stated that Paxil "separated statistically from placebo" on a primary endpoint. The article also did not explicitly state that Paxil failed to demonstrate efficacy on all of the secondary endpoints that had been identified in the protocol.

35. The JAACAP article presented the results of Study 329 as favorable, based on Paxil having demonstrated efficacy on the four secondary endpoints that were not identified in the protocol and which were added after the study had begun but before the results were unblinded. The JAACAP article's abstract stated that Paxil "is generally well tolerated and effective for major depression in adolescents." The JAACAP article's conclusion stated that "[t]he findings of this study provide evidence of the efficacy and safety of the SSRI, [Paxil], in the treatment of

adolescent depression."

36. The article disclosed that serious adverse events ("SAEs") were experienced by 11 patients in Study 329 who received Paxil, five patients who received imipramine, and two patients who received the placebo. An earlier draft of the article stated that of the 11 SAEs experienced by Paxil patients, "worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment." A **GSK** employee suggested that the contractor change this section of the article. The revised version printed in JAACAP stated: "Of the 11 patients [who had serious adverse events while taking Paxil], only headache (1 patient) was considered by the treating investigator to be related to [Paxil] treatment."

GSK Used the Article in JAACAP to Promote Paxil for Children and Adolescents

37. The contractor hired by **GSK** to help prepare the medical journal article provided drafts of the article to the head of **GSK**'s Paxil marketing team.

38. On or about August 16, 2001, **GSK**'s Paxil marketing team sent a copy of the JAACAP article to all of the approximately 1,900 **GSK** sales representatives who sold Paxil. A cover memorandum summarizing the article (the "**GSK** Cover Memo") stated

in bold type:

> This 'cutting-edge,' landmark study is the first to compare efficacy of an SSRI and a TCA with placebo in the treatment of major depression in adolescents. *Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression.

39. The **GSK** Cover Memo also stated:

> In conclusion, the findings of this study provide evidence of the efficacy and safety of Paxil in the treatment of adolescent depression. Here's another example of GlaxoSmithKline's commitment to Psychiatry by bringing forth "cutting edge" scientific data. Paxil is truly a REMARKABLE product that continues to demonstrate efficacy, even in this understudied population.

40. The **GSK** Cover Memo did not disclose that Paxil failed to demonstrate efficacy on the protocol-defined primary and secondary endpoints of the same study. The **GSK** Cover Memo also did not disclose that **GSK** had completed two other studies that also did not demonstrate that Paxil was effective in treating depression in children and adolescents.

41. The **GSK** Cover Memo did not state that Paxil was not approved for the treatment of children and adolescents. The **GSK** Cover Memo stated that the article was for sales representatives' information only and should not be used with or distributed to doctors, and both the Cover Memo and the article were stamped "FOR REPRESENTATIVES' INFORMATION ONLY."

42. Some **GSK** sales representatives used the JAACAP article

to urge doctors to prescribe Paxil to treat depression in children and adolescents.

GSK Did Not Publicize the Results of Studies 377 and 701

43. **GSK** learned the results of Study 377 in 1998 and the results of Study 701 in 2001. Paxil failed to demonstrate efficacy on any of the endpoints in either study.

44. **GSK** did not hire a contractor to help write medical journal articles about the results of Studies 377 and 701, as it had with Study 329.

45. **GSK** did not inform its sales representatives about the results of Studies 377 and 701.

Safety Issues

46. After **GSK** provided to the FDA the results of Studies 329, 377, and 701, as well as additional statistical analyses performed by GSK, some of which suggested a possible increased suicidality associated with Paxil use in patients under age 18, the FDA conducted a broad inquiry into the safety of Paxil, other SSRIs, and other antidepressants to treat depression in patients under age 18.

47. On or about June 19, 2003, the FDA recommended that Paxil not be used to treat depression in patients under age 18.

48. On or about October 27, 2003, the FDA stated that antidepressants should be used only with caution to treat

depression in patients under age 18.

49. On or about October 15, 2004, the FDA required all antidepressants, including Paxil, to include on their labels a "black box warning" stating that antidepressants increased the risk of suicidal thinking and behavior in short-term studies in patients under age 18.

GSK Provided Sales Representatives With Other Information Which Was Used to Promote the Use of Paxil in Children and Adolescents

50. In 1999, **GSK** created a 150-person neuroscience specialty sales force to promote Paxil to psychiatrists. On or about September 28, 1999, **GSK** paid a child psychiatrist, whose research primarily dealt with patients under age 18, to speak at the launch meeting of **GSK**'s neuroscience specialty sales force. According to a subsequent internal **GSK** newsletter reporting on the event, this child psychiatrist discussed the results of Study 329 and said that **GSK** had a "window of opportunity." According to the internal **GSK** newsletter, this child psychiatrist told the neuroscience sales representatives that, as a result of Study 329, "We can say that paroxetine has both efficacy and safety data for treating depression in adolescents."

51. On or about February 14, 2001, **GSK** sent a copy of a medical journal article about the use of Paxil for adolescent obsessive compulsive disorder ("OCD") to all of the approximately

1,900 **GSK** sales representatives who sold Paxil. An accompanying memorandum summarizing the article stated: "This study suggests that *Paxil* is an effective short-term treatment for OCD in children [and] adolescents (aged 9-15 years) and has fewer AE's [adverse events]." The memorandum stated that the information was for sales representatives' information only and should not be used with or distributed to doctors.

52. From 2000 to 2002, some **GSK** sales representatives used information provided by **GSK** to urge doctors to use Paxil to treat children and adolescents with depression, OCD, and other psychiatric conditions.

GSK Used Paxil Forum Events to Promote Paxil for Children and Adolescents

53. **GSK** held eight "Paxil Forum" events at resorts in Puerto Rico, Hawaii, and California in 2000 and 2001. **GSK** invited psychiatrists who prescribed large amounts of SSRIs to attend the events. Each of **GSK**'s approximately 150 neuroscience sales representatives could attend up to two of the events per year, and each representative could invite up to two different psychiatrists to each event. The 3-day Paxil Forum events included presentations about Paxil and other topics. The events also included dinners and recreational activities such as deep sea fishing, kayaking, snorkeling, sailing, horseback riding,

balloon rides, and golf. **GSK** paid for the psychiatrists' air fare, lodging, meals, recreational activities, and provided to each of them an honorarium of $750. The Paxil marketing team organized, attended, and participated in the Paxil Forum events.

54. **GSK** paid a leading child psychiatrist to speak at four of the eight Paxil Forum events in 2000 and 2001. At each of these four Paxil Forum events, this child psychiatrist encouraged other doctors to use SSRIs to treat depression and social anxiety disorder in patients under age 18. This child psychiatrist claimed that patients treated with Paxil in Study 329 showed "significantly greater improvement" than patients who received the placebo.

55. To promote the use of Paxil in children and adolescents, some **GSK** sales representatives purposely invited psychiatrists with a significant percentage of patients under age 18 to attend the Paxil Forum events at which the child psychiatrist recommended the use of SSRIs for children and adolescents.

56. Following the Paxil Forum events, some **GSK** sales representatives gave doctors during sales calls copies of the slides shown during the Paxil Forum events by the child psychiatrist referenced in Paragraph 52 above. The slides reported only select, favorable results from Study 329. The

slides did not report the unfavorable results from Study 329 or other studies of Paxil's efficacy in treating depression in children and adolescents. The slides also did not state that the FDA had not approved the use of Paxil in patients under age 18. The slides distributed by the **GSK** sales representatives were false and misleading.

57. **GSK** monitored the prescriptions written by psychiatrists who attended the Paxil Forum events in 2000 to determine whether the events increased Paxil's market share. **GSK** concluded that the Paxil Forum events in 2000 "had a significant impact on Paxil market share in the months after attendance." GSK found that the percentage of Paxil prescriptions relative to other SSRI prescriptions prescribed by psychiatrists who attended the Paxil Forum events in 2000 increased when compared to the percentage prescribed by psychiatrists who had not attended the Paxil Forum events. Individual **GSK** sales representatives continued to monitor whether psychiatrists who attended the Paxil Forum events in 2001 increased their Paxil prescriptions after attending the events.

GSK Used Dinner Programs to Promote the Use of Paxil in Children and Adolescents

58. **GSK** sponsored dinner programs, lunch programs, spa programs, and similar activities to promote the use of Paxil in

children and adolescents. At such events, **GSK** paid a speaker to talk to an audience of doctors. **GSK** paid for the meal or spa treatment for the doctors who attended. These events were approved in advance by **GSK**'s district sales managers and by **GSK**'s speakers bureau.

GSK Used Samples to Promote the Use of Paxil in Children and Adolescents

59. **GSK** provided each sales representative with a list of doctors on whom the sales representatives should make sales calls. The lists specified how frequently sales representatives should make sales calls on each doctor. Sales representatives were required to call most frequently on doctors who prescribed the most SSRIs.

60. **GSK** encouraged its sales representatives to give doctors free Paxil samples during the sales calls. **GSK**'s purpose in distributing free samples was to allow doctors to start patients on Paxil, with the hope that the patient would be shifted to a paid Paxil prescription if the treatment was successful.

61. Beginning in or around August 2003, **GSK** began attempting to remove from its Paxil call lists doctors who exclusively treated patients under age 18. This process continued until at least on or about May 11, 2005. Thus, prior

to in or around August 2003, **GSK** required its sales representatives to make sales calls on, and encouraged its sales representatives to provide Paxil samples to, doctors who treated only patients under age 18. There was no FDA-approved use for Paxil in patients under age 18.

DISTRIBUTION OF PAXIL

62. Throughout the relevant time period of the above-described actions, **GSK** distributed Paxil in Massachusetts and elsewhere and held Paxil for sale in Massachusetts and elsewhere.

DISTRIBUTION OF MISBRANDED PAXIL

63. From on or about April 3, 1998, through in or around the end of August 2003, in the District of Massachusetts, and elsewhere, defendant

GlaxoSmithKline LLC

did introduce and cause the introduction into interstate commerce, directly and indirectly, into Massachusetts and elsewhere from outside of Massachusetts, Paxil, a drug within the meaning of the FDCA, 21 U.S.C. § 321(g), that was misbranded, in that its labeling was false and misleading.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1), and 352(a).

COUNT TWO - WELLBUTRIN

(Distribution of a Misbranded Drug: Inadequate Directions for Use 21 U.S.C. §§ 331(a), 333(a)(1) & 352(f)(1))

64. The allegations contained in paragraphs 1 and 3 through 10 are realleged and incorporated herein as if set forth in full.

GSK'S PROMOTION OF WELLBUTRIN FOR UNAPPROVED USES

65. **GSK** manufactured, distributed, and sold the prescription drug Wellbutrin for human use. Wellbutrin was **GSK**'s trade name for the drug bupropion hydrochloride.

66. At all times relevant to the Information, Wellbutrin was approved by the FDA only as a treatment for major depressive disorder in adults age 18 or older.

67. From 1999 to 2003, Wellbutrin was not approved for any use other than to treat major depressive disorder in adults.

68. To increase its profits from Wellbutrin, from in or about 1999 through 2003, **GSK** promoted the sale and use of Wellbutrin for a variety of uses for which **GSK** had not received FDA approval including:

a. for weight loss and the treatment of obesity;

b. to treat sexual dysfunction;

c. as an "add-on" drug to treat the side effects of other antidepressant medications, including weight gain and sexual dysfunction;

d. to treat Attention Deficit Hyperactivity Disorder ("ADHD") and other attention disorders;

e. to treat addiction to drugs, alcohol, or gambling;

f. to treat other mental diseases such as anxiety and bipolar disorder;

g. to treat patients under age 18; and

h. with dosing regimens different than those in the label.

69. **GSK** encouraged sales representatives to provide messages about off-label uses of Wellbutrin during one-on-one sales calls with doctors.

70. **GSK** sales representatives sometimes referred to Wellbutrin as "the happy, horny, skinny pill" as a way to remind doctors of the unapproved uses for Wellbutrin that they were promoting.

71. **GSK** used speaker programs to spread off-label information about Wellbutrin to doctors. **GSK** trained and paid doctors to speak to other doctors at hundreds of promotional events per year that were organized by **GSK**'s sales representatives. At many of these events, speakers recommended the use of Wellubutrin for unapproved uses. Some of these speakers also made additional false and misleading claims about Wellbutrin's safety and efficacy for approved and unapproved uses.

72. Two of **GSK**'s most frequently used speakers, who each

spoke more than 800 times and were each paid more than $1.5 million by **GSK** from 2000 to 2003, recommended Wellbutrin for a wide variety of unapproved uses, including for weight loss, to treat sexual dysfunction, to treat ADHD and other attention disorders, and even for patients with bulimia or who were abruptly discontinuing alcohol (both of which were specifically contraindicated in Wellbutrin's labeling).

73. **GSK** paid doctors to attend lavish meetings in places such as Jamaica and Bermuda during which **GSK** provided off-label information about Wellbutrin in a manner to encourage doctors to write Wellbutrin prescriptions for unapproved uses of the drug. **GSK** tried to disguise the promotional nature of these meetings by characterizing them as "speaker training" meetings.

74. **GSK** paid doctors to attend "Local Advisory Boards," "Regional Advisory Boards," and Special Issues Boards" during many of which **GSK** provided information about unapproved uses of Wellbutrin.

75. **GSK** called these meetings "advisory board" or "consultant" meetings to create the pretense that **GSK** was gathering information and feedback from the doctors. In fact, there generally was little consulting provided by the doctors during these meetings and **GSK** made no real effort to capture and disseminate the advice it supposedly obtained.

76. **GSK** held such sham advisory board meetings repeatedly and frequently, sometimes holding more than one such meeting on the same day in the same city or hotel, with similar off-label agendas for many events, and the same speakers.

77. **GSK** also sponsored extensive continuing medical education ("CME") programs for doctors during which off-label information about Wellbutrin was disseminated. Although CME programs were ostensibly independent, in certain CME programs, **GSK** influenced the content and frequently selected the location and the speakers and invited many of the attendees, and **GSK** in some instances determined how much the speaker was paid.

78. **GSK**'s sales representatives frequently arranged for the speakers at CME programs to be the same doctors who spoke most frequently at **GSK**'s Wellbutrin promotional events. In some instances, **GSK**'s sales representatives knew that these speakers would deliver at the CME programs the same off-label information they provided during promotional programs.

79. **GSK** sales representatives distributed and played for doctors certain purportedly independent CME materials in the form of audiocassettes or DVDs that **GSK** had funded and/or prepared and which contained messages about unapproved uses of Wellbutrin.

DISTRIBUTION OF WELLBUTRIN

80. Throughout the relevant time period of the above-described actions, **GSK** distributed Wellbutrin in Massachusetts and elsewhere and held Wellbutrin for sale in Massachusetts and elsewhere.

DISTRIBUTION OF MISBRANDED WELLBUTRIN

81. From in or about January 1999 through in or about December 2003, in the District of Massachusetts, and elsewhere, defendant

GlaxoSmithKline LLC

did introduce and cause the introduction into interstate commerce, directly and indirectly, into Massachusetts and elsewhere, from outside of Massachusetts, Wellbutrin, a drug within the meaning of the FDCA, 21 U.S.C. § 321(g), which was intended for use for the treatment of sexual dysfunction, for weight loss, addiction, ADHD, and as an add-on to other antidepressant drugs and for other conditions and which was misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that its labeling lacked adequate directions for such uses.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1).

COUNT THREE - AVANDIA

(Failure to Report Data to FDA: 21 U.S.C. §§ 331(e), 333(a)(1) & 355(k)(1))

82. The allegations in paragraphs 2 through 4 are realleged and incorporated by reference herein.

REQUIRED REPORTING OF INFORMATION REGARDING DRUGS TO THE FDA

83. Under the FDCA, the term "drug" included articles that (1) were intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans; and (2) were intended to affect the structure or any function of the human body. 21 U.S.C. § 321(g)(1)(B) and (C).

84. A drug was a "new drug" if it was, in part, "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof ...." 21 U.S.C. § 321(p)(1). To be lawfully introduced into interstate commerce, new drugs required an approved marketing or investigational application. 21 U.S.C. §§ 331(d) and 355. Approved marketing or investigational applications included New Drug Applications ("NDAs"). 21 U.S.C. § 355.

85. To obtain FDA approval of an NDA, the sponsor was required to demonstrate, to FDA's satisfaction, that the drug was

both safe and effective for each of its claimed uses. 21 U.S.C. § 355(b). Toward this end, the NDA sponsor was required to provide, to the satisfaction of FDA, substantial evidence, including data generated in adequate and well-controlled clinical investigations, that demonstrated that the drug was safe and effective when used in accordance with the proposed labeling for its intended uses. 21 U.S.C. § 355(d). An NDA sponsor was not permitted to promote or market the drug until the FDA had approved the NDA.

86. Once the NDA had been approved, the holder of the NDA was required to provide the FDA certain periodic reports of data relating to clinical experience to permit the FDA to determine, among other things, whether grounds for withdrawal of the NDA existed based upon clinical experience showing that the drug was unsafe for use under the conditions of use for which it was approved. 21 U.S.C. §§ 355(k)(1), (e). These periodic reports of data were intended to provide the FDA an overview of all safety-related information learned by the holder of the NDA during that quarter or year, and thereby facilitate the FDA's ability to spot drug safety trends.

87. Among other reporting, the holder of the NDA was required to submit to the FDA certain reports regarding postmarketing adverse drugs experiences. 21 C.F.R. § 314.80.

These reports were required to include, among other information, "a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated)." 21 C.F.R. § 314.80(c)(2)(ii)(c).

88. Also among other reporting, the holder of the NDA was required to file an Annual Report each year regarding the approved drug. 21 C.F.R. § 314.81(b)(2). Among other information required to be included in the Annual Report was a "status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by the FDA . . . ." 21 C.F.R. § 314.81(b)(2)(vii); and a "status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant." 21 C.F.R. § 314.81(b)(2)(viii).

89. At all times material to this Information, it was a crime, in violation of Title 21 United States Code, Section 331(e) to fail to make reports required by Section 355(k)(1), including reports of data relating to clinical experience, and other data and information, as necessary for the FDA to determine whether the NDA approval should be withdrawn or suspended for any reason set forth in Section 355(e).

DEVELOPMENT OF AND STUDIES REGARDING AVANDIA

90. One of the prescription drugs that was developed by **GSK** was Avandia (rosiglitazone maleate), a diabetes medication. Avandia was one of a class of drugs known as thiazolidediones that were designed to increase insulin sensitivity. The FDA approved the NDA application for Avandia in May 1999. Thereafter, **GSK** promoted, sold, and distributed Avandia into interstate commerce in the United States, including within the District of Massachusetts.

91. In 2001, **GSK** initiated two separate studies at the request of European regulatory authorities as postmarketing commitments to further evaluate the cardiovascular safety of Avandia. Those two studies were known as Study 211 and RECORD.

A. The **GSK** protocol for Study 211 indicated that this study was initiated because "rosiglitazone (like other thiazolidnediones) causes a mild increase in plasma volume. An increase in plasma volume might aggravate existing cardiac failure unless appropriate diuretic therapy is initiated . . . . This study will investigate the effect of rosiglitazone in addition to background anti-diabetic therapy on cardiac structure and function and cardiovascular morbidity and mortality in type 2 diabetic patients with pre-existing CHF [congestive heart failure[(NYHA grade I/II). . . ."

B. The **GSK** protocol for RECORD indicated that this study was initiated because rosiglitazone "also increases body weight (albeit without altering known weight-associated cardiovascular risk factors), has a multifactoral effect on lipids (some effects putatively beneficial, some putatively adverse), and leads to a modest increase in plasma volume . . . . There is a need formally to evaluate long term cardiovascular outcome, both for those who receive the most widely used oral combination therapy (sulphonylurea (SU) plus metformin (MET), and for those who are given rosiglitazone in addition to their first-line therapy (metformin or SU)."

92. In its 2001 Periodic Report for Avandia, **GSK** did not notify the FDA of the initiation of Study 211 and RECORD, despite the regulatory requirement that each periodic report contain "a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated)." 21 C.F.R. § 314.80(c)(2)(i)(c).

93. Moreover, in each of its Annual Reports for Avandia between 2001 and 2007, **GSK** did not provide the FDA with a status report on certain postmarketing studies being performed by, or on behalf of, **GSK**, despite the regulatory requirement to provide that information in 21 C.F.R. § 314.81(b)(2)(viii). Some of the studies that were omitted from certain of those Annual Reports

included Study 211, RECORD, and APPROACH, all of which involved cardiovascular safety issues.

94. Additionally, in its 2007 Annual Report for Avandia that was submitted to the FDA, **GSK** did not provide the FDA with a status report of the post-marketing study, ADOPT, which concerned clinical efficacy, despite the regulatory requirement to provide that information in 21 C.F.R. § 314.81(b)(2)(vii).

FAILURE TO MAKE REQUIRED REPORTING TO FDA

95. Beginning in or about 2001 and continuing until in or about September 2007, in the District of Maryland and elsewhere, the defendant,

GLAXOSMITHKLINE LLC

did fail to make required reporting of data relating to clinical experience and other data and information regarding Avandia, as required by law, to the United States Food and Drug Administration.

All in violation of 21 U.S.C. §§331(e), 333(a)(1), and 355(k)(1).

FORFEITURE ALLEGATIONS

(21 U.S.C. §§ 334, 853 and 28 U.S.C. § 2461(c))

96. Upon conviction of one or more of the offenses charged in Counts One and Two of this Information, defendant

GlaxoSmithKline LLC

shall forfeit to the United States pursuant to 21 U.S.C. § 334 and 28 U.S.C. § 2461(c), any quantities of Paxil that between April 3, 1998 and the end of August 2003, and any quantities of Wellbutrin that between January 1999 and December 2003, were introduced into interstate commerce in violation of 21 U.S.C. §§ 331(a) and 352(a) and 352(f)(1).

97. If any of the property subject to forfeiture, as a result of any act or omission of the defendant:

a. cannot be located upon the exercise of due diligence;

b. has been transferred or sold to, or deposited with, a third party;

c. has been placed beyond the jurisdiction of the court;

d. has been substantially diminished in value; or

e. has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to 21 U.S.C. § 853(p), incorporated by reference in 28 U.S.C. § 2461(c), to seek forfeiture of any other property of the defendant up to the value of the property subject to forfeiture, that is $43,185,600.

All pursuant to 21 U.S.C. §§ 334 and 853, and 28 U.S.C. § 2461(c), and Rule 32.2 of the Federal Rules of Criminal Procedure.

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Date: July 2, 2012

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All pursuant to 21 U.S.C. §§ 334 and 853, and 28 U.S.C. § 2461(c), and Rule 32.2 of the Federal Rules of Criminal Procedure.

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