

EXPERT REPORT
DAVID A. KESSLER, M.D.

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I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978. I did my pediatrics training at Johns Hopkins Hospital.

2. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

3. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal medical and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume, including a list of my published books and articles, is included in Appendix C. Cases in which I have appeared as a witness in the last four years, and expert witness fee are attached in Appendix D.

4. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within FDA. They included, among others, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. I introduced changes in the device approval process to ensure that it meets high standards. During my tenure as Commissioner, the FDA announced a number of new programs, including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to

improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems. I created an Office of Criminal Investigation within the Agency.

5. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I serve on the boards of Aptalis Pharma and Tokai Pharmaceuticals. In these advising and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical industry.

6. The documents provided to me by counsel, or that I accessed independently from various sources, including, but not limited to, FDA's website, are listed in Appendix E to this report. At my request, Appendix E was prepared by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

7. In this report, I use the term Bayer to refer to Bayer Corporation, Bayer Pharma AG, Bayer Schering Pharma AG, Bayer HealthCare LLC, Bayer Pharmaceuticals Corporation, Berlex Laboratories, Berlex, Inc. and Schering AG. Berlex Laboratories was the U.S. subsidiary of the German pharmaceutical company Schering AG. In mid-2006, Schering was acquired by Bayer Pharmaceuticals. On April 4 2007, Berlex changed its name to Bayer Healthcare Pharmaceuticals. (April 4, 2007 Bayer Press Release, *Bayer HealthCare Pharmaceuticals Officially Launches in the United States*, http://www.pharma.bayer.com/scripts/pages/en/news_room/news_room/news_room7.php).

8. It is my understanding that in 2001 Jenapharm became fully owned by Schering. From 1996 to 2001, Schering owned approximately 75 per cent of Jenapharm. (*Schering AG to take full control of Jenapharm*, October 15, 2001, IAC (SM) Newsletter Database (TM)).

II. SUMMARY OF OPINIONS

9. The manufacturer, not FDA, is primarily responsible for the safety of its products.

10. FDA regulations and state law provide independent and complementary layers of consumer protection.

11. Bayer violated its duties under FDA regulations and state law by selectively presenting data as to thromboembolic events, which did not adequately inform FDA, doctors or consumers of the thromboembolic risks, from pre-marketing to the present.

12. Bayer engaged in extensive off-label promotion of Yasmin and YAZ for unapproved uses, in violation of FDA regulations, to increase sales. That off-label promotion increased the risk of thromboembolic events in patients in violation of state law duties.

III. FDA REGULATIONS AND STATE TORT LIABILITY USUALLY OPERATE INDEPENDENTLY, EACH PROVIDING A SIGNIFICANT YET DISTINCT LAYER OF CONSUMER PROTECTION

13. It is the purveyor of a drug that has responsibility to assure that its products meet both state consumer protection and FDA laws and regulations. It is the purveyor of a drug that is responsible for the safety of its product.

14. FDA regulation of a drug cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product may fail to identify potential problems presented by the product.

15. It was my opinion while Commissioner of FDA, and remains to this day, that the two systems of state consumer protection and federal food and drug regulation should and do operate in a complementary but independent manner.

16. As I have written and testified before the United States Congress, the Federal Food Drug and Cosmetic Act (FDCA) grants FDA substantial authority over the approval,

labeling, and promotion of pharmaceutical products. But, nothing in the FDCA, or in FDA's implementing regulations, relieves a manufacturer of its duty to act according to the company's internal knowledge about a product and its potential risks.

17. A fundamental problem FDA faces is that, by necessity, drugs are approved on the basis of less-than-perfect knowledge. Risks that are rare, appear as common illnesses, have long latency periods, result from drug interactions, or have adverse impacts on subpopulations, often go undetected in clinical testing. If a drug company has reason to know that the risks of a drug may result in adverse events, it has a responsibility to inform physicians and health care providers.

18. A drug company has a responsibility, independent of what FDA directs it to do, to alert physicians and patients to risks that were unknown to or poorly understood by the FDA, but were known to the company. This duty predates by decades the advent of federal regulation of drugs. (*See, e.g., Thomas v. Winchester*, 6 N.Y. 397 (1852)).

19. FDA's regulations make clear that a drug company has a duty to warn and modify labeling without delay when hazards emerge with one of its drugs. The regulations expressly authorize the company to make labeling changes, and take other steps to inform physicians and patients of emerging risks, without advance approval from the Agency. Such responsibility complements, not undercuts, FDA's job of protecting consumers from dangerous drugs.

20. Drug companies have an obligation to revise a label "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have not been definitely established." (21 CFR § 201.57(c)(6), 21 C.F.R. § 314.70 (c)(6)(iii)(A)-(C) *See generally*, Kessler D. A. and

Vladeck D. C., *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, Georgetown Law Journal, 2008 for a discussion of manufacturers' responsibility to change the label in the face of new safety information.)

21. Manufacturers have superior resources that are or should be committed to overseeing the safety of the drugs they market. As a result, manufacturers invariably get safety information before the FDA does and have access to information that is not available to the FDA.

22. Moreover, as the Institute of Medicine and Government Accountability Office have noted, during prior decade, FDA's ability to oversee drug safety has been constrained, especially during the post-approval portions of a drug's life. Specifically, the Institute of Medicine, in its report titled, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," has stated that, "the drug safety system is impaired by the following factors: serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER that is not optimally functional; and unclear and insufficient regulatory authorities particularly with respect to enforcement." The report further stated, "the committee found that FDA, contrary to its public health mission, and the pharmaceutical industry, contrary to its responsibility to the users of its products (and its shareholders), do not consistently demonstrate accountability and transparency to the public by communicating safety concerns in a timely and effective fashion." (Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 2007, p.4; http://www.nap.edu/openbook.php?record_id=11750&page=4).

23. The General Accounting Office stated in its report titled, "Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process" stated,

“Two organizationally distinct FDA offices, the Office of New Drugs (OND) and the Office of Drug Safety (ODS), are involved in postmarket drug safety activities. OND, which holds responsibility for approving drugs, is involved in safety activities throughout the life cycle of a drug, and it has the decision-making responsibility to take regulatory actions concerning the postmarket safety of drugs. OND works closely with ODS to help it make postmarket decisions. ODS, with a primary focus on postmarket safety, serves primarily as a consultant to OND and does not have independent decision-making responsibility. ODS has been reorganized several times over the years. There has been high turnover of ODS directors in the past 10 years, with eight different directors of the office and its predecessors. In the four drug case studies GAO examined, GAO observed that the postmarket safety decision-making process was complex and iterative...FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process are unclear, including ODS's participation in FDA's scientific advisory committee meetings organized by OND. Insufficient communication between ODS and OND has been an ongoing concern and has hindered the decision-making process. ODS does not track information about ongoing postmarket safety issues, including the recommendations that ODS staff make for safety actions. FDA faces data constraints in making postmarket safety decisions. 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.” (Drug Safety: Improvement

Needed in FDA's Postmarket Decision-making and Oversight Process, GAO-06-402, March 31, 2006, pgs.4-5).

24. Thus, what a drug company knows about a drug and what the FDA knows may be different.

25. The duties of a pharmaceutical company are based not only on FDA laws and regulations, but also on the risks presented by a drug about which the company knew, should have known, or should have investigated. Bayer's responsibility for the safety of its product and the adequacy of its warnings exists regardless of what FDA did or did not do.

IV. BAYER FAILED TO DISCLOSE THROMBOEMBOLIC RISK INFORMATION IN A TIMELY FASHION TO FDA, PHYSICIANS, AND THE PUBLIC

A. The Serious Adverse Events Observed In The Jenapharm Survey Should Have Been Reported To The FDA Prior To Approval

26. From October 2000 to October 2002, Jenapharm, a Schering subsidiary, conducted a postmarketing surveillance safety and efficacy study of Petibelle, the German equivalent to Yasmin involving 11,751 subjects. (BHCPYAZ005272425-682, Schellschmidt-154).

27. The Jenapharm report on page 70 stated: "In terms of thromboembolic events, the clinical database reported the occurrence of 7 events, i.e., 1 case of Embolism, 5 cases of Thrombosis, and 1 case of Thrombophlebitis . . . The assessment of GMS/Drug Safety confirmed the 4 following cases of thromboembolism: 1) Three cases of leg thrombosis; and 2) One case of pulmonary embolism . . ." (BHCPYAZ005272425-682 at 494, Schellschmidt-154).

28. The Jenapharm report on page 90 stated there were 8 confirmed Serious Adverse Drug Reactions [SADR, also known as SAEs], and 4 confirmed cases of thromboembolism. (BHCPYAZ005272425-682 at 514, Schellschmidt-154).

29. Included in the cases on page 90 was case 1244, which was not included in the cases listed on page 70. (BHCPYAZ005272425-682 at 514 and 494, Schellschmidt-154).

30. A description of case 1244 on page 59 of the Jenapharm report stated that the event was “assessed as ‘questionable thromboembolism’ in the CIOMS [European adverse event reporting] form.” (BHCPYAZ005272425-682 at 483, Schellschmidt-154).

31. It would be reasonable to say there were 8 possible cases of thromboembolism (subject numbers, 1237 [BHCPYAZ005272482, 494, 514], 1244 [BHCPYAZ005272483, 494, 514], 2287 [BHCPYAZ005272486, 494, 514], 2444 [BHCPYAZ005272487, 494, 514], 2465 [BHCPYAZ005272488, 494, 514], 1080 [BHCPYAZ005272489, 494], 2677 [BHCPYAZ005272491], and 290 [BHCPYAZ005272492, 494]), in the Jenapharm study, with 4 cases confirmed, (subject numbers, 1237, 2287, 2444 and 2465), in addition to the other non-thromboembolic SAEs in the Jenapharm report. (BHCPYAZ005272425-682). [Note: It is also reasonable to say that there were 9 possible cases of thromboembolism if one included subject number 1809, which the Jenapharm Report stated: was assessed by Bayer/GMS Drug Safety as “Thromboembolism Not Confirmed;” in Section 12.3.2.2.2, “but signs of thromboembolism were negated;” and in a footnote, “evaluated by Global Medical Surveillance/Drug Safety as possible sign of cerebrovascular thrombosis but thrombosis was not confirmed (and therefore not coded as such).” (BHCPYAZ005272490, 494, Schellschmidt-154).

32. The study report concluded, “There were no unexpected safety occurrences.” (BHCPYAZ005272425-682 at 433, Schellschmidt-154).

33. FDA regulations require that a manufacturer must submit as part of its New Drug Application “A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by

the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug ...” (21 C.F.R. § 314.50(c)(5)(iv)).

34. FDA regulations require that “The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These ‘safety update reports’ are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section.” (21 C.F.R. § 314.50(d)(5)(vi)(b)).

35. FDA has stated that, “Updates of safety information are required under the regulations to include ‘new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling,’ in essentially the same format as the integrated summary. Because the content of the update will depend on the nature of the additional data, it will generally be useful to consult with the reviewing division before preparing the update. It is possible to provide the safety update information as a report that refers only to the new data obtained since the last update or since the original submission, but it is preferable to provide a document incorporating the new data with the data and analyses in the initial integrated summary of safety information, as well as showing the new data. If the additional data are relatively few and come principally from foreign sources or other studies that have not been incorporated into overall analyses in the initial submission, it may be sufficient to concentrate on the serious or potentially serious adverse events, or an

unusually high frequency of a less serious event, providing a narrative description of these events.” (FDA, Center for Drug Evaluation and Research, “Guideline for the Format and Content of the Clinical and Statistical Sections of an Application,” July 1988, p.33-34).

36. Thus, all serious adverse events were required to be reported to FDA as part of Bayer’s New Drug Application whether they were expected or not. This includes updates of serious adverse events while the NDA review was underway.

37. Furthermore, any increase in the incidence rate of serious adverse events should have been reported expeditiously to the FDA. As FDA set out in March 1995 in its *Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* which was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):

There are situations in addition to single case reports of “serious” adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include: For an “expected,” serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

[Emphasis added]. (*Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, March 1995, p. 7).

38. Bayer provided separate Safety Updates for the periods March 17, 2000 to July 10, 2000 (November 6, 2000 submission) and July 10, 2000 to March 1, 2001 (March 27, 2001 submission) to the FDA according to the FDA’s Medical Reviewer. (Medical Officer’s Review of NDA 21-098, April 13, 2001, p. 25; BHCPYAZ006885770-811 at 798).

39. In the introduction to the Safety Update submitted on March 27, 2001, Berlex stated the following: “. . . this report refers only to new data obtained during the reporting period. These additional data are relatively few, therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, and subjects who failed to complete a clinical study due to an AE are described.” (BHCPYAZ011510501-508 at 501).

40. Based on Bayer’s Safety Update Report, Bayer knew to report “serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, and subjects who failed to complete a clinical study due to an AE.” (BHCPYAZ011510501-508 at 501).

41. FDA’s Medical Officer wrote in a section of his pre-approval review: “Spontaneous reports from foreign marketing experience: Since the launch of Yasmin (also known as Petibelle) in November 2000, 1 death (presumably due to a myocardial infarct or pulmonary embolus) and serious adverse events (SAEs) in 7 women have been reported.” (Medical Officer’s Review of NDA 21-098, April 13, 2001, p.26; BHCPYAZ006885770-811 at 799).

42. The FDA Medical Officer summarized the information about thrombotic events in his report as follows: “Nonfatal Serious Adverse Events. Four of the 7 subjects experienced nonfatal SAEs that were reported as thrombotic or thromboembolic in nature. Brief histories for these subjects are as follows: 1) a 22 year old women [sic] switched from an unknown oral contraceptive to Yasmin and after 1 week suffered a stroke (posterior cerebral infarct). The woman had previously had 3 to 4 migraine attacks with associated transient hemiparesis yearly that had been treated with sumatriptan. After a migraine attack in December

2000, she was treated with rizatriptan. Her headache resolved but the hemiparesis and visual disturbance persisted, and she was diagnosed as having had a stroke. 2) A 35 year old woman reported severe dizziness, a fast heart rate, and pain in her leg 8 days after the start of Petibelle. She had previously used an oral contraceptive for 5 years. Petibelle was discontinued. Her clinical exam was normal and she recovered without any treatment. The gynecologist did not suspect a venous thrombosis or a pulmonary embolism, but on query could not exclude them as the cause of this woman's clinical symptoms. 3) After 3 days of using Petibelle, a woman with bronchial carcinoma and a history of 20 years of oral contraceptive use, developed a venous thrombosis in her leg. 4) A 22 year old woman changed from the oral contraceptive Diane-35, which she had used for about 5 years, to Yasmin in December 2000. In January 2001, she developed a deep venous thrombosis in her leg. Thrombolysis was performed." (Medical Officer's Review of NDA 21-098, April 13, 2001, p.26; BHCPYAZ006885770-811 at 799).

43. The FDA medical reviewer also summarized the death of a 47 year old markedly obese woman who had received Prostin for 7-10 days to initiate menses just prior to starting Petibelle. On February 21, she developed dyspnea and was taken to the hospital. The cause on the death certificate was "myocardial infarct" although a pulmonary embolus could not be ruled out. (Medical Officer's Review of NDA 21-098, April 13, 2001, pgs. 26-27; BHCPYAZ006885770-811 at 799-800).

44. The Jenapharm study report contained 5 patients who had serious thrombotic events, 4 were confirmed and one was labeled as "questionable." These include subjects 1237, 1244, 2287, 2444, and 2465, of which 1244 was "questionable." The report also contained an additional 4 subjects who had serious thrombotic adverse events that were "downgraded" to non-

serious. These included subjects 1080, 1809, 2677 and 290. (BHCPYAZ005272425-682 at 482, 483, 486, 487, 488, 490, 494-95, Schellschmidt-154).

45. From my review, it appears that subject 1244 was reported to and discussed by the FDA Medical Officer in his April 13, 2001 report, but it appears that the other serious thromboembolic events in the Jenapharm study were not mentioned in FDA's medical review. (BHCPYAZ005272425-682 at 483, Schellschmidt-154; and Medical Officer's Review of NDA 21-098, April 13, 2001, p.26; BHCPYAZ006885770-811 at 799).

46. The dates of onset of the serious thromboembolic or possible thromboembolic adverse events in the Jenapharm study were subject 1237 (00324-JPH) –March 22, 2001; Subject 1244 (00011-JPH) –December 20, 2000; Subject 2287 (00150-JPH) –April 2, 2001; Subject 2444 (00081-JPH) –Jan 19, 2001; and Subject 2465 (00152-JPH) –February 7, 2001. (BHCPYAZ005272425-682 at 482, 483, 486, 487, 488, Schellschmidt-154).

47. The FDA Officer concluded, "It is difficult at this time to assess the overall significance of the reported thrombotic or thromboembolic adverse events in women using Yasmin in Germany as the reporting period covers only a 4 month interval and there is likely to be underreporting of such events. Additional postmarketing safety data obtained over a longer period would help to clarify the significance of these adverse events." (Medical Officer's Review of NDA 21-098, April 13, 2001, p. 27; BHCPYAZ006885770-811 at 800).

48. The Jenapharm study period ranged from October 2000 to October 2002. (BHCPYAZ005272425-682 at 425, Schellschmidt-154).

49. Dr. Juergen Dinger, a Bayer employee, served as Vice President of Development and Medical Director of Jenapharm in 2000. (Dinger CV, Schellschmidt-94A, no Bates numbers).

50. Bayer, in its Safety Update for Reporting Period July 10, 2000-March 1, 2001, reported under a heading, “1.4.4 Epidemiological Studies,” that the EURAS study was scheduled to begin in February 2001 and discussed the primary objectives of EURAS and the number of patient cycles expected to be observed. (BHCPYAZ011510501-508 at 504).

51. Bayer did not tell the FDA in the section headed “Epidemiological Studies” that the Jenapharm postmarketing surveillance study had been ongoing since October 2000. (BHCPYAZ011510501-508 at 504).

52. The Jenapharm study was an epidemiological study that involved 1,527 investigators in Germany. (BHCPYAZ005272425-682 at 426, Schellschmidt-154).

53. On April 4, 2001, a Memorandum of Telecon between FDA’s Regulatory Manager for the Division of Reproductive and Urologic Drug Products, Jeanine Best, and Bayer’s Regulatory Affairs Officer, Nancy Velez, stated that, “The Division is concerned about the recently reported death in a woman during her second treatment cycle with Petibelle, in part, because the actual cause of death is not well documented in the information provided to date. Although the death is attributed to a pulmonary embolus, other causes of death such as a cardiac arrhythmia secondary to an electrolyte disorder do not appear to have been excluded. . . . You also state the ‘number of thromboembolic events is lower than expected in the estimated population receiving the drug during the initial marketing period.’ Please provide the basis for your statement that the number of events is lower than expected based on actual experience with reported numbers of thromboembolic adverse events and deaths during a comparable period following the launch of other combination oral contraceptives.” (BHCPYAZ013656292-296 at 293).

54. Thus, FDA was concerned about the rate of thromboembolic disease in patients taking Yasmin before the FDA approved Yasmin on May 11, 2001.

55. It is my opinion that Bayer had a duty to provide FDA with the data involving serious events that occurred in the Jenapharm study and prior to FDA rendering its decision. This is underscored by the fact that the rate of thrombotic events in the Jenapharm data was greater than the 4.1/10,000 women years that was stated by the FDA Medical Officer as the reported incidence of VTE's from OC. (Medical Officer's Review of NDA 21-098, April 13, 2001, p. 27; BHCPYAZ006885770-811 at 800).

56. The number of cases of reported VTE seen in the Jenapharm study exceed what Bayer knew was the reported incidence rate for idiopathic venous thromboembolic events (VTE), which were stated by Bayer to be 4.1/10,000 exposed women years and 4.2/10,000 exposed women years in two large European data base studies (Am J Obstet Gynecol 179 S78-86 1998; Human Reproductive Update 5:688-706, 1999, respectively). (BHCPYAZ001164703-707 at 705). The range of thromboembolic events in the completed Jenapharm study is in the range of 8.0 to 16.0 thrombotic events/10,000 (based on range of 4 to 8 cases discussed in the Jenapharm report). The rate would certainly have been even higher if calculated at the time of Yasmin's approval because by that time study subjects 1237, 1244, 2287, 2444 and 2465 had the onset of their adverse events and the number of women years (WY) was only a fraction of the 5,048 WY (as set forth in Bayer's June 2004 draft White Paper) in the completed study. (BHCPYAZ015732254-267 at 264, Schellschmidt-93). Assuming proportional enrollment over the two year period, the number of WY as of the date of approval of Yasmin on May 11, 2001 would have been approximately 30% of the final total. The adverse VTE event rate would have been 5/1514 WY, which would equal 33/10,000 WY. This rate is substantially higher than the

4.1/10,000 cited by both Bayer and FDA at the time of approval and would certainly have raised significant concerns about Yasmin. (BHCPYAZ001164703-707 at 705; Medical Officer's Review of NDA 21-098, April 13, 2001, p. 27; BHCPYAZ006885770-811 at 800).

57. FDA guidelines and regulations make it clear that: "The unexplained omission of any report of investigations made with the new drug by, or on behalf of, the applicant, or of any pertinent reports of clinical experience received or otherwise obtained by the applicant from published literature or other sources, may constitute grounds for refusing to approve the application [(21 CFR 314.125(b)(14))." (FDA, Center for Drug Evaluation and Research, *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*, July 1988, p. 10).

58. The need for full and up-to-date reporting was of special importance in light of FDA's repeated concerns about the drug both pre and post approval. Bayer knew that FDA referred to its approval decision as being on a "thin fuse" because of the Agency's safety concerns about Yasmin's potential risk of hyperkalemia. (BHCPYAZ001762728-730 at 730; BHCPYAZ001231958-981 at 968; PL-561).

59. According to a January 10, 2002 Bayer response to a FDA request for additional information, Bayer lists in a table five foreign serious labeled events from an observational trial with Jenapharm report numbers. According to that report, case 00081-JPH was received by the manufacturer on April 23, 2001; 00150-JPH was received by the manufacturer on August 7, 2001; 00152-JPH was received by the manufacturer on August 14, 2001; 00192-JPH was received by the manufacturer on September 25, 2001; and 00324-JPH was received by the manufacturer on November 28, 2001. (BCHPYAZ013658708-764 at 758). According to other Bayer documents, case 00081-JPH was received on January 23, 2001.

(BHCPYAZ011266475-478 at 477; BSPYAZ003155142-145 at 144). Four of these five adverse events occurred prior to FDA's decision on Yasmin; 00081-JPH on January 19, 2001; 00150-JPH on April 2, 2001; 00152-JPH on February 7, 2001; 00192-JPH on May 25, 2001; and 00324-JPH on March 22, 2001. (*See, supra*). In addition, 00011-JPH occurred on December 20, 2000, and appears to have been received by the manufacturer, according to the manufacturer, on January 8, 2001. (BHCPYAZ000997092-100 at 093). It was reported in a table to FDA on or about March 27, 2001. (BCHPYAZ000098826-856 at 841) (Bayer also listed cases 00150-JPH; 00152-JPH and 00324-JPH in a December 14, 2001 response to the FDA). (BHCPYAZ013658532-580 at 566, PL-550).

60. In light of FDA's concern about the risks of Yasmin prior to approval, it was Bayer's duty to provide FDA, as part of its NDA, with all relevant safety data. Bayer knew that its subsidiary/affiliate, Jenapharm, was conducting an epidemiological observational surveillance study, and therefore, Bayer should have sought to gather the serious adverse events that took place in the Jenapharm study in a prompt fashion and reported those results to the FDA. Bayer, through Jenapharm, had an obligation to assure that the investigators in the Jenapharm study promptly reported serious adverse events, especially those about which FDA was concerned.

61. In any case, Bayer should have reported case number 00081-JPH, which occurred on January 19, 2001 and was received by the manufacturer on either January 23, 2001 or April 23, 2001, prior to FDA's NDA decision on Yasmin. (*See supra*).

62. In my opinion, if I had become aware when I was at the FDA, of the adverse events that had occurred in the ongoing Jenapharm Postmarketing Surveillance Study, I would have sought to investigate what was known or knowable about the incidence of serious adverse

events, and would not have moved forward on a decision on NDA approval until such time as the results of the investigation were completed.

B. Bayer Decided Not To Inform FDA Of An Adverse Reaction Prior To Approval Of Yasmin

63. On April 17, 2001, almost a month before FDA was to make its decision on Yasmin, Bayer's Dr. Marie Foegh, wrote in an e-mail to her colleague, Juergen Dinger, about an adverse reaction involving a pulmonary embolism that occurred in March 2001 [case no. 01184-CDS]. As she indicated in her e-mail, she "was going to talk to the Medical Reviewer" that day about the pending Yasmin New Drug Application. "I delayed the call when I realized we had this additional case and lacking any further information. I will be most grateful for your help and for any further information that may be easily available, such as age, days on treatment, blood pressure, weight, height, how long in hospital, treatment etc." [Emphasis added].

(BSPYAZ003112476-477 at 477, PL-545).

64. On that same day, in response to her email, Dr. Foegh was informed by a Bayer colleague that the patient "is a non-smoker, there was no previous or concomitant medication documented up to Visit 3... the volunteer suffered from a lower abdominal pain (March 2001). The tentative diagnosis was an acute appendicitis. This was not confirmed in a following abdominal operation. But a pelvic venous thrombosis was diagnosed. Postsurgical the volunteer developed a pulmonary embolism. The investigator said that the volunteer would be in good condition." (BSPYAZ003112476-477 at 476, PL-545). The "Suspect Adverse Reaction Report" for this patient states that the event occurred on March 28, 2001 (BHCPYAZ001634980-986 at 980); that the initial report was received by the manufacturer on April 2, 2001 (BHCPYAZ001634980-986 at 980); with supplemental reports in May 2001 (BHCPYAZ001634980-986 at 981); and that the manufacturer's report was not prepared until

June 20, 2001, after the FDA had approved the Yasmin NDA. (BHCPYAZ001634980-986 at 980, and at the footer of every page).

65. Based on the information I have reviewed, there is no indication that Dr. Foegh shared the information about the pelvic venous thromboembolism and pulmonary embolism with the FDA medical reviewer before FDA reached its decision to approve Yasmin the next month.

66. Bayer had reason to be concerned about whether FDA would approve its application for Yasmin.

67. According to teleconference meeting minutes dated July 5, 2000, Bayer was told by FDA that, “There is a real emphasis in the Agency now to address risk management issues pre-approval whenever possible;” and that they had “two signals of concern for Yasmin: potential for hyperkalemia, and possible fetal toxicity (due to a single case of esophageal atresia);” and that “addressing these potential risks more thoroughly pre-approval has been considered and discussed at the Office level and above, particularly since Yasmin poses no known benefits over other approved oral contraceptives; to be very explicit, a non-approval action of this NDA had been considered and discussed.” (BHCPYA2001634361-365 at 363, PL-540).

68. In a teleconference on May 9, 2001, it was stated by Dr. Florence Houn, FDA’s Office Director, that, “there has been a great deal of discussion at the Division, Office and Center levels regarding the type of action be taken on Yasmin due to its risk/benefit profile,” and “that the final action had not yet been determined....” In another teleconference with FDA, on May 11, 2001, “Dr. Houn reminded Berlex that throughout the Agency, including senior CDER management, there remains concern about Yasmin. The minutes state that the concern throughout the Center regarding the risk of hyperkalemia is at such a level (there is a ‘thin fuse’)

that if a problem is found with Yasmin, such as contraindicated patients being prescribed Yasmin having clinical problems, the sponsor will be called in to discuss further regulatory action needed to ensure safety with the product... Appropriate marketing was stressed by FDA and Berlex agreed.” (BHCPYAZ018735057-059 at 059, PL-544).

69. An e-mail dated June 21, 2001 from Bayer’s Nancy Velez, referring to the same patient [case no. 01184-CDS] as discussed above by Dr. Foegh stated, “This is the famous case that we spent a day trying to decide if it was reportable and convincing Trish that it was not.” (BHCPYAZ001634978-979 at 978, PL- 548).

70. Considering the fact that Bayer was told that, “there is a real emphasis in the agency now to address to address risk management issues preapproval whenever possible,” it was imperative for Bayer to share all data that could be relevant to Yasmin’s safety with the Agency before the Agency made its decision. (BHCPYAZ001634978-979 at 978, PL- 548).

71. Moreover, the requirements, as noted *supra*, of what needs to be included in a New Drug Application, i.e., any information that could be relevant to the safety of the drug and that safety updates needed to be made while an application was pending, required the company to share the data about this patient.

72. It was the Agency, who, on April 4, 2001, requested more information to evaluate the VTE risk of Yasmin. (BHCPYAZ013656292-296 at 293). It was the Agency again, on November 30, 2001, that highlighted the risk of venous thromboembolism events by communicating reports of adverse reaction to the company. (BHCPYAZ000104703-706 at 704, Breitfeld-51). The Agency on December 20, 2001, initiated a teleconference and requested all serious venous thromboembolic events be compiled by the company. (BHCPYAZ011289721-723 at 721-722, PL-553).

73. It is the responsibility of the purveyor of a drug to find, identify, highlight and bring attention to potential problems.

74. In contrast to taking such actions, it appears that Bayer failed to timely disclose and report what was known and knowable about thromboembolic incidence from the Jenapharm study; failed to report case 00081-JPH to the Agency prior to the Agency's NDA decision; and also failed to report case 01184-CDS prior to the Agency's decision. As noted above, in my opinion, had I, or a medical review officer, known these facts prior to approval, further investigation would be warranted before a decision on Yasmin's NDA could be made. These facts would impact the Agency's risk-benefit equation about the drug and whether it could be approved.

C. **FDA Requested a Proposed Change to the Label Warning of an Increased Risk, and Bayer Did Not Provide FDA with any Proposed Changes to the Label**

75. FDA did its own analysis of spontaneous reporting data. The results of FDA's spontaneous reporting analysis raised concerns within the Agency about the safety of Yasmin. On January 16, 2003, the FDA Center for Drug Evaluation and Research prepared a Memorandum that, "reviewed and evaluated AERS [Adverse Event Reporting System] reports of serious thromboembolic and thrombotic adverse events in women using Yasmin compared to Ortho Tri-Cyclen, Alesse, and Mircette. The objective was to determine if the occurrence of these adverse events in women using Yasmin is greater than that in women using other oral combined hormonal contraceptives." (PL-79, p.1, no Bates numbers). Reporting rates were calculated for the first sixteen to twenty-one months of marketing of each product, based on numbers of reported events divided by person years of exposure. The events analyzed included deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction. (PL-79, pgs. 4-6). The Memorandum discussed the limitations of "adverse event reporting rates as a proxy to

incidence rates.” (PL-79, p. 15). The Memorandum concluded, “The reporting rate for serious thromboembolic and thrombotic events attributed to Yasmin during the first months of marketing in the U.S. was 4.3 times the reporting rate for Alesse, twice the reporting rate for Mircette, and 1.6 times the reporting rate for Ortho Tri-Cyclen.” (PL-79, p. 19). According to the FDA the source of the information and the calculations were as follows: “The AERS database is the source for the reporting rates. Three high level MEDRA codes were used: Embolism and Thromboembolism, Coronary Artery Disorders, and Central Nervous System Vascular Disorders. The cases were looked at individually, to eliminate duplicates. Once groupings were identified, reporting rates were calculated using prescription data from IMS. It was noted that there were more foreign Yasmin cases. This was a restricted analysis for U.S. women and a restricted analysis for other products for the first two years post-marketing. Calculated prescription rates were multiplied by 21 pills and divided by 365 days. Calculations were done for thrombotic events. Reporting rates were done for all four oral contraceptives (OC), and rate ratios for Yasmin were done individually.” (BHCPYAZ013665788-791 at 789).

76. On June 26, 2003, the FDA told Bayer, “We are very concerned about the number of postmarketing thromboembolic adverse events, particularly thromboembolic-related deaths, reported in Yasmin users. Based on information in the FDA Adverse Events Reporting System (AERS) database as of June 23, 2003 and information reported directly to NDA 21-098, we are aware of 14 thromboembolic or ischemic adverse events that have resulted in deaths in Yasmin users. Six of these deaths occurred in women in the United States. Five of these 6 deaths were first reported to the FDA after April 1, 2003.” (BHCPYAZ1262185-188 at 186, PL-630).

77. In the above June 26, 2003 letter, FDA told Bayer that, based on its concerns, “Because of these recent reports, we believe that a change in Yasmin labeling and possibly additional actions are now warranted.” (BHCPYAZ1262185-188 at 186, PL-630).

78. FDA stated to Bayer, “Submit to the Division by July 14, 2003 your proposal for a change in labeling for Yasmin regarding thrombotic risks, including pulmonary embolus, stroke, and death, and provide the rationale for your proposed labeling change.” (BHCPYAZ1262185-188 at 186, PL-630).

79. In response to FDA’s request for a change in the label on July 7, 2003, Bayer stated “Our postmarketing surveillance data to date do not show a signal that suggests a higher thromboembolic risk for Yasmin.” (BHCPYAZ105040-113 at 046; PL631).

80. On July 12, 2003, Dr. Jeff Borenstein, consultant to Bayer, wrote to Bayer’s marketer, Jeff Frick a “Strategy to Avoid Labeling Change.” (BHCPYAZ008972298-300 at 299, PL-700).

81. On July 15, 2003, Bayer’s Charles Walsh wrote to Dr. Paul Pradip and other Bayer colleagues, “that the agency has agreed to postpone the discussion of a Yasmin labeling change regarding thromboembolic (TE) risk until it has received all of Berlex’s data.” Walsh went on, “FDA has given us until July 28th (the original deadline) but is ‘encouraging’ Berlex to submit as much of the data as possible by July 24th.” (BHCPYAZ006761254-258 at 254, Walsh-10).

82. Walsh also stated that, “the key message for us in Drug Safety is that FDA is very concerned about the safety profile of the drug; particularly should there be any ‘further worrisome postmarketing [AE] reports.’” (BHCPYAZ006761254-258 at 254, Walsh-10).

83. Walsh further stated, “in view of this situation, I would just ask that should you receive any serious reports involving Yasmin over the coming weeks to let me . . . know as soon as you can. In the event that you are on the phone with the [health care practitioner] HCP or consumer, I would urge you to gather as much information as possible on the case, especially any personal or family history or any other ‘risk factor’ information from the Yasmin questionnaire.” (BHCPYAZ006761254-258 at 254, Walsh-10).

84. On July 28, 2003, Bayer, in response to FDA’s request to submit a new warning label, did not submit any such proposal, but rather stated to FDA in a letter, “After an in depth analysis of all available data, including data from the EURAS study, there is no evidence that the thromboembolic risk for YASMIN exceeds the known risk for other combined oral contraceptives. Therefore, as stated in our July 7, 2003 response, we believe that the current YASMIN label accurately reflects the clinical profile of the drug.” (BHCPYAZ104890-030 at 892, PL-632).

85. By July 2003, Bayer had completed its Jenapharm study. According to Bayer’s description of the Jenapharm study in an October 17, 2001 Periodic Safety Update Report for the period 07.03.2001 – 06.09.2001, the Interim Report should have been available in early 2002 and a final report later in 2002. (BHCPYAZ015256198-331 at 224-225, PL-284). While Bayer listed, from the Jenapharm observational study, one case of a serious thromboembolic event in its Safety Update Report for the period July 10, 2000 – March 1, 2001, (BHCPYAZ000098826-856 at 841) [this case report from Jenapharm observational study was actually listed in a “Summary of Spontaneous Reports for Yasmin], there is no mention of Jenapharm study in section 1.4.4 titled “Epidemiological Studies.”(BHCPYAZ000098826-856 at 838-839). Five cases of serious thromboembolic events from the Jenapharm observational study

were reported in a January 10, 2002 response to FDA requests. (BHCPYAZ013658708-764 at 758). Bayer failed to provide any analysis of the incidence rate in the Jenapharm study to FDA. (*See above*).

86. In my opinion, Bayer employed a strategy to avoid strengthening Yasmin's VTE warning and selectively presented data to the FDA.

D. Bayer Knew Based On Its Own Analysis That Yasmin Had An Increase In The U.S. Reporting Rate For DVT, PE, ATE And Confirmed VTEs Compared To Three Other COCs

87. FDA had repeatedly expressed concerns over adverse thromboembolic events with Yasmin and YAZ, including contacts and communications on the following dates: April 4, 2001; November 30, 2001; December 20, 2001; March 5, 2002; April 4, 2002; September 30, 2002; October 17, 2002; January 29, 2003; June 23, 2003; June 26, 2003.

(BHCPYAZ013656292-296 at 293; and BHCPYAZ001250106-126 at 117-120; Fiedler-38).

88. On August 7, 2003, Bayer convened a meeting of consultants and company employees to address "FDA concerns" about VTE risks of Yasmin. (BHCPYAZ014467337-339 at 337, Foegh-35). The recommended actions included, "The next response to the FDA needs to be a scientific write-up that lays out the issues." (BHCPYAZ014467337-339 at 338, Foegh-35).

Ultimately, after several drafts, a "White Paper" was submitted to the FDA on August 17, 2004.

(BHCPYAZ011715030-076, Schellschmidt-98, BHCPYAZ011701241-244,

BHCPYAZ011701237-239, BHCPYAZ011715027-029).

89. On June 2, 2004, in a draft of the August 17, 2004 White Paper, Bayer employees wrote, "Compared to the three other OCs, Yasmin has a several fold increase in the reporting rates for DVT, PE, ATE and confirmed VTEs. The reporting rate for Thrombosis NOS was also increased, but not to the same magnitude and there were too few deaths reported for a meaningful comparison." (BHCPYAZ015732254-267 at 264; Schellschmidt-93).

90. The draft White Paper also stated, “When considering only serious AEs, the reporting rate for Yasmin was 10 fold higher than that with the other products which were very similar in magnitude. The differences in reporting of serious AEs remained after the ATE and VTE events events [sic] were removed. Hence, there appears to be a general increase in the reporting pattern of Yasmin.” (BHCPYAZ015732254-267 at 265; Schellschmidt-93). It also reported that “When considering all AEs, Yasmin and Alesse had markedly higher reporting rates than Tri-cyclen and Mircette.” (BHCPYAZ015732254-267 at 265; Schellschmidt-93).

91. The draft White Paper included a table that revealed 5 fatal TEs compared to 0 for Alesse and Mircette and 1 for Tri-Cyclen. The Total Fatal TE’s per Estimated Package Year was 0.7 for Yasmin compared to 0 for Alesse and Mircette and 0.5 for Tri-Cyclen. The total confirmed VTEs/estimated Package Years for Yasmin were 6.9 (48 absolute cases) compared with 1.5 (8) for Alesse, 1.5(3) for Tri-Cyclen and 2.3 (8) for Mircette. The table showed that Yasmin had higher (2.9(20), 4.0(28), 0.7 (5) respectively) reporting rates for DVT’s, PE and Thrombosis NOS. (BHCPYAZ015732254-267, at 265; Schellschmidt-93).

92. Bayer knew that FDA’s triggers for “stating increase in risks” included “Reporting rates 2 to 5 fold higher than similar products.” (BHCPYAZ014467337-339 at 338, Foegh-35).

93. Analysis of spontaneous reporting data has limitations including, but not limited to, the voluntary nature of the reporting; effects of media attention; different time periods of introduction; different reporting patterns across sponsors; and different perceptions, characteristics and prescribing patterns of products. Even with its limitations, analysis of spontaneous reporting data is an important, recognized, and vitally used tool by the FDA and the pharmaceutical industry for detecting safety signals.

94. On or about August 11, 2004, Berlex employees wrote a near final draft of the White Paper that was viewed as a “convincing scientific paper,” among other statements in the section labeled “7 Summary” stated that, “Overall, spontaneous reporting data do signal a difference in the VTE rates for Yasmin and other OC users. However, assessment of spontaneous ADR reporting data from different products is not the preferred approach to assess the safety of a single product if data from a direct comparison, such as in the EURAS study, is available. The on-going Ingenix study should provide more insight on event data and the user risk profiles in the US. A significant difference between US and European data on VTE incidences in OC users is not expected.” (BHCPYAZ015693328-354 at 329 and 350, Schellschmidt-96).

95. On or about August 11, 2004, Ed Bradley, a Berlex employee, wrote to company colleagues with specific comments regarding Section 7 in the draft White Paper that: “The spontaneous reporting data do NOT signal a difference in VTE rates for Yasmin and other OC uses. We see NO signal of a difference.” [Emphasis in original]. Those comments were not accompanied by any additional data. (BHCPYAZ001201294-295 at 295, Wallander-20; BHCPYAZ018818931-933 at 933).

96. In my opinion, Bayer’s spontaneous reporting analysis demonstrated a safety signal about Yasmin and VTE risk.

E. Bayer Omitted From Its Analysis That It Presented To The FDA, The Data Showing That Yasmin Had An Increase In The Reporting Rate For DVT, PE, ATE, And Confirmed VTEs Compared To Three Other COCs

97. Bayer’s analysis in its draft White Paper that demonstrated an increase in the US reporting rate for DVT, PE, ATE and confirmed VTE’s compared to three other COC’s, was not included in the final version of the White Paper that Bayer submitted to the FDA on August 17, 2004. (Compare BHCPYAZ015732254-267, at 265; Schellschmidt-93 with

BHCPYAZ011701241-244, BHCPYAZ011701237-239, BHCPYAZ011715027-029, BHCPYAZ011715030-076, Schellschmidt-98).

98. Bayer, in the final White Paper that it submitted to the FDA on August 17, 2004, did not include the statement that was in the section summary of its draft white paper that: “Overall, spontaneous reporting data do signal a difference in the VTE rates for Yasmin and other OC issues . . . [See *supra*].” (BHCPYAZ015693328-354 at 350, Schellschmidt-96; BHCPYAZ011701241-244, BHCPYAZ011701237-239, BHCPYAZ011715027-029, BHCPYAZ011715030-076 at 57-58, Schellschmidt-98).

99. It appears, based on the information that I have reviewed, and it is my opinion, that Bayer presented a selective view of the data, and that presentation obscured the potential risks associated with Yasmin. In my opinion, Bayer had a duty to present a full and balanced view of all the data and analysis concerning Yasmin to the FDA and healthcare professionals and failed to do so.

F. Bayer Omitted Data From The Jenapharm Postmarketing Surveillance Study In Its Final White Paper That It Submitted To The FDA On August 17, 2004

100. As discussed *supra*, Section IV.A., the Jenapharm study was carried out between October 2000 and October 2002. The study report was not completed until 2009, seven years after the study was concluded. (BHCPYAZ005272425-682, Schellschmidt-154).

101. In the study report, there was neither an analysis of the incidence rate, nor of the significance of the number of cases of thromboembolism in the Jenapharm study. The only analysis presented was a “Frequency Analysis” of 0.06% based on the 7 cases. (BHCPYAZ005272425-682 at 564, Schellschmidt-154).

102. A June 2004 draft of the Working Paper that was to be submitted to the FDA included a section heading for the Jenapharm survey (Section 2.1.2.3.) Under that heading were

the numbers 11670 and 5048 PYs. (BHCPYAZ015732254-267, at 264; Schellschmidt-93).

These appear to refer to the number of subjects and the number of “patient years” (PYs) of exposure in the completed study.

103. The number of cases of thromboembolism in the Jenapharm study (either 8 or 4) in approximately 5000 patient years, represents an incidence rate that warrants analysis and attention and raises a potential safety signal because the rate of thrombotic events is in the range of approximately 8.0 to 16.0 thrombotic events/10,000 patient years. Bayer, in its White Paper, cited the incidence rate of Yasmin as 6.7/10,000 (for all VTEs and ATEs) and 6.1/10,000 (for all VTEs). (BHCPYAZ011701241-44; BHCPYAZ011701237-39; BHCPYAZ011715027-29; BHCPYAZ011715030-76 at 36; Schellschmidt-98). The FDA medical reviewer in 2001 cited an incidence rate in OC as 4.1/10,000 (for VTEs). (Medical Officer’s Review of NDA 21-098, April 13, 2001, p. 27BHCPYAZ006885770-811 at 800).

104. No discussion of the Jenapharm study was included in the final White Paper that Bayer submitted to the FDA on August 17, 2004. (BHCPYAZ011701241-44, BHCPYAZ011701237-39, BHCPYAZ011715027-29, BHCPYAZ011715030-76, Schellschmidt-98).

105. In my opinion, Bayer had a duty to include the results and analysis of the Jenapharm study in its White Paper presentation to the FDA in 2004.

106. Separate and apart from the Jenapharm study and Bayer’s White Paper, Bayer’s Medical Director of Clinical Development, Dr. Carole Sampson-Landers, wrote to Bayer colleagues on September 15, 2003, “As a follow-up to the ISS [Integrated Summary of Safety] meeting today, I obtained a copy of a publication [ACOG Clinical Review, July/August 1999] which gives the risk of VTE in low-dose OC users as 16-30 cases per 100,000 woman-years.

This appears to be lower than we cite in the ISS [6.6 per 10,000 woman-years] and therefore, I do not believe we should use it as a reference.” (BHCPYAZ014190303-304 at 304, Lauber-Huber-15). The document appears to indicate that Bayer’s Dr. Sampson-Landers did not want to highlight that there was a lower than known published historical rate with low dose contraceptives compared to what was being detected with Bayer’s product. The 10/16/2003 ISS submitted by Bayer, in section 8.2.10.8 titled, Venous and arterial thromboembolic events, states that in clinical studies “of Yasmin 30 and Yasmin 20 (both regimens), the calculated VTE/ATE incidence per 10,000 woman-years in 6.6/0.0....This incidence of 6.6/0.0 per 10,000 woman-years is in accordance with the incidence rate observed in an on-going European active surveillance study....” The ACOG Clinical Review was not referenced in this section. (BHCPYAZ000377124-000382670 at 377191.)

G. Bayer Failed to Disclose VTE Risk Information to FDA, Physicians and the Public in 2008

107. No later than April 4, 2008, Bayer received a data file that contained a study in the form of an unpublished manuscript titled, “Hormonal contraception and risk of venous thromboembolism [VTE]: Dose reduction matters,” authored by Øjvind Lidegaard, et al. (hereinafter “Lidegaard study”). (BSPYAZ002212629-2642 at 630).

108. The Lidegaard draft study dated 1.3.2008 concluded that use of oral contraceptives “with desogestrel, gestodene or drospirenone implied a higher risk of VTE than OC with levonorgestrel.” (BSPYAZ002212629-642 at 630-631).

109. Bayer employees shared the Lidegaard study results within the company and to external advisors. (BSPYAZ020414480-484 at 480-481; BSPYAZ002212629-642 at 629 and 630; BCHPYAZ002541413-414, Schellschmidt-108; BSPYAZ002213457-460).

110. Bayer employees knew in April 2008 that Dr. Lidegaard planned to present his data, and did so at a conference of the European Society for Contraception (ESC) in Prague, on May 2, 2008. (BSPYAZ020414480-484 at 481; BSPYAZ001971974, Prinz-9).

111. Bayer did not inform the FDA or healthcare professionals in the United States of the Lidegaard study until August 14, 2009, when the results were published and publicly released in the British Medical Journal. Ilka Schellschmidt, Bayer's Head of Global Medical Affairs, Women's Healthcare, acknowledged in the affirmative when asked to confirm that the data was received from Dr. Lidegaard in April 2008, and the company made a decision not to provide that to the FDA until it was published in 2009. (Schellschmidt, Deposition Transcript, June 15, 2011, at 360:10-18). Dr. Schellschmidt acknowledged ("The numbers are the same, that's correct") that the relative risk and confidence interval for oral contraceptives containing drospirenone compared to those containing levonorgestrel in Lidegaard's April 2008 draft manuscript were identical to the numbers in the article published in August 2009 (RR=1.64, 95% CI, 1.27 to 2.10). (Schellschmidt, Deposition Transcript, June 15, 2011 at 362:5-363:2; BSPYAZ002212630-642 at 631, Schellschmidt-4; BSPYAZ001080828-835 at 828, Schellschmidt-69).

H. Bayer Failed to Disclose VTE Risk Information to FDA, Physicians and the Public in 2010

112. In about January 2010, Bayer employees received data tables of an analysis by Dr. Susan Jick that revealed an increased odds ratio for Yasmin compared to levonorgestrel containing oral contraceptives (hereinafter "Jick U.S. study"). (Wallander, Deposition Transcript, May 9, 2011, at 111:13-15, 112:3-113:11, May 10, 2011, at 278:14-282:9; BSPYAZ013688769-770 at 774-779, Wallander-14).

113. On March 19, 2010, Dr. Jick wrote in an email to Bayer Employee Mari Ann Wallander, "...I do think we have useful results to present to the world." (BSPYAZ013726389-390 at 390).

114. Between March 24 and April 7, 2010, Bayer submitted a new drug supplemental application regarding warnings about the use of Yasmin and YAZ from the Lidegaard study and a 2009 Dutch study. (BSPYAZ008654327-330, PL-617; BSPYAZ008642667-670, PL-619; BSPYAZ008635700-702, PL- 621; BSPYAZ008654357-361, PL-622; BHCPYAZ011786489-504, PL-627; FDA Supplemental Approval Letters, Apr. 7, 2010, BHCPYAZ013675226-265 and BHCPYAZ025889979-90026).

115. To the best of my knowledge, at no time during those submissions with the FDA did Bayer reveal to the FDA the results or methodology of the Jick U.S. study. It appears that the first time Bayer told the FDA that Bayer was in possession of draft manuscripts that included Jick's data was sometime after Jick's appearance on a Canadian Television program in January, 2011. (Plouffe, Deposition Transcript, March 9, 2011, at 70:16-74:6).

116. Jick's U.S. Study was published in the British Medical Journal in April, 2011. Dr. Wallander acknowledged that the odds ratio and confidence interval comparing levonorgestrel versus drospirenone provided to her by Dr. Jick in January 2010 were identical to the numbers in the published article in April 2011 (OR=2.4, 95% CI 1.7 to 3.4). (Wallander, Deposition Transcript, May 12, 2011, at 833:3-834:14).

117. FDA regulations require that when submitting a supplemental application that "All procedures and actions that apply to an application under 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change." (21 CFR 314.71 (b)). 21 CFR 314.50 (d) (5) (iv) requires that a company submit a

“description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product...derived from clinical investigations...”

118. In my opinion, Bayer should have submitted to the Food and Drug Administration the data that it had about the Jick U.S. study as part of its supplemental new drug application no later than April, 2010.

I. Importance Of Timely Disclosure Of The Lidegaard And Jick Study

119. The issue of increased risk of oral contraceptives with differing progesterone components has been the subject of debate and controversy in the medical and regulatory arenas.

120. There has been significant interest on the part of both European and US regulatory authorities in assuring a thorough assessment of the risk of varying combination oral contraceptives (COCs).

121. All studies to date assessing the risk associated with varying contraceptives have strengths and limitations.

122. In light of the fact that there is ongoing controversy and debate, a company has the duty both to FDA and healthcare professionals to assure that all data that can shed light on important safety issues are shared transparently with the FDA and healthcare professionals in a timely fashion.

123. Bayer’s duty to disclose data in a timely fashion to FDA was further heightened because Bayer knew that FDA had VTE risk as a focus and highest priority (“There [sic] focus or highest priority now appears to be VTE”) (BHCPYAZ001320547-550 at 547, PL-584) and that the FDA had repeatedly expressed concern about VTE risk. (*See supra*).

124. Drug companies’ critiques of the data do not obviate the duty of the company to share the data with the FDA and health care professionals in a timely fashion. That allows the FDA and healthcare professional to independently assess the significance of the findings.

125. The fact that data has not been published does not obviate the need for the data to be disclosed when it relates to safety issues about a drug. Bayer shared unpublished interim data from the EURAS and Ingenix studies with the FDA.

126. In my opinion, Bayer failed to disclose to FDA and healthcare professionals in a timely fashion data from the Lidegaard and Jick U.S. study.

V. BAYER VIEWED THE REGULATORY ENVIRONMENT REGARDING YASMIN AND YAZ' SAFETY AS A THREAT

127. In a November 14, 2005 Global Brand Marketing Plan, Bayer listed under the heading “Threats,” “Safety discussion (VTE, hyperkalemia).” (BSPYAZ004306340-419 at 346; Lezzaiq-16).

128. In a March 31, 2008 Global Brand Marketing Plan, Bayer’s Strategic Product SWOT [“Strengths, Weaknesses, Opportunities and Threats”] Analysis for the “Yasmin Family,” under a heading labeled “Threats,” listed “Conservative regulatory environment regarding safety.” (BHCPYAZ006141556-627 at 565, PL-195).

129. Bayer stated in the document that a risk was “Emergence of further studies on the safety of drospirenone and ongoing discussion about its safety profile.” (BHCPYAZ006141556-627 at 619; PL-195).

130. Bayer, in the same document, in a table headed “Marketing Risks, Upsides and Contingencies – How to offset risk,” listed “Gain key opinion leaders endorsement;” “Build consumer awareness of PMS/severe PMS and build up patient advocacy groups;” “Leverage data from EURAS and INGENIX study and actively communicate the results;” “Continue to build on the positive risk/benefit profile of ‘drsp’.” (BHCPYAZ006141556-627 at 619, PL-195).

131. On September 4, 2006, an email from Bayer Dr. Kerstin Uhl-Hocgraeber, discussed the safety risks that could arise from uncontrolled observational trials, and stated the

team “was asked to come up with a proposal for a new study design in order to minimize the risk.” (BHCPYAZ007631145-147 at 147, Prinz-15). As noted, *supra*, on August 7, 2003 Bayer assembled a group of outside consultants and company employees to discuss VTE and FDA concerns at an expert meeting [hereinafter “expert meeting”]. Minutes of the meeting suggested that Bayer prepare “a review of the cases that have been reported with a focus on risk factors,” and “also include cases reported with other OCs.” (BHCPYAZ014467337-339 at 338, Foegh-35). Bayer knew from consultant Greg Burkhardt that “FDA triggers for stating increase in risks” include “Reporting rates 2 to 5 fold higher than similar products.” (BHCPYAZ014467337-339 at 338, Foegh-35). At the meeting, an outline for a write-up to the FDA was stated. The outline suggested a review of the postmarketing data for Yasmin which was to include the reporting rates. The “Conclusion” of the Write-up “should be no signal, but you are watching closely.” (BHCPYAZ014467337-339 at 339, Foegh-35). That conclusion was arrived at before Bayer did the recommended analyses. Thus, it appears that the conclusion was predetermined and aimed at “defending” the drug, rather than the result of an objective review.

132. On August 12, 2004, Bayer’s Dr. Juergen Dinger wrote to Bayer’s Jeff Frick in an email. In discussing a draft White Paper, to be sent to the FDA (see *supra*), Dr. Dinger wrote: “The 12 month’s comparison vs. Evra will be clearly more favorable than the 18 month’s comparison (based on incomplete Evra data). I will distribute the new reporting rates after having clarified some details...” (BHCPYAZ016167167-182 at 167, Foegh-21). Prior to the August 12, 2004 email, Bayer had first carried out an 18 month comparison, and then a 12 month comparison, but ended up selecting the 12 month data for inclusion in what the company presented to the FDA in its White Paper. (BHCPYAZ015693328-354 at 340Schellschmidt-96; BHCPYAZ011701241-244 BHCPYAZ011701237-239, BHCPYAZ011715027-029,

BHCPYAZ011715030-5076 at 5044, Schellschmidt-98; *See also*, BHCPYAZ015510844, Foegh-17 [Email from Dr. Juergen Dinger to Harri Helajarvi, dated July 1, 2004 Re: YAZ – FDA Letter re: Tcon, “Dear Harri, You should analyse the OCs that have the highest percentage of fatal outcomes (according to your graph). Best regards Juergen.”]).

133. In my opinion, Bayer’s plan to “offset risk” by “leverag[ing] the safety data in the EURAS and Ingenix studies” and “continu[ing] to build the positive risk benefit profile of drsp study” represents a bias favoring Yasmin and YAZ, rather than presenting full and accurate information about VTE risk to FDA and healthcare professionals.

VI. BAYER’S MARKETING PLAN INCLUDED AND RELIED UPON PUBLICATIONS OF THE EURAS, INAS, AND INGENIX STUDIES WHICH WERE NOT INDEPENDENT

134. Bayer’s “YASMIN Family 2007-2008 Global Brand Marketing Plan” included a “Publication Plan” for scientific/medical publications. This Publication Plan included EURAS and INAS studies that were carried out and authored by Juergen Dinger and colleagues at a company called ZEG. (BHCPYAZ012207797-867 at 857-859, Lezzaiq-20).

135. Prior to working at ZEG, Dr. Juergen Dinger was an employee at Bayer from 1989 to 2004. (Dinger CV, Schellschmidt-94A).

136. Dinger ““worked on Yasmin at Bayer for many years and then left and joined ZEG.” (Velez, Deposition Transcript, March 31, 2011, at 69:5-8). During the time he was at Bayer, Dinger was working on and monitoring the EURAS study, and attended meetings where the EURAS study was reported. (Velez, Deposition Transcript, March 31, 2011, at 369:9-14).

137. Dinger presented or discussed EURAS data at an “Expert Meeting” on August 7, 2003 where it appears that a predetermined conclusion was reached. (*See supra*). (BHCPYAZ014467337-339 at 339, Foegh-35).

138. In July 2004, Bayer employee Dinger, along with colleagues Dr. Marie Foegh, and Jeff Frick edited, and Dinger co-authored a paper that included an Interim analysis of the salient results of the EURAS study. (BHCPYAZ015529754-806 at 754-756 and 772-774).

139. Dinger presented and explained EURAS data at an FDA meeting in October, 2004 as an employee of Bayer. (BHCPYAZ000100081-108, PL-672).

140. Dinger left Bayer and went to work at ZEG in 2005. (Dinger CV, Schellschmidt-94A).

141. Bayer's "Publication Plan" included seven EURAS published or to be published articles, and 15 abstract and poster presentations on EURAS and INAS, where Dinger was lead author on six of the seven papers and 11 of the 15 posters and abstracts, and co-author on the remainder. (BHCPYAZ012207797-867 at 857-859, Lezzaiq-20).

142. Bayer's publication plan that was part of its "Global Brand Marketing Plan" also involved work by Dr. J. Seeger on Ingenix studies. (BHCPYAZ012207797-867 at 857-859, Lezzaiq-20).

143. Bayer's publication plan included three papers that were published or to be published on the Ingenix study. (BHCPYAZ012207797-867 at 857, Lezzaiq-20).

144. A goal of Bayer was to "leverage" the safety data in the EURAS and Ingenix studies. (BHCPYAZ012207797-867 at 853; BHCPYAZ 006141556-627 at 619, Lezzaiq-20).

145. In a Yasmin Family 2008/2009 Global Brand Marketing document, in a table headed "Marketing Risks, Upsides and Contingencies – How to offset risk" arising from further safety studies, Bayer listed "Leverage data from EURAS and INGENIX study and actively communicate the results;" "Continue to build on the positive risk/benefit profile of 'drsp';" "Successfully conduct INAS Study for YAZ." (BHCPYAZ006141556-627 at 619, PL-195).

146. In an August 12, 2003 email from Juergen Dinger to Bayer's Dr. Marie Foegh, Dinger wrote: "Thank you for your excellent minutes. . . However, there is one important issue: Garth McBride informed me that Prof. Stock insists that the global head of risk management and the chairperson of the steering committee are in the driver seat of the Ingenix Study. I am sure that Prof. Stock did not want to exclude the BU. Therefore, I propose that MF, JD, and GMcB are responsible." Thus it appears that the Ingenix study was not independent of Bayer as Bayer employees were "in the driver seat" of the Ingenix study. (BHCPYAZ019107640-648 at 640, Atkinson-23).

147. A November 14, 2005, Global Brand Marketing Plan for Yasmin, LCM stated under the heading "EURAS,"

The interim results as of 17 Jan 2005 demonstrate no increased risk of thrombotic events for Yasmin® compared to other OCs. The data were included in the European 5 year renewal response, the Angeliq complete response to the FDA and the YAZ® OC/PMDD Safety Update. The next interim report, consisting of main tables, is scheduled for August 2005 (database lock July 2005). The final report will be available by mid 2006. (BSPYAZ004306340-419 at 368, Lezzaiq-16; BSPYAZ001540805-884 at 833, Lezziaq-18).

148. Under the heading INGENIX it stated: "The interim report covering the 2Q is available, giving no raise [sic] to concern. On 24 May 2005 an internal meeting to discuss the structure of the final Ingenix report, scheduled for Jan 2006, is scheduled. The next Advisory Board is scheduled for June 2005." (BSPYAZ004306340-419 at 368; Lezzaiq-16; BSPYAZ001540805-884 at 833, Lezziaq-18).

149. In a June 28, 2006 email, Dr. Juergen Dinger wrote to Bayer employee Margret Krikowski and included a budget plan for the EURAS, LASS and INAS studies, and others, and named the file: "Defence Studies budget 2006-20 . . ." (BSPYAZ002337618-626 at 618, PL-568).

150. No later than April 4, 2008, as noted above, Bayer received the draft Lidegaard manuscript, which reported a statistically significant increased risk of VTEs with drospirenone (DRSP) – containing OCs, compared to levonorgestrel (LNG) –containing OCs. (BSPYAZ002212630-642, Schellschmidt-4; and BSPYAZ002212629).

151. Bayer knew, and a EURAS article stated that the primary cardiovascular outcome that was of interest was the hazard ratio for VTEs between DRSP-containing OCs and LNG-containing OCs. (Schellschmidt, Deposition Transcript, June 14, 2011, at 928:6-12; and PL-112, p.345, 351).

152. The Ingenix study, as approved by Bayer, did not have a comparison of VTE incidence between DRSP-containing OCs and LNG-containing OCs – rather the study compared Yasmin to a combined group of “other OCs.” In fact, the Ingenix article published in 2007 compared VTE incidence among Yasmin users to VTE incidence among users of “other OCs” without specifying the rate according to particular progestins. (Schellschmidt, Deposition Transcript, June 14, 2011, at 939:16-949:2).

153. No later than April 9, 2008, Bayer contacted Ingenix to inquire as to the possibility of reanalyzing the data to compare Yasmin VTE incidence rates to other OCs according to their specific progestin including a direct to comparison to LNG-containing OCs. (Schellschmidt, Deposition Transcript, June 14, 2011, at 947:4-950:13; and Ingenix0000120-23 at 23, Schellschmidt-16).

154. On May 1, 2008, Ingenix responded to Bayer stating that they could conduct a reanalysis of the original study data for approximately \$68,000. (Schellschmidt, Deposition Transcript, June 14, 2011, at 952:3-953:2; and BSPYAZ008613694-697 at 697, Schellschmidt-15).

155. On June 20, 2008, Ingenix employee, Jeanne Loughlin, stated that Bayer had decided not to fund the proposal that would have compared Yasmin VTE incidence directly to LNG-containing OCs. (Schellschmidt, Deposition Transcript, June 14, 2011, at 957:2-12; and Ingenix0000341, Schellschmidt-17).

156. A similar set of circumstances occurred in 2009-10, following the publication of the Lidegaard study in the British Medical Journal in August 2009, published contemporaneously with a Dutch study, authored by A. van Hylckama Vlieg, that also found increased risk of VTE with DRSP versus LNG-containing OCs. (Schellschmidt-115 and 114.)

157. In November 2009, Bayer's Richard Lynen wrote to Ingenix's John Seeger, asking whether the Ingenix data could be reanalyzed to compare DRSP incidence of VTE according to the specific progestin in other OCs, including a direct comparison to LNG. (Schellschmidt, Deposition Transcript, June 14, 2011, at 960:12-961:8).

158. Ingenix's Seeger responded, stating that Bayer had previously requested such an analysis and that such an analysis could be done. (Schellschmidt, Deposition Transcript, June 14, 2011, at 961:19-962:5; BHCPYAZ016955184-185 at 184, Schellschmidt-18).

159. On March 31, 2010, Bayer contracted with Ingenix to provide a frequency table with the percentage of subjects who used several OCs in the "Other OC" category but without the outcome data that would have shown the number of VTEs in each progestin user population and from which the incidence rates could have been calculated and compared. (Schellschmidt, Deposition Transcript, June 14, 2011, at 968:9-969:14; Ingenix0000236-237, Schellschmidt-20).

160. In June 2010, Ingenix's "final report" included a table of the frequency analysis of use of each of several "Other OCs." The table showed that the LNG-containing OCs

was used by only about 18 percent of the Ingenix population. (BHCPYAZ016438004-008 at 008, Schellschmidt-21).

161. Bayer's Richard Lynen, stated that the percentage "for LNG is low" and "would perhaps not be sufficiently robust." (Schellschmidt, Deposition Transcript, June 14, 2011, at 984:11-985:13; and BHCPYAZ016478265-267 at 266, Schellschmidt-24).

162. The June 2010 "final report" included a statement that the "Other OCs" group included a mixture of different generations of OCs. Desogestrel and norgestimate made up about 47 percent of the "Other OCs" groups and were described as "third generation OCs", (BHCPYAZ016438004-008 at 008, Schellschmidt-21 and Schellschmidt, Deposition Transcript, June 14, 2011, at 972:23-974:14). On July 23, 2010, Ingenix's John Seeger wrote to Bayer Richard Lynen "attached please find the Yasmin frequency report' which contained the frequency data but reference to "generations" was removed. Bayer's Lynen then sent "the amended report" to his colleagues. (BHCPYAZ 010593910-14 at 10 and 14, Schellschmidt-22 and Schellschmidt, Deposition Transcript, June 14, 2011, at 975:15-977:4).

163. In my opinion, Ingenix's work on DRSP-containing OCs was not independent of Bayer, as Bayer made the decision not to compare DRSP-OCs to LNG-OCs in the Ingenix study, despite the recognition in the EURAS study that such comparison was the primary cardiovascular outcome of interest.

164. On October 20, 2009, Bayer submitted to FDA, a Clinical Expert Statement dated October 16, 2009 that stated, "To ensure full independence in the conduct of the study, Bayer Schering provided funding to two independent third parties, who enjoy wide acceptance and recognition as centers of excellence in the field. For EURAS, this was the ZEG (Center for Epidemiology and Health Research, Berlin, Germany). For the USA, this was the Ingenix (i3

Drug Safety, Ingenix, Waltham, Massachusetts, USA) group...A number of publications in the scientific literature has also resulted from both studies.” (BHCPYAZ006643417-448 at 429, PL-435)

165. An April 22, 2011 Bayer press release stated that: “Bayer has sponsored several independently-conducted, large-scale, prospective, observational safety studies on the use of COCs including the EURAS study and its follow up study, i.e. the LASS study, as well as the Ingenix study and the INAS study.” (PL-714).

166. In March 2000, Interpublic Group of Companies (IPG) reported 22% ownership of ZEG, which was acquired through a merger with NFO Worldwide. (IPG S-4, 3/1/00 at E-8). IPG’s website describes itself as “one of the world’s premier advertising and marketing services companies” (<http://www.interpublic.com/interpublicgroupinfo>). IPG reported 55% ownership interest in ZEG in 2001, 2002 and 2003. (April 1, 2002 IPG 10-K Filing, Exhibit 21, p.16; March 28, 2003 IPG 10-K Filing, Exhibit 21, p.23; March 15, 2004 IPG 10-K Filing, Exhibit 21, p. 18). On July 10, 2003, IPG completed its sale of NFO Worldwide to Taylor Nelson Sofres (TNS), which thereby acquired the 55% ownership of ZEG. (March 31, 2003 IPG Form 10-Q Filing). TNS is a “custom market research company,” according to its website (<http://www.tnsglobal.com/>). On October 29, 2008, TNS was acquired by WPP, PLC, which thereby acquired the 55% ownership of ZEG. (April 2009 WPP PLC Form 6-K Filing). The 55% interest in ZEG is currently held by WPP subsidiary, Kantar Health, which in turn is part of the Kantar Group, which is part of a market research consultancy of WPP that also includes TNS. (July 5, 2011 Hoover’s Company Records, TNS Group Holdings Limited, p.2). According to the TNS-WPP-Kantar-website, WPP “is the world’s largest communications services group. Through its operating companies, the Group provides a comprehensive range of

advertising and marketing services including advertising; media investment management; consumer insight; public relations and public affairs; branding and identity; healthcare communications; direct, digital, promotion and relationship marketing and specialist communications.” (<http://www.tnsglobal.com/tns/tns-wpp-kantar/>). WPP’s subsidiaries have included Burson-Marsteller, Hill & Knowlton, Ogilvy Group and Young & Rubicam. Currently, Kantar Health owns 55% of ZEG; Juergen Dinger owns 12% of the shares, and Lothar Heinemann owns 33%. (Hoppenstedt Firmenprofile, 3/21/11).

167. The EURAS article was published in the journal *Contraception*. The editor-in-chief of the journal *Contraception* has been Dr. Daniel Mishell, a paid consultant to Bayer (see *infra*).

168. Bayer has been responsible for a substantial portion of ZEG’s revenue. (See e.g., INAS and EURAS budgets, BSPYAZ010645915-935 at 934-935, Schellschmidt-02; and BHCPYAZ000672720-728 at 728, Schellschmidt-05).

169. In my opinion, the EURAS, INAS and INGENIX studies were not independent of Bayer’s “marketing” efforts.

VII. BAYER PROMOTED YASMIN AND YAZ FOR OFF-LABEL USES, IN VIOLATION OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT

A. Summary of Opinions Regarding Off-label Promotion

170. When FDA approves a New Drug Application, the approval applies to a particular use for an indication, dosage form, dose regimen, population or other use parameter mentioned in the approved labeling. These refer to the uses for which FDA has considered the information submitted by the Applicant with regard to the safety and efficacy of the drug.

171. A manufacturer may not promote or market a drug for uses or indications that have not been approved, and such actions are described as “off-label promotion.” (See Appendix A).

172. Bayer studied Yasmin for use, among other conditions, in treatment of women with PMS but the pivotal trial (BHCPYAZ013308369-397 at 389, 394) did not demonstrate efficacy in PMS. (BSPYAZ006778075-077 at 075; LP-268). Furthermore, FDA specifically told Bayer that the “PMS claim is not acceptable at this time ...” (BSPYAZ016716263-273 at 267).

173. Yasmin and YAZ were both approved for the specific indication of oral contraception. Yasmin was approved for that indication in May 2001, and it has not received approval for any other indications since then. (BHCPYAZ001145341-382, PL-625). YAZ was approved for oral contraception in March 2006; it received subsequent approval for the condition known as “Premenstrual Dysphoric Disorder” (PMDD) in October 2006. (BHCPYAZ6986879-6922, PL-626; BHCPYAZ002094187-230, Atkinson-21). Bayer knew that PMS was different than PMDD. Neither drug was ever approved for “Premenstrual Syndrome” (PMS), “severe PMS” or for the “relief of the physical and emotional symptoms associated with the menstrual cycle.” YAZ was also approved for “moderate acne vulgaris” in January 2007, but it was neither approved for “acne,” nor for general benefit to skin condition. (BHCPYAZ002238854-909).

174. Despite the specific and limited indications for which Yasmin and YAZ were approved, Bayer engaged in a planned, systematic and extensive campaign of off-label promotion of the products for PMS, “severe PMS,” relief of the physical and emotional symptoms associated with the menstrual cycle, acne, and benefits to the skin. Bayer’s actions

violated FDA regulations and state law duties, and resulted in an FDA “Warning Letter” as to certain specific advertisements for YAZ in 2008. (BHCPYAZ007990073-080, PL-204).

175. Bayer’s off-label promotion campaign included marketing to physicians, direct-to-consumer (DTC) ads in print and televised media, Internet ads, use of third party physicians who were paid by Bayer, and a global publication plan that involved drafting articles for physicians to author in medical journals.

176. Bayer’s documents indicate that the purpose of the off-label promotion of Yasmin and YAZ was to increase market share and profit to the company. Bayer’s documents show that the company knew there was a small market for the approved indications of PMDD and moderate acne vulgaris, and a much larger market for PMS and acne/clear skin. The documents reveal a corporate strategy to sell to the larger market despite the approval for the smaller-market uses and indications.

177. Off-label promotion of Yasmin and YAZ unnecessarily and inappropriately exposed patients to risks of serious injury or death due to venous thrombotic events.

B. Off-Label Promotion Is Illegal And In Violation Of The Federal Food, Drug and Cosmetic Act

178. The marketing and promotion of a drug for an intended use that has not been approved by the FDA is considered “off-label” promotion.

179. The off-label promotion of an approved drug for an unapproved use is a violation of the Federal Food Drug and Cosmetic Act.

180. In Appendix A, I discuss the legal, regulatory and policy basis for why off-label promotion is illegal under the Federal Food Drug and Cosmetic Act in the context of FDA’s mission, standards for approval, scientific standards to establish safety and effectiveness, how drugs are regulated based on their intended conditions of use, the statutory and regulatory

misbranding provisions of the Act, and the fact that pharmaceutical manufacturers knew that off-label promotion was and remains illegal.

181. Simply put, drugs may not be marketed or promoted for indications or conditions that are not included in the approved labeling. Off-label promotion has serious impacts on public health, as described *infra*.

182. Bayer understood that any advertising and promotion had to “Be consistent with labeling (prescribing information).” (BHCPYAZ006135260-344 at 272, LP-100). Bayer knew that one of the most common violations in marketing and promotions included “Broadening of Indication.” (BHCPYAZ006135260-344 at 273, LP-100; PhRMA Guiding Principles Direct to Consumer Advertisements About Prescription Medicines, November 2005, PL-380).

C. Yasmin And YAZ Were Approved By The FDA As Oral Contraceptives. YAZ Was Also Approved For Premenstrual Dysphoric Disorder. Neither Drug Was Approved For Premenstrual Syndrome (PMS)

183. Yasmin and YAZ contain drospirenone (DRSP) and ethinyl estradiol.

184. Drospirenone is a 17-a spironolactone derivative with progestational, anti-mineralocorticoid, and anti-androgenic properties. The active estrogen moiety in these products is ethinyl estradiol, which is complexed with another agent to protect against degradation.

185. YAZ contains drospirenone 3 mg/EE 0.02 mg tablets, which is less EE than in the Yasmin tablets (DRSP 3 mg/EE 0.03 mg tablets).

186. Yasmin and YAZ are the only contraceptive products marketed in the U.S. that contain the progestin DRSP. (March 16, 2006, FDA Medical Review, 21-676, p. 2).

187. On August 4, 1997, Bayer submitted IND 53,905 serial No. 025 for Yasmin for treatment of premenstrual syndrome (“PMS”). (BHCPYAZ013310473-474).

188. On May 14, 1999, Bayer submitted an NDA 21-098 for the prevention of pregnancy which was approved which was developed from IND 51,693. (BHCPYAZ013611618-620). An approvable letter was issued on March 17, 2000 and again on July 10, 2000. (BHCPYAZ001250106-0126 at 111-112, Fiedler-38).

189. On June 14, 1999, FDA told Bayer that the “PMS claim is not acceptable at this time....” (BSPYAZ016716263-273 at 267).

190. On Nov. 8, 1999, FDA told Bayer that PMDD is a more viable indication than PMS because a November 4th, 1999 advisory committee concluded “PMS is still not clearly defined.” (BHCPYAZ000086759-775 at 759).

191. Yasmin was approved in May 2001 for the prevention of pregnancy in women who elect to use an oral contraceptive. Yasmin was not approved for any other indication including PMS, PMDD, acne, or the physical and emotional symptoms of the menstrual cycle. (BHCPYAZ001145341-382, PL-625).

192. On October 16, 2003, Bayer filed NDA 21-676 for YAZ for the prevention of pregnancy in women of child bearing years. (BHCPYAZ013499927-945).

193. YAZ was approved for the prevention of pregnancy in women who elect to use an oral contraceptive in March 2006. (BHCPYAZ6986879-6922, PL-626).

194. YAZ was also approved in October, 2006 for the “treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.” (BHCPYAZ002094187-230 at 193, Atkinson-21). The efficacy of Yasmin for the treatment of PMDD has been questioned by European regulatory authorities. (Marr, Exhibit-Y, no Bates numbers).

195. According to the INDICATIONS AND USAGE section from the FDA-approved product labeling (PI): “YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS).” (BHCPYAZ002094187-230 at 193, Atkinson-21).

196. Appendix B to this Report lists the diagnostic criteria for PMDD and PMS.

197. YAZ was also approved in 2007 for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy, and have achieved menarche. According to the approved labeling, YAZ should be used for the treatment of moderate acne only if the patient desires an oral contraceptive for birth control. YAZ was not approved for use in acne, only moderate acne vulgaris. (BHCPSR5380362-0378 at 363; PL-629).

198. Additionally, the BRIEF SUMMARY PATIENT PACKAGE INSERT and DETAILED PATIENT PACKAGE INSERT state that “YAZ has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious cluster of symptoms occurring before menstruation.” The inserts also state, “If you or your healthcare provider believes you have PMS, you should only take YAZ if you want to prevent pregnancy; and not for the treatment of PMS.” (BHCPSR5380362-0378 at 371; PL-629).

199. The approved labeling of Yasmin and YAZ cite the following as non-contraceptive health benefits:

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron-deficiency anemia

- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies
- Effects from long-term use
- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer.

200. The brief summary patent package insert cites the following:

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

201. None of the additional health benefits listed in the above-described section of the approved labeling include changes in emotional symptoms including moodiness, anxiety, depression, irritability, weight loss, bloating, nor any of the symptoms of PMDD which include,

in part: markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being “keyed up” or “on the edge;” marked affective liability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating; nor PMS which includes, in part: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal, breast tenderness, abdominal bloating, headache, and swelling of extremities. (See Appendix B).

202. Only YAZ was studied and shown to be effective for PMDD and moderate acne vulgaris in defined populations. Any promotion of YAZ or Yasmin for the emotional symptoms associated with the menstrual cycle or PMS or “acne” would be off-label and prohibited.

D. Bayer Carried Out A Systematic And Extensive Campaign To Market Yasmin And YAZ For Treatment Of “PMS” And “Acne” Despite Knowledge That These Products Were Not Approved Or Indicated For Those Conditions.

a. Off-Label Promotion of Yasmin

203. As described in this section and further sections below, Bayer’s documents show a plan to market Yasmin for PMS and acne, which constituted "off-label" promotion.

204. Bayer’s Vice President of Marketing for Female Health, Donald Atkinson, on January 17, 2003, had explained according to minutes of a SBU Gynecology & Andrology Management Board Meeting that, “according to Yasmin’s ATU Tracking Survey, relief of PMS

symptoms is as important as cycle control for physicians' selection of COC brands. Their data substantiated that treatment of PMS was given as the major reason why physicians in the USA were switching patients to Yasmin. He stated that Berlex has created customer expectations in this indication..." [Emphasis added] (BHCPYAZ018952716-722 at 720, Atkinson-14).

205. A Bayer document dated March 3-5, 2003, under the section "Branding: Dominic & Jeff," stated, "Right message includes brand reinforcement, delivery of 'core message' on every call. Lot's [sic] of examples, handouts to read. Key to success in 2003 is the quality of our message...it must be consistent to 'brand' a permanent image into doctor and patients minds." Under a subsection labeled "Yasmin," the document stated in a bulleted list: "Say goodbye to PMS, Birth Control with a bonus, Dual Properties, unlimited benefits, Beyond birth control, A little something for everyone...Yasmin for your new start patients." [Emphasis added] (BHCPYAZ021527149-153 at 152).

206. A November 1, 2004 e-mail from Bayer's Heike Prinz to Philip Smits stated, "Our positioning and the messages for YAZ still need some 'finetuning' which will be done over the next couple of weeks based on the findings of our market research activities. We will also need to convince the gynecologists that YAZ not only works for physical but also for emotional symptoms of PMS/PMDD. The fact that gynies rather use the term 'severe PMS' instead of PMDD is a real opportunity as it is our marketing strategy to target the much broader segment of premenstrual symptoms (not just PMDD)." [Emphasis added] (BSPYAZ005069319-320 at 319, LP-39).

207. A PowerPoint presentation on strategic marketing by S. Karrer on or about April 1, 2005 titled "The Yasmin Family – Lessons Learned: Lessons and Opportunities," contained a slide with the heading "Opportunities: To foster drsp penetration in US" and

included these items listed as bullets: “Increase physician awareness/acceptance as well as more aggressive consumer related activity (DTC); Extensive use of drsp family branding strategies as explained above; Off-label promotion of added benefits as PMS, well-being and extended regimen; Pro-active safety surveillance: Safeguard drsp family against negative publicity (EURAS/Ingenix and subsequent studies).” An earlier slide stated: “The US HC market represents almost 60% of the world market with an expected increase of 4% until 2010. It is therefore critical for our world-wide drsp sales and objectives.” [Emphasis added]. (BHCPYAZ012344260-290 at 271, 269, LP-89).

208. A Bayer 2005 Brand Plan stated that the “Key Selling Messages” for Yasmin through the Professional Journal Article Channel were “PMS data” and “Acne data.” (BHCPYAZ009460069-0213 at 136, PL-423).

209. On September 15, 2005 Bayer’s Dr. Wolfgang Eder wrote to Bayer’s Heike Prinz re: Yasmin LCM Global Brand Marketing Plan—Draft that “one of the lessons learned in Yasmin was that none of the benefits (acne weight and premenstrual symptoms) is in the label. It is still possible to convey the benefits through other means.” [Emphasis added] (BHCPYAZ017765874, Lezzaiq-34).

210. Bayer decided that Yasmin’s lifecycle management “uniqueness” would “be rooted in the beneficial effects of drsp on physical and emotional symptoms associated with the menstrual cycle.” (BSPYAZ004306340-419 at 343, Lezzaiq-16; BSPYAZ001540805-884 at 808, Lezzaiq-18).

211. A Global Brand Marketing Plan Yasmin LCM, under “Opportunities,” stated “Become 1st choice for the target group of OC users who show symptoms consistent with severe

PMS/PMDD.” (BSPYAZ004306340-419 at 401, Lezzaiq-16; BSPYAZ001540805-884 at 866, Lezzaiq-18).

212. Bayer stated that the ability to communicate and profit from additional benefits despite a basic label (OC only) “made Yasmin® the No. 1 OC worldwide and represents an opportunity upon which we can capitalize with LCM [lifecycle management] of drsp.” [Emphasis added] (BSPYAZ004306340-419 at 344, Lezzaiq-16).

213. Bayer stated that, “Strong marketing efforts (esp. on PR & DTC) communicating additional benefits led to high acceptance of Yasmin. • despite basic labeling (OC only). (BHCPYAZ12207800-841 at 801).

214. In a 2005 Brand Plan for Yasmin, it was stated that the Key Selling Message through physician detailing was, “Chemistry Makes the difference OBGYNs — benefits of drsp.” (BHCPYAZ009460069-0213 at 136, PL-423). The benefits of DRSP were not indicated on Yasmin’s label.

215. The label discusses DRSP in the Description Section, Pharmacodynamics Section, Pharmacokinetics Section, Warnings Section, Precautions Section, Dosage and Administration Section, and the How Supplied Section with parallel references to the patient package insert sections. The references to DRSP relate to its chemistry and pharmacology and its potential adverse events and risks. (BHCPSR5380362-0378, PL-629).

216. In fact, rather than a offering a specific benefit, FDA required Bayer to state that in the warning section of both Yasmin and YAZ’s approved label that the drugs contain “3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone.” (BHCPSR5380362-378at 365, PL-629).

217. On July 10, 2003, in a letter to Bayer, FDA stated that the anti-M properties of Yasmin pose a risk rather than a benefit and any promotion of the antimineralocorticoid benefits would be misleading. Specifically, the FDA stated “Drospirenone has antimineralocorticoid properties, which means that it can work against the body's normal mechanism for regulating salt and water balance, a situation that can lead to hyperkalemia in high risk patients, resulting in potentially serious heart and health problems.” (BSPYAZ006287885-889 at 885, PL-212).

218. In 2003, television advertisements, and in 2004 and 2005 print advertisements in a professional journal, Bayer implied that Yasmin’s anti-mineralocorticoid properties provided benefits to the consumer by stating “Chemistry like no other” (along with an image of a couple dancing) (*Obstetrics & Gynecology*: Vol. 103, No. 2, February 2004; Vol. 103, No. 4, April 2004; Vol. 103, No. 103, No. 5, May 2004; Vol. 103, No. 6, June 2004; Vol. 104, No. 1, July 2004; Vol. 104, No. 2, August 2004; Vol. 104, No. 4, October 2004; Vol. 104, No. 6, December 2004; Vol. 105, No. 1, January 2005; Vol. 105, No. 2, February 2005; Vol. 105, No. 4, April 2005) and “The difference a little chemistry can make” (along with a voice-over that asks, “why settle?”). (“GoodBye Kiss” Television Ad, Plaintiff’s Exhibit 313).

219. One of the company’s corporate objectives was “support off-label promotion of Yasmin via publications, symposia.” (Lezzaiq-14, p.64, Bates number cut off).

220. In April 6, 2005 minutes of the Global Brand Team Meeting, the section titled “Lessons Learned” included “Promote off-label use in Yasmin in extended regimen in order to grow sales and bridge to YAZ extended.” (BHCPYAZ020211373-377 at 376, PL-196).

221. In a September 29, 2004 “Regulatory History of DRSP” on a slide labeled “YAZ extended regimen – Market Situation,” a Bayer employee stated, “Widespread off-label

use of extended cycles in EU and US for various conditions/bleeding disorders.”

(BHCPYAZ001231862-903 at 865).

222. From an email dated February 05, 2004, it appears that Bayer attempted to develop a strategy to attract doctors to their booth at an ACOG meeting to ask questions about Yasmin and where “off-label” questions would be handled by Bayer’s “medical education” section. (BHCPYAZ009128318-319 at 318, PL-12).

223. In addition, as documented below, Bayer: 1) used its sales force to promote Yasmin off-label (*See Section F*); 2) used third-party physicians to promote Yasmin off-label to the public (*See Section G*) and 3) sponsored non-independent CME activities for off-label promotion of Yasmin. (*See Section K*).

224. In my opinion, Bayer marketed Yasmin off-label for PMS and acne, which were not approved indications.

b. Off-Label Promotion of YAZ

225. The campaign of off-label promotion for PMS and skin benefits that began with Yasmin, continued and grew with YAZ, as part of the Life Cycle Management (LCM) and branding of the “Yasmin family.” This occurred even before YAZ was first marketed in the United States in April 2006 and thereafter, as shown in the documents referenced below and in subsequent sections.

226. A 2004 strategy document circulated by Leslie North, shows that Bayer knew that “the area of hormonal contraception” was a “highly saturated, highly competitive therapeutic area, which has substantial public health implications.” (BHCPYAZ009460069-0213 at 101, PL-423).

227. Bayer knew that “The launch of YAZ will have much of the same baggage as Yasmin, with a highly competitive, commodity-like market. YAZ will be launched initially with

only an indication for contraception, with the hope that sNDAs will be approved for the treatment of the symptoms of PMDD (in 2005) and acne (in 2006).” (BHCPYAZ009460069-0213 at 101, PL-423).

228. Bayer knew that the “promotion of Yasmin and YAZ” took the company into “uncharted territory, as it is highly unusual for a FHC company to actively promote two OCs, in the same patient population, for the same indication, with the same labeling, to the same target physicians.” (BHCPYAZ009460069-0213 at 101, PL-423).

229. Bayer also asked, “How do we overcome the perception that YAZ is just another 20–mcg pill or just a low dose Yasmin?” (BHCPYAZ009460069-0213 at 105, PL-423).

230. The company struggled with the question, “Once we get the indication for PMDD symptoms, how do we take advantage of an indication that affects only 3–5% of the US women?” (BHCPYAZ009460069-0213 at 105, PL-423).

231. Bayer decided in its new product, YAZ, to “build DRSP equity and differentiate from other progestins to achieve market share leadership.” (BHCPYAZ009460069-0213 at 118, PL-423).

232. The goal was to “Brand DRSP as differentiating factor.” (BHCPYAZ009460069-0213 at 118, PL-423).

233. Bayer’s strategy was to increase consumer awareness and build up patient advocacy for PMS/severe PMS even if YAZ did not get an approval for a PMDD indication. (BHCPYAZ006141556-627 at 619; PL-195).

234. Bayer decided to include in the plan the objective to “optimize DTC initiatives to drive consumer demand.” (BHCPYAZ009460069-0213 at 118, PL-423).

235. In a “FHC [Female Healthcare] Product PR [Public Relations] Overview” with the Issue listed as “PMDD Data Presentation” at ACOG May 8-11, 2005, under “Sales and Marketing Q & A’s” in response to a question “Will YAZ work for PMS too?,” the document stated, “While we have not yet studied YAZ among women with symptoms less severe than those who are classified as having PMDD, it is reasonable to expect that if YAZ can reduce symptoms among women with PMDD, it would help alleviate less severe, yet still often troublesome and debilitating, symptoms, called PMS.” (BHCPYAZ008428231-234 at 234).

236. A July 6, 2005 email from Bayer employee Jin Li Allen to Dan Atkinson, discussed a strategy to educate about PMDD and YAZ “as well as to lead them to the pms.com and yas-us.com web sites.” (BHCPYAZ008274975-976 at 976; LP-153).

237. As noted above, on September 15, 2005 Bayer’s Dr. Wolfgang Eder wrote to Bayer’s Heike Prinz re: Yasmin LCM Global Brand Marketing Plan—Draft that “One of the lessons learned in Yasmin was that none of the benefits (acne weight and premenstrual symptoms) is in the label. It is still possible to convey the benefits through other means.” (BHCPYAZ017765874, Lezzaiq-34 [Emphasis added]).

238. On October 8, 2005, RTC’s Kathy Conroy wrote in a memorandum to Bayer employees, stating, “Berlex has opted to build a premenstrual symptom assessment tool to be used across channels/discipline for the 2006 PMDD Education and YAZ CRM campaigns. The tool should ask questions that focus on key elements of the symptoms of PMS and PMDD...” The assessment tool had four key areas: emotional and physical premenstrual symptoms; lifestyle; timing in which premenstrual symptoms occur; and interference of emotional and physical premenstrual symptoms in work, relationship with others and sense of well-being. (BHCPYAZ011801509-512 at 509. PL-307).

239. According to Conroy, “All four areas directly affect the severity–level and prevalence [sic] of a woman’s premenstrual syndrome. The assessment tool will yield a personalized branded assessment sponsored by a KOL [Key Opinion Leader], Dr. Rapkin. The personalized assessment will not serve as a self-diagnosis tool, but rather a tool to: 1) help better understand symptoms, 2) serve as a discussion tool w your HCP [Healthcare Provider] to see what option is best for you.” (BHCPYAZ011801509-512 at 509. PL-307).

240. Furthermore, according to Conroy, “Total responders should be split into overall ‘severity’ segments. We may need to take a new direction here, because ultimately, EVERYONE is a good candidate for YAZ.” (emphasis in original) (BHCPYAZ011801509-512 at 509. PL-307).

241. The assessment, according to Conroy, divided severity into three categories: severe PMS or possible PMDD; moderate premenstrual symptoms; and mild to no premenstrual symptoms. (BHCPYAZ011801509-512 at 511. PL-307).

242. Under the segment “moderate premenstrual symptoms,” Conroy wrote, “In the 10 days before your period, you’re probably experiencing symptoms of premenstrual syndrome. An evaluation by a healthcare professional would be necessary to know for sure. He or she may recommend prescription medication in addition to lifestyle modifications that could have a significant positive impact on the severity of your premenstrual symptoms.” (BHCPYAZ011801509-512 at 511, PL-307).

243. Bayer knew that “Up to 80% of women suffer some type of premenstrual syndrome.” (BHCPYAZ009460069-0213 at 104, 167, PL-423).

244. As noted above, Bayer decided that Yasmin’s lifecycle management “uniqueness” would “be rooted in the beneficial effects of drsp on physical and emotional symptoms associated with the menstrual cycle.” (BSPYAZ004306340-419 at 343, Lezzaiq-16).

245. Bayer knew that “Most women suffer from physical and emotional symptoms around their menstrual cycle, which negatively impact their daily lives.” (BSPYAZ004306340-419 at 360, 373, Lezzaiq-16). As noted above, a Global Brand Marketing Plan Yasmin LCM, under “Opportunities,” stated “Become 1st choice for the target group of OC users who show symptoms consistent with severe PMS/PMDD.” (BSPYAZ004306340-419 at 401, Lezzaiq-16).

246. In fact, as documented below, Bayer’s marketing was not limited to severe PMS; instead, Bayer continued to market and promote the product for PMS.

247. As noted above, Bayer 2005 Brand Plan stated that its “Key Selling Messages” for Yasmin through the Professional Journal Article Channel was “PMS data” and “Acne data.” (BHCPYAZ009460069-0213 at 136, PL-423).

248. As noted above, Bayer stated that the ability to communicate and profit from additional benefits despite a basic label (OC only) “made Yasmin® the No. 1 OC worldwide and represents an opportunity upon which we can capitalize with LCM [lifecycle management] of drsp.” [Emphasis added] (BSPYAZ004306340-419 at 344, Lezzaiq-16).

249. Bayer decided that the “Frame of Reference – Primary Benefit” of YAZ would be that it “Provides better relief of symptoms associated with the menstrual cycle.” (BSPYAZ001540805-884 at 825, Lezzaiq-18).

250. Bayer decided that one of “Key Selling Messages” for YAZ would be “clinically proven to reduce premenstrual/menstrual symptoms” and to “help improve skin condition.” (BSPYAZ001540805-884 at 825, Lezzaiq-18).

251. Bayer's "selling messages" were not limited to marketing and promoting YAZ for PMDD or moderate acne.

252. A Bayer marketing executive, Heidemarie Schnell wrote: "Copy –Use YAZ tested terms 'feeling anxious' vs. 'nervous'; Stay away from all the 'depression stuff'. (vs. YAZ='moody')." (BHCYPAZ011799856-857 at 856, Schnell-334).

253. Those terms "moody" and "feeling anxious" are emotions of everyday life and do not convey the severity of the clinical symptomatology of PMDD, which must include at least five of the following with at least one of the symptoms, being among the first 4 on the list (*See Appendix B*):

Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts

Marked anxiety, tension, feelings of being "keyed up" or "on the edge"

Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)

Persistent and marked anger or irritability or increased interpersonal conflicts

Decreased interest in usual activities (e.g., work, school, friends, hobbies)

Subjective sense of difficulty in concentrating

Lethargy, easy fatigability, or marked lack of energy

Marked change in appetite, overeating, or specific food cravings

Hypersomnia or insomnia

A subjective sense of being overwhelmed or out of control

Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

254. In handwritten notes Bayer marketing executive, Heidemarie Schnell wrote under the heading, “PMS [?]/PMDD Revisions: Y &R, Jeff, Karen”, the following: “Connecting severe PMS and PMDD, and n[?]ow YAZ helped” followed by “change ‘severe PMS’ to ‘PMS.’”[[?] indicate handwriting ambiguity]. (BHCPYAZ011999135-300 at 236, Schnell-38). Bayer’s strategy documents stated that it could reach 70% of women of reproductive age with a PMDD indication which was more consistent with a PMS market share than the single digit percentage of women that Bayer knew had PMDD.

255. A December 8, 2005, Marketing Team Commissioning Paper with the name Yasmin LCM, Team Leader Heike Prinz and including Leslie North, Region US, listed under the heading “Strategic Guidance” the following: “Develop an integrated marketing strategy for all brands of the Yasmin family;” “Successfully launch YAZ globally;” “Prepare and develop the PMS/PMDD market through YAZ (~~indication is crucial~~.)” A comment highlighted the words YAZ and deleted “indication is crucial” with the comment stating “What if we don’t get the indication? We would try to sell PMS/PMDD anyway.” (Strikethrough in original) (BHCPYAZ021793557-3558 at 557, LP-121).

256. As part of a Global Strategic Marketing document titled, “YAZ within Global drsp’ Strategy,” Bayer employees wrote: “What do we really do at the GBU level? What kind of support is Strategic Global Marketing is [sic] really supposed to offer? How can a small event in the beginning make a big change at the end to gain a sustainable competitive... How can a thin slice of knowledge stretch a long way?” (BSPYAZ005174841-5010 at 4933; also Lezzaiq-10, p.93).

257. The answer according to Bayer employees, as documented in the above Global Strategic Marketing document: “PMDD...it is as easy as saying severe PMS...”

(BSPYAZ005174841-5010 at 933; also Lezzaiq-10, p.93, Bates numbering absent from document).

258. The strategy involved dispersing the concept, not of PMDD as approved by the FDA, but of PMDD/severe PMS. (BSPYAZ005174841-5010 at 935; also Lezzaiq-10, p.95, Bates numbering absent from document).

259. Bayer decided that one of “Key Selling Messages” for YAZ would be “clinically proven to reduce premenstrual/menstrual symptoms” and to “help improve skin condition.” (BSPYAZ001540805-884 at 825, Lezzaiq-18).

260. Bayer’s “selling messages” were not limited to marketing and promoting YAZ for pregnancy prevention, PMDD or moderate acne.

261. In a 2007 YAZ end-of-the-year report written by Ogilvy Public Relations Worldwide stated that the company “Needed to bundle PMDD with broader lifestyle issue...to attract major media attention.” (BHCPYAZ026067979-995 at 984, LP-474).

262. Because of that need they “Reframed PMDD as severe menstrual symptoms to optimize awareness.” (BHCPYAZ026067979-995 at 984, LP-474).

263. Bayer knew that the “Stigma and low incidence of PMDD (3% – 5%) has limited media appeal.” (BHCPYAZ026067979-995 at 984, LP-474).

264. Bayer had research conducted to evaluate the potential impact of three YAZ print ads. The questions the research was directed at answering included: Did the advertising favorably impact the brand image? And, did the advertising increase call to action? (BHCPYAZ008932327-376 at 330, PL-206).

265. In a March 27, 2008 email, Paul Bedard shared the key findings of the research that suggested that all of the print ads studied had the ability to “have some positive impact on

women’s impulse desire to discuss YAZ with their physician.” (BHCPYAZ008932327-376 at 327, 337, PL-206).

266. Bayer studied eye tracking of its print ads—including the “Balloons” advertisement. Eye tracking data showed that the ad as designed attracted little attention to the safety information in the ads and much greater attention to the claims of positive benefits. (BHCPYAZ008932327-376 at 341, 373, PL-206).

267. As mentioned above, Bayer’s research showed that the tested ads, including “Balloons,” conveyed more than twice the awareness of the message that YAZ helps/relieves symptoms of PMS, compared to the message that YAZ helps relieve the symptoms of PMDD/severe PMS. (BHCPYAZ008932327-376 at 372, PL-206).

268. Bayer developed a “tactical plan for the YAZ ‘Dating: Keep the Balance’ campaign, a high impact consumer campaign that examined the impact of premenstrual symptoms on a broader lifestyle issue—dating and relationships...the campaign centers on original research—a branded landmark survey on dating an relationship—to create a credible and newsworthy context for promoting YAZ and its key benefits. To that end, survey questions/outcomes will be designed so that the role of YAZ in managing premenstrual symptoms and preventing pregnancy becomes a focal point....” (BHCPYAZ026058703-711 at 704, PL-487).

269. As part of YAZ’s approval, the FDA required that Bayer take special precautions to make sure that healthcare providers and patients used YAZ only in certain instances of PMDD and not PMS. FDA stated: “The Applicant [Bayer] will need to conduct an educational program for healthcare providers that (1) stresses the importance of distinguishing PMDD from Premenstrual Syndrome (PMS) and (2) provides guidance on how to accurately

identify women who have PMDD. The program must also stress that if a woman is not currently using a hormonal contraceptive product or was not intending to use a hormonal contraceptive product for prevention of pregnancy, she should not use DRSP/EE for treatment of the symptoms of PMDD.” (Clinical Team Leader Memorandum, 1/23/06; Scott Monroe, M.D., Reviewer, § 1.3.1 at 3).

270. In its Complete Response regarding YAZ’ indication for PMDD, Bayer submitted a brief outline of its “Educational Outreach Protocol for Providers and Patients.” The stated objectives of the program are to:

- Educate healthcare providers on the diagnostic criteria and the various existing tools to differentiate and identify the various premenstrual disorders.
- Educate healthcare providers on the interpretation of one of the tools (the Daily Record of Severity of Problems [DRSPS, the instrument used for the primary endpoint in the PMDD trials]) used to assess the severity of a patient’s premenstrual disorder.
- Educate healthcare providers on the treatment options.
- Educate women on the advantages of using diaries to better understand their symptomatology, and foster better discussion with their healthcare provider.
- Provide women with opportunities to increase their understanding and awareness of PMDD and the treatment options available to them. (DRUP Clinical Team Leader Memorandum, 09/27/06; Lisa Soule, M.D., Reviewer, § 1.3.1, at 2).

271. Several teleconferences were held between the FDA and the Applicant to refine the features of the Outreach program. In a submission dated September 14, 2006, the Applicant noted the following revised features of the program:

- The program will provide clear statements that YAZ is first and foremost

an oral contraceptive that should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control.

- The educational outreach for patients and health care providers (HCPs) will establish a clear understanding of what PMDD is. HCPs will be educated on the DSM-IV criteria, including the use of a prospective diary. Patients will be encouraged to complete a prospective daily diary to use in discussions with their HCPs.

- Materials provided to HCPs will include information about how to diagnose PMDD, such as the DSM-IV criteria for diagnosis of PMDD.

- The print and TV campaigns intended for consumers, in development, will clearly identify that YAZ is an OC with unique risks and benefits and will provide clear statements that YAZ should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control. The campaign seeks to educate women on the differences between PMS and PMDD through education on PMDD and encouragement to complete a prospective daily diary. The HCP will make the differential diagnosis between PMS and PMDD. (DRUP Clinical Team Leader Memorandum, 09/27/06; Lisa Soule, M.D., Reviewer, § 1.3.1, at 2).

272. Despite FDA's Requirements and Bayer's agreement to educate women on the differences between PMS and PMDD, Bayer strategically stretched the market for YAZ beyond PMDD.

273. Even before Yasmin and YAZ were approved or marketed, Bayer knew that "severe PMS" and "PMDD" were not the same entity. In a March 11, 1999 document, Peter Boerrigter wrote, "To All; Just to prevent any misinterpretation of terminology right from the beginning, please, take note of the following—PMDD is NOT the more severe form of PMS."

[Emphasis in original]. Those notes are cited in an email from Bayer's Reinhard Franzen to Bayer's Jeff Frick on March 15, 1999 with the statement by Mr. Franzen, "good clarification...let's make sure everybody understands RF." (BHCPYAZ022311275-1276, LP-272).

274. A 2006, global strategic marketing document titled, "A Briefing Document on the Yasmin® Oral Contraceptives Family" shows that Yasmin was positioned as follows: "Provides relief of premenstrual symptoms (U.S.)" and "Improves how a woman feels physically and emotionally (RoW)." The document also stated that YAZ was positioned as "the only oral contraceptive with drsp that is clinically proven to relieve the physical and emotional symptoms associated with the menstrual cycle." (BSPW3529059-9092 at 9069, Lezzaiq-5).

275. An e-mail dated March 7, 2007, from Rose Talarico, Associate Director, Public Relations, to numerous Bayer employees stated: "Today's issue of the Chicago Sun Times highlights YAZ for PMDD in an article, 'A PMS Solution That Actually Helps.' The article is written in a Q & A format and includes most our key the [sic]messages in our press materials, such as how YAZ with drsp differs from other OCs, its 24/4 day dosing regimen and the fact that YAZ is the only OC that is FDA approved for treating 'PMS'. Additionally, PMDD is differentiated from PMS and described as 'symptoms that are severe enough to interfere with school, work or relationships with others' (again, directly from our media materials). The Chicago Sun Times is one of the top 10 daily newspapers in the U.S., with 900,000+ impressions." (BHCPYAZ009001726-729, at 728, PL-199).

276. A 2007 Berlex document titled "YAZ/Yasmin 2007 Briefing document/Tactical recommendations" listed under "Threats" –"FDA restriction on marketing communication for YAZ and PMDD." (BHCPYAZ011816240-262 at 242, PL-322).

277. The same document stated “PMDD indication could niche/stigmatize YAZ.” (BHCPYAZ011816240-262 at 242, PL-322).

278. A 2007/2008 Global Brand Marketing Plan for YASMIN Family 2007/2008 identified opportunities for “Possibility to do unbranded DTC [Direct to Consumer] for PMS/PMDD.” (BHCPYAZ012207797-841 at 807, Lezzaiq-20).

279. The Marketing Plan under the heading Strategic Product SWOT [Strengths, Weaknesses, Opportunities, Threats] Analysis for Yasmin listed as a strength, “Profiling in added benefits (PMS, acne, period management).” The SWOT analysis listed as a weakness, “Lack of labeled benefits.” (BHCPYAZ012207797-841 at 806, Lezzaiq-20).

280. The Marketing Plan stated under “Communication Focus” in response to the question, “What is the primary benefit we want to convey via health outcomes data?” that “YAZ® improves functionality and reduces impairment due to PMS/PMDD.” (BHCPYAZ012207797-841 at 839, Lezzaiq-20).

281. A YAZ Global Strategy PowerPoint Presentation (hereinafter, “presentation”) by Samer Lezzaiq, dated March 8, 2007, that was an “Update on Global Activities” held in Cartagena, Colombia, described PMDD as a “niche that’s not a niche!” (BHCPYAZ012436948-979 at 950, Lezzaiq-38).

282. The presentation noted that YAZ was registered in four countries including the United States for oral contraceptive use and PMDD and acne; in Colombia for oral contraceptive use and PMDD; in the Ukraine for oral contraceptive use and PMDD and acne; and in Brazil for oral contraceptive use. (BHCPYAZ012436948-979 at 964, Lezzaiq-38).

283. The presentation noted that the prevalence of PMS in Europe was 33% and in Latin America 47%; in contrast the prevalence of symptoms for PMDD in Europe was 2.5% and in Latin America 6%. (BHCPYAZ012436948-979 at 967, Lezzaiq-38).

284. In the presentation, a slide labeled “What do we want to say?” had two columns. The first column was headed “LABEL”; the second column was headed “CBP (“Core Brand Promise”) [Lezzaiq, Deposition Transcript, February 3, 2011, at 696:5-17] TRANSLATION.” Under the column headed “LABEL,” the slide stated: “OC to treat Premenstrual Dysphoric Disorder (PMDD).” Under the column headed “CBP TRANSLATION,” the slide stated: “The only OC, *clinically proven to relieve emotional and physical symptoms of the menstrual cycle.*” [Emphasis in original]. Under the heading “LABEL” was the phrase “treats acne”; under the heading “CBP TRANSLATION” was the phrase, “The OC that has a positive skin profile.” (BHCPYAZ012436948-979 at 969, Lezzaiq-38; and Lezzaiq-10, p.27, Bates numbering absent from this document).

285. In the presentation, the slide after the slide labeled, “What do we want to say?” had the heading “YAZ in the U. S.” Under that heading the phrase “the fast and furious” was written. (BHCPYAZ012436948-979 at 970, Lezzaiq-38).

286. Other slides in the presentation stated that “YAZ sales uptake in the U.S. is very strong and above the forecast,” and “YAZ has the fastest sales uptake in comparison to other major birth control pills in the U.S.” (BHCPYAZ012436948-979 at 971-972, Lezzaiq-38).

287. A draft of a March 31, 2008 Global Brand Marketing Plan (hereinafter, “Marketing Plan”), titled Yasmin Family 2008/2009, involving, among others, Leslie North, U.S. Brand Manager, stated under section 4.3 Positioning--Yasmin that, “For women 15-18 – 30 years requiring contraception (new users, switchers), Yasmin® is the oral contraceptive that – Provides

relief of premenstrual symptoms (US).” The document also states that YAZ was to be positioned as the “only oral contraceptive that is clinically proven to relieve the physical and emotional symptoms associated with the menstrual cycle.” (BHCPYAZ006141556-627 at 590, PL-195).

288. The Marketing Plan also stated that the “Yasmin Family will continue to be the most important growth driver in the global WH [Women’s Health] business.” (BHCPYAZ006141556-627 at 592, PL-195; *See also* BHCPYAZ012207800-841 at 800).

289. The Marketing Plan stated under “Public Relations: Focus of Effort” for YAZ that the goal was to “Build awareness for PMS/PMDD and the symptoms associated with menstrual cycle” and “‘own’ the PMS/PMDD opportunity with YAZ®.” (BHCPYAZ006141556-627 at 608, PL-195).

290. The Marketing Plan under “Website Development: Focus of Effort” stated that for YAZ that the goal was to “Build awareness for PMS/PMDD, build brand awareness.” (BHCPYAZ006141556-627 at 608, PL-195).

291. The Marketing Plan had a “Global Opinion Leader Development Strategy” to select for the “Target Market” “Experts for PMS/PMDD worldwide.” (BHCPYAZ006141556-627 at 610, PL-195).

292. The Marketing Plan stated that “The goal is to drive global sales for the whole Yasmin family from today (2007) 1.04 bn Euros up to 2.8 billion Euros in 2018...thus allowing us to grow our market leadership position in FC [Female Contraception].” (BHCPYAZ006141556-627 at 559, PL-195).

293. Bayer knew that YAZ was not approved for the treatment of premenstrual syndrome (PMS); that there was a difference between PMS and PMDD; and that YAZ had not been evaluated for PMS.

294. Bayer knew that “PMS is a less serious cluster of symptoms occurring before menstruation. If you or your healthcare provider believes you have PMS you should only take YAZ if you want to prevent pregnancy; and not for the treatment of PMS. In addition, if women choose to use the Pill for contraception, they should know that YAZ is also indicated for the treatment of premenstrual dysphoric disorder (PMDD). For women who choose the Pill for contraception, YAZ is the only birth control pill proven to help treat the emotional and physical symptoms of PMDD, that are severe enough to impact a woman’s life. YAZ has not been evaluated for the treatment of PMS, a less serious cluster of symptoms occurring before menstruation. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.” (BHCPYAZ026094620-624 at 622-623, LP-411).

295. In my opinion, Bayer promoted YAZ for “off-label” uses in violation of the Federal Food, Drug and Cosmetic Act.

c. Bayer’s Advertising Campaigns Were Misleading

296. Bayer utilized in marketing and promotion two 60 second direct-to-consumer (DTC) broadcast television advertisements titled, “Not Gonna Take It” and “Balloons.”

297. According to the FDA, the TV ads encouraged use of the drug in circumstances other than those for which the drug had been approved, over-stated the benefits of the drug and minimized the risks associated with YAZ. (October, 3, 2008 DDMAC Letter, BHCPYAZ007990073-080, PL-204).

298. According to FDA’s Division of Drug Advertising, Marketing, and Communications Director Thomas Abrams in a letter dated October 3, 2008, to Reinhard Franzen, President of Bayer: “The TV ads misleadingly suggest that YAZ is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, given the overlap in certain symptoms between

premenstrual syndrome (PMS) and PMDD, and the material limitation on YAZ's PMDD indication (that it has not been evaluated for the treatment of the less serious condition, PMS), the TV Ads misleadingly suggest that YAZ is appropriate for treating women with PMS, who may not be appropriate candidates for this drug. We note that despite listing certain symptoms of PMDD, nowhere do the TV Ads use the full phrase "premenstrual dysphoric disorder," to more completely distinguish PMDD from PMS, thereby increasing the likelihood that a viewer, in light of the claims and presentations described below, will understand it to be the same as, or substantially similar to, PMS." (BHCPYAZ007990073-080 at 075, PL-204).

299. According to the FDA, "The totality of the visual and audio presentations in both TV ads suggest that YAZ is approved to treat women with any severity of the symptoms presented, including women with PMS, when this is not the case." (BHCPYAZ007990073-080 at 076, PL-204).

300. In addition, FDA concluded that the audio communication of serious risk disclosures in the advertisement was minimized by distracting visuals, numerous scene changes, and other competing modalities such as the background music, which combined to interfere with the presentation of risk information. According to the FDA, "These complex presentations distract from and make it difficult for viewers to process and comprehend the important risks being conveyed." FDA went on to state, "This is particularly troubling as some of the risks being conveyed are serious, even life-threatening. The overall effect of the distracting visuals, graphics, concurrent supers and background music is to undermine the communication of important risk information, minimizing these risks and misleadingly suggesting that YAZ is safer than has been demonstrated by substantial evidence or substantial clinical experience." (BHCPYAZ007990073-080 at 078, PL-204).

301. As noted above Bayer studied eye tracking of its print ads—including the “Balloons” advertisement. Eye tracking data showed that ads as designed attracted little attention to the safety information in the ads and much greater attention to the claims of positive benefits. (BHCPYAZ008932327-376 at 341, 373, PL-206).

302. Bayer’s research showed that the tested ads, including “Balloon,” conveyed more than twice the awareness (11vs.5) and description (16 vs. 8) of the message that YAZ helps/relieves symptoms of PMS compared to the message that YAZ helps relieve the symptoms of PMDD/severe PMS. (BHCPYAZ008932327-376 at 345 and 372, PL-206).

303. Bayer understood that FDA regulations require that risk and benefits in advertising and promotion be presented with enough detail to accurately represent the risks and benefits of the drug. This requires that the amount of time, space, font size, contrast and placement devoted to benefits/risks be such that the audience understands and recalls the benefits and risks of the drug. Furthermore, Bayer understood that FDA requires that risk information not be minimized, or subject to distraction, and that it be integrated along with the benefits. (BHCPYAZ006135260-344 at 278, 280, 281, LP-100).

304. FDA concluded that the TV ads misbranded the drug in violation of the Federal Food Drug and Cosmetic Act and its implementing regulations. (BHCPYAZ007990073-080 at 078, PL-204).

305. The YAZ TV advertisement displayed numerous balloons throughout the ad with symptoms such as irritability, moodiness, feeling anxious, bloating, fatigue, muscle aches, headaches, increased appetite, and acne. (BHCPYAZ007990073-080 at 075, PL-204).

306. As FDA has pointed out, the symptoms displayed are commonly seen in women with PMS. The TV advertisement omitted the limitation that YAZ has not been

evaluated for the treatment of PMS. The TV ad also failed to convey that YAZ is only indicated for women who experience the symptoms presented to such a degree that they have PMDD, rather than PMS. (BHCPYAZ007990073-080 at 075-076, PL-204).

307. As FDA has pointed out, the TV advertisement suggests that YAZ is approved to treat women that have any severity of symptoms presented, regardless of whether their symptoms are actually severe enough to constitute PMDD. (BHCPYAZ007990073-080 at 076, PL-204).

308. Bayer knew prior to the FDA Warning letter that an ad involving balloons with symptoms written on the balloons was “risky” because it “implies the symptoms go away forever and the imagery feels light-hearted which pulls away form [sic] the severity. Plus, the movement implies YAZ is appropriate for ALL women. So we’re revising to be more about YAZ upfront, and you’re letting go of concerns about pregnancy and symptoms and acne.” (BHCPYAZ023317561-562 at 561, PL-312).

309. On December 29, 2006 Bayer had been informed by the FDA in a letter from an FDA Regulatory Review Officer that certain proposed promotional materials that the company had submitted were misleading because they “fail to adequately communicate the approved indication for YAZ, thereby suggesting the drug is useful in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience.” (BHCPYAZ009007250-255 at 251, PL-193).

310. FDA stated that Bayer’s violations were concerning “from a public health perspective.” (BHCPYAZ007990073-080 at 073, PL-204).

311. In response to the October 3, 2008 FDA Warning Letter, Bayer stated they pulled the television commercial “Balloons.” The other TV commercial, “Not Gonna Take It,”

had not run on television since August 10, 2008. Furthermore, Bayer stated to the FDA that it “reviewed all other promotional materials currently being used for YAZ and have withdrawn certain pieces from use....” Bayer also stated that in addition, “field sales personnel (for both Bayer and its affiliate, Intendis Inc., which promotes YAZ to dermatologists) have been advised to discontinue use of the withdrawn pieces.” (BHCPYAZ000463697-704 at 698, Defendant's Ex.1).

312. Bayer stated in response to FDA that the “‘Balloons’ advertisement was submitted to DDMAC for pre-clearance on March 20, 2008. After repeated attempts to obtain DDMAC’s comments proved unsuccessful, Bayer ultimately withdrew the request for review on May 16, 2008 – eight weeks after the original submission.” Bayer stated that it “did not seek pre-clearance of the ‘Not Gonna Take It’ advertisement because DDMAC had previously pre-cleared a professional advertising campaign (‘Stomp’) containing similar themes and communications messages.” According to Bayer, “‘Not Gonna Take It’ was based upon that earlier professional campaign and DDMAC’s comments about it.” (BHCPYAZ000463697-704 at 697, Defendant's Ex.1).

313. In my opinion, Bayer promoted YAZ for “Off-label” uses in violation of the Federal Food, Drug and Cosmetic Act.

314. In the September 2008 issue (Vol. 112, No. 3) of the professional journal *Obstetrics & Gynecology* (known as the “Green Journal”), Bayer ran a prominent full-page advertisement similar in content to the “Balloons” television advertisement. Criticisms that the FDA enumerated about the television advertisement (*See supra*) apply equally to this print advertising campaign. (*Obstetrics & Gynecology*, Vol. 112, No.3, September 2008).

315. Further, in the January (Vol. 111, No.1), March, (Vol.111, No.3), April (Vol. 111, No.4) and May (Vol. 111, No.5) 2008 volumes of *Obstetrics & Gynecology*, Bayer ran full-page advertisements with the specific statement, featured in prominent print, that YAZ provides “Treatment of emotional and physical premenstrual symptoms severe enough to impact women’s lives.” The image focuses graphically on stopping “Fatigue”, “Bloating”, “Moodiness” and “Acne.” Criticisms that the FDA enumerated about the television advertisement (*See supra*) apply equally to this print advertising campaign.

316. On January 23, 2007, Bayer entered into a Stipulated General Judgment Agreement with the Attorney Generals of Individual States that arose out of Bayer’s actions regarding the drug Baycol that required, among other remedies, that Bayer shall comply with all applicable laws and regulations relating to the marketing, sale, and promotion of all its products, not only Baycol. The compliance agreement stated that Bayer shall not make any false, misleading, or deceptive representation regarding any of its products in violation of all applicable laws and regulations. (Stipulated General Judgment Agreement, January 23, 2007, Abrams-27).

317. As noted above, according to a Warning letter [hereinafter Warning letter] dated October 3, 2008 from Thomas Abrams, Director of FDA’s Division of Drug Advertising, Marketing, and Communications, to Reinhard Franzen, President of Bayer “The TV Ads misleadingly suggest that YAZ is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience.” (BHCPYAZ007990073-080 at 075, PL-204).

318. Bayer understood that warning letters were “generally reserved for more egregious violations, risks to public health, or blatant ignorance of FDA advisory comments.” (BHCPYAZ006135260-344 at 264, LP-100).

319. In response to the FDA warning, Bayer's revised ad stated that "YAZ is approved for pregnancy prevention. If women choose to use the Pill for contraception, they should know that YAZ is also indicated for the treatment of premenstrual dysphoric disorder, or PMDD, and moderate acne. For women who choose the Pill for contraception, YAZ® is the only birth control pill proven to help treat the emotional and physical symptoms of PMDD, that are severe enough to impact a woman's life. YAZ has not been evaluated for the treatment of PMS, a less serious cluster of symptoms occurring before menstruation. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated." (BHCPYAZ026094620-624 at 623, LP-411).

320. On February 9, 2009, Bayer entered into a modification of its Stipulated General Judgment resulting from Bayer's conduct that precipitated FDA's Warning Letter. (February 9, 2009 Stipulated General Judgment, Abrams-28).

321. Bayer understood that FDA requirements about the need to disclose safety information applied to sponsored links on the Internet. (BHCPYAZ006135260-344 at 288, LP-100).

322. Bayer understood that the same standards apply to YouTube Videos as well as all other Promotional Materials. (BHCPYAZ006135260-344 at 305, LP-100).

323. On March 26, 2009, in a letter FDA's Shefall Doshi informed Bayer that sponsored links for YAZ on the Web were incomplete and misleading because they failed to communicate any risk information. (BHCPYAZ002381533-538 at 534, 536, PL-216).

324. In July 2009, Bayer knew that the same "Goodbye to You" (Balloons) TV ad that had been taken down as a result of the October 3, 2008 Warning Letter, and which had required a \$20 million corrective ad campaign, continued to air on YouTube. The ad, posted by

one of its actresses (Desiree Grace), had received about 15,000 views between May 2008 and July 2009. Bayer's Nancy Konnerth wrote, "Ok, so here we have an ad currently running on YouTube that is in violation of FDA regulations. Shouldn't Bayer use its power to have Desiree 'pull' this video from Youtube just as it was pulled from TV?" (BHCPYAZ016737415, PL-258).

325. Despite the acknowledgment that the ad was in violation of FDA regulations, Bayer did not remove the ad in 2008-09. In a deposition on January 21, 2011, Bayer's Paul Bedard stated that he recognized "that we should make efforts to get that removed from YouTube." A YouTube document regarding the "Balloons" video, dated April 4, 2011, states, "The content has been removed." (Copyright Infringement Notification Confirmation, 4/4/11). The YouTube response, i.e., removing the video, supports the inference that Bayer could have had the ad taken down in 2008, or at any time after learning of its presence, but it did not do so. (Bedard, Deposition Transcript, January 21, 2011, at 389:18-393:3; Attachment A - Response to MDL PSC Interrogatories Set 9.)

E. Bayer's Economic Success Was Achieved, In Part, By Marketing And Promoting Yasmin And YAZ For Off-Label Indications In Violation Of The Law And Its Duty Of Care

326. As noted above, Bayer stated that the ability to communicate and profit from additional benefits despite a basic label "made Yasmin the No. 1 OC worldwide and represents an opportunity upon which we can capitalize with LCM of drsp." (BSPYAZ004306340-419 at 344, Lezzaiq-16).

327. The Yasmin brand family was seen inside Bayer as a "crown jewel" which by 2006 had a billion dollars in sales. (BHCPYAZ012108523-532 at 527, Lezzaiq-4).

328. As noted above, a draft of a March 31, 2008 Global Brand Marketing Plan (hereinafter, "Marketing Plan"), titled, "Yasmin Family 2008/2009," involving, among others, Leslie North, US Brand Manager, stated under section 4.3 Positioning – Yasmin that "For

women (15-18) – 30 years requiring contraception (new users, switchers), Yasmin® is the oral contraceptive that “Provides relief of premenstrual symptoms (US).” The document states that YAZ was to be positioned as “the only oral contraceptive that is clinically proven to relieve the physical and emotional symptoms associated with the menstrual cycle.”

(BHCPYAZ006141556-627 at 590, PL-195). The Marketing Plan also stated that “The Yasmin Family will continue to be the most important growth driver in the global WH [Women’s Health] business.” (BHCPYAZ006141556-627 at 592, PL-195). The Marketing Plan identified opportunities for “Possibility to do unbranded DTC [Direct to Consumer] for PMS/PMDD.” (BHCPYAZ006141556-627 at 566, PL-195). The Marketing Plan, under the heading “Strategic Product SWOT Analysis for Yasmin,” listed as a strength, “Profiling in added benefits (PMS, acne, period management.)” The SWOT analysis listed as a weakness “Lack of labeled benefits.” (BHCPYAZ006141556-627 at 565, PL-195). The Marketing Plan, stated under “Communications Focus,” in response to the question, “What is the primary benefit we want to convey via health outcomes data? that “YAZ® improves functionality and reduces impairment due to PMS/PMDD.” (BHCPYAZ006141556-627 at 604, PL-195). The Marketing Plan stated under “Public Relations: Focus of Effort” for YAZ that the goal was to “Build awareness for PMS/PMDD and the symptoms associated with menstrual cycle,” and “‘own’ the PMS/PMDD opportunity with YAZ®.” (BHCPYAZ006141556-627 at 608, PL-195). The Marketing Plan stated under “Website Development: Focus of Effort” for YAZ the goal was to “Build awareness for PMS/PMDD, build brand awareness.” (BHCPYAZ006141556-627 at 608, PL-195). The Marketing Plan had a Global Opinion Leader Development Strategy to select for the “Target Market” “Experts for PMS/PMDD worldwide.” (BHCPYAZ006141556-627 at 610, PL-195).

329. The Marketing Plan stated that “the goal is to drive global sales for the whole Yasmin family from today (2007) 1.04 bn Euros up to 2.8 billion Euros in 2018...thus allowing us to grow our market leadership position in FC [Female Contraception].” (BHCPYAZ006141556-627 at 559, PL-195).

F. Bayer’s Sales Force Promoted Yasmin For Off-Label Use And Made Implied Superiority Claims That Were Not Approved

330. Sales representatives’ call notes reveal promotion of Yasmin for off-label uses including PMS, claiming that the drug had unique “anti-M” properties that were effective in the treatment of PMS.

331. According to a Bayer Global Brand Marketing Yasmin LCM, dated November 14, 2005, Bayer had a strategy to “Capitalize on unique properties and OC for well-being. Yasmin® is the no. 1 OC worldwide. Its competitive advantages are its unique benefits related to the pharmacology of drsp: antiandrogenicity (acne) and anti-mineralocorticoid properties (PMS/ well-being).” (BSPYAZ004306340-419 at 354, Lezzaiq-16).

332. According to Bayer employees and as noted, *supra*, “We were able to communicate and profit from additional benefits despite a basic label (OC only). This made Yasmin® the No. 1 OC worldwide and represents an opportunity upon which we can capitalize with LCM of drsp.” (BSPYAZ004306340-419 at 344, 384, Lezzaiq-16).

333. The strategy’s target group for Yasmin was “to be enhanced beyond standard OC users, profiling the product in relief of physical and emotional symptoms of PMS (US), well-being (ROW), acne, PMDD, plus, extended regimen, libido and others.” (BSPYAZ004306340-419 at 354, Lezzaiq-16).

334. According to that strategy document, the “Therapeutic concept/Innovative elements” were “Relief of physical and emotional symptoms of PMS (US)” and the actual target

profile of patients in the United States was for “Relief of physical and emotional symptoms of PMS.” (BSPYAZ004306340-419 at 354, Lezzaiq-16).

335. Bayer’s strategy was to “capitalize on consumers’ awareness on ‘added benefits.’” (BSPYAZ004306340-419 at 354, Lezzaiq-16).

336. By marketing Yasmin and YAZ for its special properties, Bayer was giving physicians “Reasons to Believe.” (BSPYAZ004306340-419 at 360, 373, Lezzaiq-16).

337. A Bayer employee wrote “What was Bill Clinton’s catchy slogan from his 1992 presidential campaign? ‘It’s the economy, stupid’ -The power of context: -Although it is a widely used phrase now and is often cited as a Clinton campaign slogan, ...Drsp, with it’s unique anti-M (and anti-A) *unique* benefits, is the link that sticks to the physicians.” (emphasis in original) (Lezzaiq-10, p. 96; BSPYAZ005174841-5010 at 4936).

338. One of Bayer’s key selling messages for Yasmin was that it “contains the unique progestin ‘drsp’ that: is the spironolactone analogue with dual properties Anti-M and Anti-A that relieve pre-menstrual symptoms; reduces fluid retention related symptoms... most closely resembles natural progesterone.” (Lezzaiq-10, Page 18; BSPYAZ005174841-5010 at 4858).

339. Bayer positioned YAZ as “a better delivery system for ‘drsp’” with a “unique 24/4 regimen allows 3 extra days of anti-A and anti-M activity; 30 hour half life extends ‘drsp’ into placebo interval; lower EE levels allow more pronounced ‘drsp’ effect.” (BHCPYAZ012165328-339 at 333, Lezzaiq-45).

340. Bayer positioned Yasmin: “To physicians, nurses, pharmacists, YASMIN is the OC that contains the unique progestin, drospirenone, a spironolactone analogue, with

antimineralocorticoid and antiandrogenic dual properties that help relieve menstrual symptoms.” (BHCPYAZ009460069-213 at 099, PL-423).

341. Bayer positioned YAZ: “For health care providers, YAZ is the only OC that accentuates the benefits of drsp through its unique regimen to help women look and feel great.” (BHCPYAZ009460069-213 at 099, PL-423).

342. According to Bayer the “Key differentiator will be drsp and its resulting anti-M and anti-A benefits.” (BHCPYAZ012207797-841 at 816, Lezzaiq-20).

343. Thus Bayer used the anti-mineralocorticoid (anti-M) properties as a way to promote Yasmin and YAZ for PMS and relief of physical and emotional symptoms associated with the menstrual cycle which were not approved indications for Yasmin or YAZ.

344. As noted above, in 2004 and 2005 print advertisements in a professional journal (*Obstetrics & Gynecology*), Bayer implied that Yasmin’s anti-mineralocorticoid properties provided benefits to the consumer by stating “Chemistry like no other” (along with an image of a couple dancing). (*Obstetrics & Gynecology*: Vol. 103, No. 2, February 2004; Vol. 103, No. 4, April 2004; Vol. 103, No. 103, No. 5, May 2004; Vol. 103, No. 6, June 2004; Vol. 104, No. 1, July 2004; Vol. 104, No. 2, August 2004; Vol. 104, No. 4, October 2004; Vol. 104, No. 6, December 2004; Vol. 105, No. 1, January 2005; Vol. 105, No. 2, February 2005; Vol. 105, No. 4, April 2005).

345. On October 9, 2004, a sales representative made a sales call and noted in a sales call report “Yasmin reminder for patients with PMS type symptoms.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

346. On May 26, 2004, a sales representative noted in the call record “Yasmin and Anti-M property reminder with newspaper article with success and popularity of Yasmin.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

347. On January 6, 2005, a sales representative noted in a sales call report “anti M property with Yasmin.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

348. On January 26, 2005, a sales representative noted in a sales call report “Also discussed ‘D’ piece and dual properties of Yasmin.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

349. On April 28, 2005, a sales representative noted in a sales call report “Saw in office and discussed Anti M property of Yasmin and well tolerated pill of all OCs.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

350. On July 14, 2005, a sales representative noted in a sales call report “Yasmin worldwide success and well tolerability due to Anti M property.” (Sales Call Report, BHCPCS000319430-9453 at 9433).

351. On December 1, 2006, a sales representative noted in a sales report “Discussed Anti M property and diuretic effect.” (Sales Call Report, BHCPCS000319430-9453 at 9436).

352. By claiming “anti-M” properties, Bayer made claims that were not consistent with the drugs’ approved labeling.

353. In fact, Bayer was informed by FDA that it should not make claims that YAZ is superior to other contraceptive drug products when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, when Bayer suggested the following: “Drospirenone is the #1 preferred progestin among OB/GYNs,” FDA responded that

this claim is misleading because it implies that YAZ offers particular treatment benefits versus its comparators because it contains drospirenone. (BHCPYAZ006129042-047 at 045, PL-215).

354. In addition to promoting “benefits” of DRSP to consumers, Bayer also promoted YAZ to physicians in advertisements. The October 2006 (Vol.108, No.4), July 2006 (Vol.108, No.1), August 2006 (Vol.108, No.2), September 2006 (Vol. 108, No.3, Part 1) issues of *Obstetrics and Gynecology* contained a full page advertisement, with the headline, “The only 24/4-day OC with drsp.” The image of a young woman who was “celebrating” and who conveyed a positive affect provided the supportive visual image of the message. The ad contained, in smaller print, a disclaimer about the potential risk of drsp and hyperkalemia.

355. In a deposition of Bayer’s Leslie North, she testified, “It is true that the risks associated with an additional 3 days of drospirenone is unknown.” (North, Deposition Transcript, February 26, 2011, at 1041:21-23 and 1042:2).

356. As noted above, rather than offering a specific benefit, FDA required Bayer to state that in the warning section of both Yasmin and YAZ’ approved label that the drugs contain “3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone.” (May 2003 Yasmin Label, BHCPYAZ001504233-274 at 242; YAZ October 2006 Label, BHCPYAZ002094184-230 at 196).

357. Moreover, FDA, on July 10, 2003, in a letter to Bayer, stated that the anti-M properties of Yasmin pose a risk rather than a benefit and any promotion of the antimineralocorticoid benefits would be misleading. Specifically FDA stated “Drospirenone has antimineralocorticoid properties, which means that it can work against the body’s normal mechanism for regulating salt and water balance, a situation that can lead to hyperkalemia in

high risk patients, resulting in potentially serious heart and health problems.”

(BSPYAZ006287885-889 at 885, PL-212).

358. On January 26, 2006, Berlex’s general counsel received the following email from Izumi Hara, Senior Vice President and General Counsel at Warner Chilcott: “Yvonne, I just wanted to let you know that we are now getting dozens of calls from our sales representatives - from all around the country - informing us that Berlex sales representatives are promoting YAZ to physicians in advance of FDA approval and that in addition to planning events in anticipation of a March launch are sharing detailed product information - such as the half life of drospirenone and the effect on PMS and PMDD with doctors now. You might want to look into that as such activity violates the law and I am sure it is not something you sanction.” (BHCPYAZ018818575-576 at 576, Atkinson-26).

359. In my opinion, Bayer’s sales force promoted Yasmin for off-label use and made implied superiority claims that were not approved.

G. Bayer Used Third Party Physicians To Promote Yasmin Off-Label To The Public In Violation Of The Federal Food, Drug And Cosmetic Act

360. As noted in Appendix A, physicians who are independent of the company may prescribe a drug for a non-approved use if such prescribing is, in the opinion of the physician, in the best interests of the patient.

361. Physicians may not promote a drug for non-approved uses.

362. Any statements made by physicians who receive payment from a pharmaceutical company are attributable to the pharmaceutical company. Any such statements must be in conformance with all applicable laws including the prohibition against “off-label” uses.

363. One of the company's corporate objectives was to "support off-label promotion of Yasmin via publications, symposia." (Lezzaiq-14 p. 65).

364. A November 2004 Bayer document titled, "Public Relations Recommendations for YAZ & Yasmin" listed "Book interviews for Yasmin spokesperson — high-profile GYN (Dr. Judith Reichman)." (BHCPYAZ 026054360-408 at 387, LP-422).

365. Bayer was involved contractually with Dr. Judith Reichman to promote Bayer's products. (BHCPYAZ028170150-0161, Frick-13A)

366. Bayer paid Dr. Reichman \$450,000 dollars, for among other rights, to be the exclusive sponsor of her book tour, and had rights to review her book titled, "Slow the Clock Down" prior to its publication. (BHCPYAZ028170150-0161 at 150-152, Frick-13A).

367. Dr. Reichman agreed to make best efforts to include Client Product related messages in all media interviews including national, local and internet media interviews. (BHCPYAZ028170150-0161 at 150, Frick-13A).

368. Bayer paid for promotional activities of Dr. Reichman's book including a 6 city in-person media tour, a 50 market radio tour, and an editor roundtable discussion. Bayer paid for first class air travel, meals and first class hotels. (BHCPYAZ028170150-0161 at 150, 151, Frick-13A).

369. In a May 9, 2002 email to Bayer colleagues Platkin, Konnerth and Frick with a subject heading "Judith Reichman" Bayer's Kimberly Schillace wrote: "Attached please find the contract as reviewed by legal and which incorporates the changes discussed with Jeff. I just spoke with Dr. Reichman and she definitely will mention off-label benefits of our products, [Redacted: Relevancy] as well as possible future indications." (Emphasis added) (BHCPYAZ014281874-884 at 874, LP-900).

370. Dr. Reichman's book advocated the use of Yasmin for indications beyond the FDA approved label. Dr. Reichman's book stated in discussing Yasmin: "This is probably what I would initially prescribe for Jean's PMS." (LP-903, Dr. Judith Reichman, "Slow Your Clock Down," p. 35). As noted above, PMS was not an approved label indication.

371. In another part of her book, Dr. Reichman wrote: "The latest Pill on the block, Yasmin, has a progestin that actually has *anti*-androgenic activity, potentially making it the best oral contraceptive acne blocker." (emphasis in original) (LP-903, Dr. Judith Reichman, "Slow Your Clock Down," p. 25).

372. Updated on April 1, 2004, Dr. Reichman on a Today show Health Q & A web page stated: "One pill, Yasmin, contains a progestin very similar to that produced by the ovaries. This has an excellent anti-male hormone effect on skin. Some doctors may add a diuretic (which causes fluid to be eliminated by the kidneys) called spironolactone. This pill, too, has anti-male hormone activity and reduces oil production. Yasmin has some of the activity of spironolactone." (http://today.msnbc.msn.com/id/4623970/ns/today-today_health/t/blemish-alert-ive-suddenly-got-pimples/).

373. "Updated" March 27, 2006, Dr. Reichman stated, "The birth control pill that contains the 'newest progestin on the block' (drospirenone) [sic] with an anti-androgenic effect is Yasmin. This progestin also seems to diminish bloat and acne." (http://today.msnbc.msn.com/id/12030042/ns/today-today_health/t/contraception-your-birth-control-guide/).

374. On a Today show segment interview with Campbell Brown, the video found at http://today.msnbc.msn.com/id/12030042/ns/today-today_health/t/contraception-your-birth-

control-guide/, Dr. Reichman stated: “Women who have acne, there’s a new progestin in something called Yasmin which helps with acne, weight gain and bloating.”

375. Dr. Reichman agreed to be trained by Bayer in product related messaging. (BHCPYAZ028170150-161 at 0151, Frick-13A).

376. A document about “Estimated Public Relations Budget” for “Berlex/Yasmin Initiatives” dated 6.21.05 under the heading “MD Spokesperson” stated, “Coordinate with Dr. Judith Reichman to determine availability; schedule and attend media training (2 Ogilvy PR staffers). *OOPs include trainer fee and travel; travel and entertainment, administrative costs. (Assumes Dr. Reichman’s fee will be paid directly by Berlex).*” [Emphasis in original]. The fee listed was \$10,000 and OOP was \$10,000. (BHCPYAZ007858812-813 at 8812, PL-413).

377. By paying for the promotional activities associated with Dr. Reichman’s book, Bayer was illegally promoting Yasmin for off-label uses in violation of the Federal Food Drug and Cosmetic Act.

378. According to Bayer, Dr. Lauren Streicher an OB/GYN, was a member in Bayer’s speaker panel and/or attended speaker training meetings related to Yasmin and or YAZ in 2007. Dr. Streicher was paid by Bayer for a Regional Advisory Board/Speaker Training for YAZ. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). In August, 2007 Dr. Lauren-Streicher submitted an invoice to Bayer media training on June 4 and July 24 and the satellite TV and radio tour on June 6 and July 25. (BHCPYAZ026158356-357 at 356). The transcript of a broadcast on the syndicated TV show, the Daily Buzz, quoted Dr. Streicher as saying, “We know that women that take an oral contraceptive can opt for a pill called YAZ, which is the only pill

that actually has scientifically been shown to get rid of not only the moodiness, the irritability and wanting to argue but it actually gets rid of the breast tenderness, gets rid of the dreaded bloat and gets rid of those few extra pounds and that makes a huge difference in how you go about your daily life and how you relate to the people who are important to you.”

(BHCPYAZ026202622-636 at 627-628, LP-475).

379. The transcript of a broadcast on KIMT-TV on July 25 quoted Dr. Streicher saying, “They can opt for an oral contraceptive called YAZ, which is the only pill that actually treats symptoms of not only these emotional problems but it takes off a few pounds and gets rid of the breast tenderness. It makes you feel better about yourself so that you’re not arguing with your partner.” (BHCPYAZ026202622-636 at 631, LP-475).

380. In a July 06, 2005 email, Bayer employee Kimberly Schillace to Leslie North wrote with regard to “YAZ PMDD and consumers.” “We may want to consider developing an unbranded pr campaign as well. It is something we can do through a third party even if we don’t get the indication.” (BHCPYAZ008274975-976 at 975, LP-153).

H. Bayer Extensively Promoted YAZ And Yasmin “Off-Label” Directly To Consumers As Well As Physicians

381. Bayer directly promoted YAZ and Yasmin to consumers, which is permissible under the law. Off-label direct to consumer advertising is illegal under the Federal Food Drug and Cosmetic Act.

382. Bayer knew that, according to the PhRMA guidelines, that FDA requires all DTC information “To be consistent with the FDA-approved labeling.” (PL-380, p. 3).

383. Bayer used Ogilvy Public Relations Worldwide in its advertising, public relations and promotional activities. (BHCPYAZ026067979-995, LP-474).

384. As documented above, Bayer marketed and promoted Yasmin and YAZ for off-label indications.

385. In an effort to “Differentiate YAZ from competitors and hasten uptake via multi-faceted consumer communications campaigns,” (BHCPYAZ026067979-995 at 981, LP-474) the YAZ Public Relations Strategy “reframed PMDD as severe menstrual symptoms to optimize awareness,” and bundling “with broader lifestyle issue” (BHCPYAZ026067979-995 at 984, LP-474).

386. Bayer had a media strategy surrounding YAZ’ approval with a goal to maximize media coverage in broadcast and print publications. “We are aggressively pursuing all women’s and national magazines.” “High profile media placements include the *Associated Press* (international and national), *The Wall Street Journal*, *CNBC-TV*, *National Public Radio (NPR)* and *CBS MarketWatch*.” (BHCPYAZ008500767, LP-126).

387. YAZ public relations efforts targeted and obtained placements in, among others, the Associated Press; New York Times; Wall Street Journal; USA Today; Daily Buzz; Fox and friends (national); Glamour Magazine; Good Housekeeping; Elle magazine; Family Circle; Cosmopolitan magazine; Shape magazine; Redbook magazine; WCBS – TV New York; Wal-Mart radio network; Reuters; Bloomberg; NPR; Lifetime; XM radio; Dow Jones; Voice of America; More; Marie Claire; Health; Self; Latina; and Woman’s World. (BHCPYAZ026067979-995 at 985-986, LP-474).

388. The messaging included: 1) “YAZ is the only OC demonstrating clinical significance in treating premenstrual irritability, moodiness, anxiety, bloating and increased appetite severe enough to impact a woman’s relationships, activities and work” and 2) “YAZ is a ‘must have’ this season because it goes beyond birth control to alleviate premenstrual symptoms

and acne – thereby helping woman to feel their best ‘inside and out.’” (BHCPYAZ026067979-995 at 987, LP-474) and 3) “For women who are looking for oral contraception and relief of PMS symptoms in one pill, the only FDA-approved oral contraceptive is YAZ.” (BHCPYAZ026067979-995 at 991, LP-474).

389. On March 24, 2006, Rose Talarico in an Executive Summary Memo discussing YAZ Approval Media Update stated: “To date, more than 120 media outlets have covered the FDA approval of YAZ, resulting in more than 10 million branded media impressions in the U.S. (emphasis in original). High profile media placements include the *Associated Press* (international and national), *The Wall Street Journal*, *CNBC-TV*, *National Public Radio (NPR)* and *CBS MarketWatch*. As part of our media strategy to maximize this major milestone for YAZ, we will continue to contact press to arrange interviews with our spokespeople and secure additional articles. To date, we have confirmed strong interest from *CNN ‘American Morning;’ ABC News ONE; FOX NewsEdge; CNN Radio; ABC Radio Network* and *WebMD*. Additionally, we are aggressively pursuing all women’s and national magazines. [Emphasis added]. As part of our media relations efforts to support the publication of the Yonkers/Yale data, we secured five national magazine articles that appeared over the past two-to-three months (*Women’s Day, Shape, Allure, Elle* and *Prevention*; see attached), for a total circulation of more than 11 million. [Emphasis added]. Further, we have confirmed a future placement in *O, The Oprah Magazine* (June issue); with strong interest from *Glamour, Ladies Home Journal* and *Fitness Magazine*. Our next strategy for women’s/national publications is to ensure that YAZ is included and singled out as part of any annual birth control round-up stories throughout the year.” (BHCPYAZ008500767, LP-126).

390. In the December 2005 issue of Elle magazine referenced above, the article titled “PMS AND THE PILL,” stated, “Study author Kimberly Yonkers, MD, an associate professor of psychiatry, epidemiology, and public health at Yale, attributes the new Pill’s success to the drospirenone – which was modeled after an older diuretic drug that had been found helpful with PMS – and to the fact that the 28-day cycle of Pills contains only four nonmedicated days (as opposed to the typical seven). Yonkers says the new Pill, called YAZ, will likely be available within the year.” (BHCPYAZ012559819-820 at 820, Lezzaiq-24).

391. As noted below, Dr. Kimberly Yonkers was paid by Bayer for: attending a slide development meeting; an audio program; publication-forum; forum editorial board meeting; abstract presentation at ASRM; a YAZ advisory board meeting; and an ACOG symposium. She received from the company PMDD Speaker Training; and was a member of a working group for a publication. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). In a September 20, 2006 email from Berlex Rose Talarico to numerous Bayer employees, Ms. Talarico wrote: “Attached is a YAZ media placement we secured in the September issue of Healthmagazine. The article is titled ‘Savvy Solutions to Treat PMS and PMDD’ and mentions YAZ as an ‘OC that works as well as antidepressants in lessening PMDD symptoms.’ Kim Yonkers, who was interviewed for this article, is also quoted discussing YAZ for PMDD. Healthmagazine [sic] has a circulation of 3,798,950.” (BHCPYAZ008429897-902 at 897, PL-198).

392. Ms. Talarico continued: “fyi, this is the second YAZ PMDD placement that appears in a major national publication this month. As previously reported, we secured a YAZ article in the September issue of Alluremagazine [sic] (YAZ is featured at the end of the attached

article in the section called 'Breaking the Cycle of PMS'). The article highlights the results of the YAZ PMDD studies and quotes Terri Pearlstein discussing the benefits of YAZ. Allure magazine has a circulation of 2,578,000." (BHCPYAZ008429897-902 at 897, PL-198).

393. Dr. Pearlstein was quoted in the article. "The hormone in YAZ, drospirenone (also found in Yasmin), may curb PMS more than the progestins in other pills." (BHCPYAZ008429897-902 at 902, PL-198).

394. According to Bayer, Dr. Pearlstein received PMDD speaker training for YAZ and was paid for an audio program for PMDD (YAZ); and Slide Development for PMDD (YAZ). (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs' Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). Bayer targeted health editors and sent them YAZ branded flowers with the hope that they would cover the Parallel Study at the following magazines: Allure, Glamour, Jane, Lucky, Self, Cosmopolitan, Elle, in Style, Marie Claire, and Shape. (BHCPYAZ026058331-332, LP-352).

395. A January 30, 2006 email from Bayer Heather Levis to many Bayer employees stated, "The February 14th issue of Woman's Day features a terrific YAZ branded article entitled 'Birth Control + PMS, Relief in One' which focuses on the Parallel study results. Highlights of the article read as follows: 'If you experience severe PMS symptoms, such as mood swings irritability, anxiety, fatigue, breast tenderness, and increased appetite, new birth control promises to provide significant relief. The pill called YAZ contains drospirenone (a new form of progestin) in addition to estrogen, and uses dosing cycle of 24 days on, 4 days off. A recent study showed that the drug reduced symptoms of PMDD just as well as antidepressants.' Attached is scanned copy of the placement." (BHCPYAZ006703047-048 at 047, LP-210).

396. In a January 22, 2006 email from Bayer's sales consultant Perry "Matt" Sample, in discussing the Woman's Day article, stated, "This article is a nice way of using YAZ for PMS treatment instead of just focusing on the specific PMDD patient. USE: This write up mentions a few common menstrual symptoms, use this article to ask your DRs what they think the impact of YAZ will be. This article specifically mentions 'if you suffer from PMS or PMDD and also need contraception ask your DR about YAZ.' What percent of your patient population suffers from these common symptoms? I will bring with me copy to our Tuesday meeting for all to see, hope this helps." (BHCPSR000981070, Schnell-374).

397. A January 13, 2006 email from Heather Levis to many Bayer employees stated: "YAZ Branded coverage Shape Magazine: The February issue includes an article on YAZ titled 'A new cure for serious PMS' in the Live Healthy News section." (BHCPYAZ006752790-794 at 790, Schnell-375).

398. Direct to consumer advertising changes the role that physician play as intermediaries between pharmaceutical companies and patients.

399. Bayer understood and stated that "YAZ (and virtually all birth control pills) have become largely consumer brands, and the physician, consequently has become a 'dispenser' rather than an advisor." (BHCPYAZ012667671-688 at 680, Lezzaiq-40).

400. A Global Brand Marketing Plan for Yasmin identified that one of the "Global Marketing Effort Priorities" was to "Utilize global PR around the 'drsp' evidence/data we have so women see 'drsp' as the 'must have' component." (BSPYAZ004306340-419 at 365, Lezzaiq-16).

401. A Bayer document that was attached to an email from Beth Bell to Heike Prinz and titled, "Yasmin for Newsletter 12.7.ZIP" stated, "The role of public relations and media

outreach in the success of YASMIN was extremely successful. Favorable YASMIN mentions appeared in the ‘what’s new’ and ‘women’s health’ sections of every leading magazine targeted to our audience. Dr. Judith Reichman, the medical correspondent of the Today show, was a strong on-air supporter and YASMIN was mentioned favorably on all major news and talk shows. Public relations started a ‘buzz’ about the product and its unique benefits that we could not directly address in our paid promotion. PR messaging was based upon YASMIN/drsp’s unique chemistry and menstrual cycle benefits.” [Emphasis added]. (BHCPYAZ008393865-867 at 866).

402. In this same document, Bayer stated, “A first for Berlex, Direct-to-Consumer (DTC) promotion was launched six months after product introduction. The positioning for the brand followed a similar approach as with the physician campaign highlighting how ‘chemistry makes the difference’ and that the chemistry of YASMIN is different. Similar to physicians, this message tested well with consumers and enabled us to achieve true synergy between the professional and consumer audiences. The ‘couple with the right chemistry’ was used in DTC promotion. Initial DTC promotion targeted print and popular magazines targeted at 18-24 year olds. TV was added in 2002 and has been successful in driving our target audience to their physicians to request YASMIN. As stated at the outset, drsp is what differentiates YASMIN from the 40 other OCs on the US market. Drsp will also be instrumental differentiator for YAZ...” (BHCPYAZ008393865-867 at 866-877).

403. Bayer understood the effectiveness of direct-to-consumer advertising.

404. For example, a document that included 2004 lessons learned stated: “Experience with DTC in 2003 and again in 2004 demonstrated that DTC has the ability to drive consumer awareness to a certain level in print, with TV further increasing awareness and growth

rate. In 2004, alongside a national print campaign that continued from the previous year, a 20 market TV campaign was launched for Yasmin. The top 20 Yasmin markets were selected based on Yasmin market share versus the national average (at or above). Concurrently, relationship marketing efforts continued to target on-line media to generate interest and awareness.” (BHCPYAZ009460069-213 at 119, PL-423).

405. The document continued: “To date, the Yasmin DTC campaign continues to be successful in building upon the awareness levels generated from the previous year. A noticeable decline in awareness was noted shortly after the campaign went dark upon receiving the FDA letter (to 10% from 13%). However, since then, our awareness levels have climbed back (up to 16%) and within the 20 markets where the TV commercial is airing, awareness levels have increased to 35% for total brand awareness, up from 19%. Initial ROI analyses show fluctuations versus the controls but are encouraging while we await results for month-5 post campaign launch, the month of greatest impact as demonstrated by the Heavy Up test conducted in 2003. These initial results not only show that awareness levels have increased substantially, but that weekly ROI have been able to hit breakeven levels. Based on results to date, the project ROI is estimated to reach 1:2.48 over 22 cycles.” (BHCPYAZ009460069-213 at 119, PL-423)

406. They “involved compelling spokespeople” to market and promote YAZ for its impact on PMS and lifestyle.” (BHCPYAZ026067979-995 at 988, LP-474).

407. On behalf of the company, a relationship expert stated on “Fox & Friends” that “There was a recent study done by YAZ. And they found that 50 percent of men and women say one of the biggest saboteurs for relationships is moodiness... And... If we’re women... we end up with those premenstrual symptoms that sometimes happen.” (BHCPYAZ026067979-995 at 989, LP-474).

408. As noted above, on behalf of the company, OB/GYN, Dr. Laura Streicher, stated in a television interview, “We know that women that take an oral contraceptive can opt for a pill called YAZ, which is the only pill that actually has scientifically been shown to get rid of... the moodiness, the irritability and that makes a huge difference in how you go about your daily life and how you relate to the people who are important to you.” (BHCPYAZ026067979-995 at 989, LP-474).

409. One of the key messages was: “For women who are looking for oral contraception and relief of PMS symptoms in one pill, the only FDA-approved oral contraceptive is YAZ.” (BHCPYAZ026067979-7995 at 991, LP-474).

410. In one public relations campaign, YAZ was positioned as a “must-have” fashion accessory.” (BHCPYAZ026067979-995 at 994, LP-474).

411. A young, hip fashion stylist was enlisted to promote the product. On the fashion stylist’s blog it stated “YAZ ME! Want clearer skin, no bloating or mood swings, and daily birth control?” (BHCPYAZ026067979-995 at 994, LP-474).

412. In 2008, the YAZ DTC consumer budget was \$58 million; in 2009 it was \$65 million; and in 2010, \$64 million. (BHCPYAZ023437205-247 at 208, PL-362).

413. Bayer understood that “90% of women that ask for a specific contraceptive brand get it.” (BHCPYAZ009460069-213 at 174, also see at 104, PL-423).

414. In my opinion, Bayer’s direct to consumer promotion, including that for “off-label” uses, altered the role that physicians play as “learned intermediaries.” Bayer’s off-label promotion of Yasmin and YAZ was in violation of Federal law and its duty of care.

I. Bayer Developed And Implemented A Global Communication Plan That Involved Drafting And Writing Articles On Yasmin and YAZ For Physicians To Author In Medical Journals

415. Adis International Ltd (Adis) was invited by Heike Prinz, Schering AG (SAG), GBU G&A, Corporate Strategic Marketing, Female Contraception, to submit a proposal for global communication planning activities for the PMDD/PMS indication of YAZ from 2004 to 2008, as part provision of service that is covered and defined in the Master Services Agreement dated November 25, 2004. (BHCPYAZ012216289-310 at 291, Lezzaiq-39).

416. Adis had a strategy of “US market penetration and ex- US market awareness is reflected in the development plans for Key Opinion Leaders (KOLs). This is a critical activity as the identification, education, support and empowerment of a pool of global KOLs to become product champions for YAZ in the PMS/PMDD indication will be a key factor in the successful commercialization of the product and penetration into the target markets. KOLs can play a crucial role in helping generate the necessary evidence to support SAG’s desired positioning and marketing messages for the product, as well as informing key audiences about YAZ and influencing prescribing behaviour.” (BHCPYAZ012216289-310 at 296, Lezzaiq-39).

417. One of the objectives was to “Identify and develop a pool of established KOLs and future ‘rising stars’ that can be called upon to author papers, present data at congresses and support educational and promotional initiatives.” (BHCPYAZ012216289-310 at 296, Lezzaiq-39).

418. According to one Bayer employee “the global publication plan (that it is executed through the master agreement done with ADIS); this would also include the YAZ publications that Berlex proposed and were agreed upon few months ago.” (BHCPYAZ002459580-582 at 581, Lezzaiq-41).

419. YAZ draft key messages included “YAZ is the first OC with proven and unique positive effects on (PMS)/PMDD”; “YAZ significantly improves symptoms and functional impairment associated with (PMS)/PMDD”; “YAZ is effective in reducing both physical as well as mood-related symptoms in women with (PMS)/PMDD.”; “YAZ is as effective as SSRIs in treating symptoms of PMDD.” (BHCPYAZ012216289-310 at 299, Lezzaiq-39).

420. The process of publishing articles included: “1) Berlex briefs ADIS, 2) Berlex follows up on the outline development, target journal suggestion, etc... 3) Berlex coordinates the contact with the authors/KOLs, 4) Berlex, authors and GBU (Marr and I) receive the first, second and final drafts, 5) GBU (I in this case) post the finalized draft for the two weeks internal approval, 6) Berlex follows up on the comments (if any) with ADIS.” (BHCPYAZ002459580-582 at 582, Lezzaiq-41).

421. Medical Articles prepared under this process included “YAZ Quality of Life Review Paper.” (BHCPYAZ012165328-5339 at 335, Lezzaiq-45).

422. On January 22, 2004, Sarah Bradbury of Adis sent Dr. Patricia Sulak an email that stated: “Dear Dr [sic] Sulak, Please find attached the Yasmin-20 efficacy study manuscript, on which you are co-author, for your review. Please could you return any comments you may have to me by” (BHCPYAZ009829091-118 at 091, Bell-35).

423. On April 14, Bayer’s Samer Lezzaiq wrote to Beth Bell, attaching “finalized drafts” and asked “would you kindly suggest US authors for both abstracts within next week.” (BHCPYAZ009334450-453 at 450, Lezzaiq-55).

424. On September 4, 2009, Account Executive Melanie West wrote Bayer’s Richard Lynen to follow-up if he “made any progress with contacting Andrea Rapkin and her

authorship of the PMDD Functional Impairment paper?” (BHCPYAZ006460200-207 at 200, Lezzaiq-57). Lynen had previously written, “I have no strong preference for which individual is associated with a particular topic. Personally, I see Andrea Rapkin as ‘fitting’ with the functional impairment piece as she is quite involved in PMDD research.” (BHCPYAZ006460200-207 at 202, Lezzaiq-57).

425. According to Bayer, Dr. Rapkin was paid for: presentations in Greece; Audio; ACOG Symposium; Monographs; Roundtable for Journal Supplements; Journal Supplements; Slide Development Meeting; Publication—Forum and participated in PMDD Speaker Training for YAZ. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010).

426. Other publications were planned to be published in medical journals including articles on “Two Acne Studies” and “Mood and behavioral effects of progestins included in OC’s and other hormonal contraceptives (as well as allopregnanolone and similar metabolites). influence on CNS Systems and Influence on symptoms-- mood, cognitive, anxiety, irritability. This is as a direct effect as well as reports of adverse effects.” The authors were “TBD” (to be determined). (BHCPYAZ00835415-421 at 415-416, Lezzaiq-44)

427. On January 26, 2004, Susan Cook wrote to Berlex’s Barry Lee that said: “As you know we had a conference call with Kim Yonkers last week regarding the article on PMDD. She believes that we can get into JAMA and we are writing the article with that submission in mind. I am attaching the first draft of the outline of the article. We are sending it to Dr. Yonkers for her feedback as well. We hope to have most of the up front part complete so that when we get

the numbers we can drop them in and submit. Please let me know your feedback.”

(BHCPYAZ009288198-203 at 198, Bell-34).

428. On July 20, 2005, Sherry Thompson, Vice President Operations of MedPro Communications, sent an email to Terri Pearlstein and Kim Yonkers, among others, that stated, “Attached please find the final documents submitted to Dr. Daniel Mishell and Contraception. I spoke with Dr. Mishell and he suggested January for a publication date if accepted, but agreed to try for October when I told him we were hoping for an earlier publication.” Attached to that email, was a letter from Dr. Terri Pearlstein to Dr. Mishell, which stated, “None of the authors has direct or indirect commercial financial incentive associated with publishing the article.”

(BHCPYAZ001256671-698 at 672-673).

429. As noted above, Kim Yonkers was paid by Bayer for: attending a slide development meeting; an audio program; publication-forum; forum editorial board meeting; abstract presentation at ASRM; a YAZ advisory board meeting; and an ACOG symposium. She received from the company PMDD Speaker Training; and was a member of a working group for a publication.

430. As noted above, according to Bayer, Dr. Pearlstein received PMDD speaker training for YAZ and was paid for an audio program for PMDD (YAZ); and Slide Development for PMDD (YAZ). (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010).

431. In response to a potential published journal article that raised concerns about increased VTE risk of Yasmin, Bayer employees, drafted a response. (BHCPYAZ014426282). On January 31, 2002, Bayer employees that were members of a “Working Group” shared data

needed for the draft letter. (BHCPYAZ014426282-286 at 282). One member of the “Working Group,” Barry Lee, wrote, “Here are many of the facts and figures needed for the draft letter....My greatest concern at this moment is that this letter will get published before we create the necessary pieces internally. Every Ortho representative in this country will use this information as a visual aid if given the chance, and we all know how they will embellish the story. We have a tremendous year going for Yasmin, I just do not want us to get derailed.” (BHCPYAZ014426282-286 at 282). Another Bayer employee, in an email on February 1, 2002, “Re: LAREB Working Group Notes” included an attachment titled, “LAREB NOTES FOR DRAFT LETTER.” In that attachment item “VI” stated, “Will discuss the use of a third party group, or an advisory board response at the next meeting. We will coordinate these activities with SAG.” Item “X” stated, “Deadline for draft letter Tuesday February 5th.” (BHCPYAZ014426282-286 at 283). On February 1, 2003, a “Drug points” titled, “Thromboembolism associated with the new contraceptive Yasmin” was published in the British Medical Journal (BMJ) by the Netherlands Pharmacovigilance center LAREB. (Schellschmidt-109). On Sunday, February 2nd, Bayer’s Jeff Frick wrote an urgent email regarding “BMJ/Yasmin/VTE” to Robert Taylor stating, “Our friends at BMJ are at it again....How are you planning to handle this issue?...” (BHCPYAZ014166355-357 at 355). On February 24, 2003, a “Task Order” was entered into between Berlex and MedPro Communications, Inc., citing the fact that the British Medical Journal recently published a letter from the Dutch Drug Safety group LAREB. The Task Order stated, “In order to provide current information on contraception and VTEs to the practicing healthcare provider, MedPro Communication, Inc. is proposing that ‘Letter to the Editor,’ both in the journal and mailed, and CME journal supplement be written. Initially, a ‘Letter to the Editor’ will be written, signed by five physicians and submitted to the

Journal of Reproductive Medicine. Upon acceptance, it will be placed on the JRM website and included in the next issue.” The Task Order included in its cost estimate, among other costs, “Writing ‘Letter to the Editor’” and “Write, distribute and submit ‘Letter to the Editor.’” (BHCPYAZ019226581-582). On February 24th, Bayer’s Barry Lee writes an email to three of Bayer’s KOLs, Drs. Shulman, Thorneycroft and Sulak and reminds them of a conference call to be held that day. The email stated, “You will also find an attachment [named “2.24.03 Draft to KOLs.doc.”] of the proposed letter addressing the VTE issue. We can use this draft as a point of reference for what needs to be incorporated in each of the personal letters.” (BHCPYAZ009188470-472 at 470, PL-20). [Note: I requested from counsel to see versions of “Draft to KOLs.” The earliest “Draft to KOL” contained in the MedPro document production was a native Microsoft Word file whose author was identified as BI05653; the company was identified as Berlex Laboratories; the last modified date was Sunday, February 23, 2003, 9:00:26; and last printed date was 2/12/2003, 12:39PM. (Screen-shot of “2.24.03DrafttoKOLs properties). The closure of the letter indicates after the word “Sincerely,” “(name) (affiliation)”. (Screen-shot of “2.24.03DrafttoKOLs, last modified 2/23/2003 9:00PM). (See also re: BI05653: BHCPYAZ015655334-335 with metadata; BHCPYAZ016044746 with metadata; BHCPYAZ016014011-012 with metadata. On February 25, 2003, MedPro Vice President for Operations, Sherry Thompson, wrote to one Bayer’s KOLs, Dr. Joseph Goldzieher, “Berlex called us yesterday after their discussion about DVTs and VTEs with you and Drs. Shulman, Thorneycroft, Sulak. They have asked us to help facilitate the following: 1. A letter to the editor that will be signed by all four doctors 2. A supplement that will go into greater detail on these issues. Dr. Lee Shulman has agreed to author the letter that you will each need to review. We hope to have a draft to you by the end of Wednesday or early Thursday. Berlex is hoping to

disseminate this letter early next week. So that the letter can be set up to be emailed, we would like electronic signatures that can be included on the letter.” (BHCPYAZ019226529). On February 27, 2003, Bayer’s Barry Lee wrote to Bayer’s Dr. Marie Foegh and stated, “It is amazing, consensus was reached on the composition of this letter at 8:00PM tonight. It is attached below for you to route to Dr. Dinger . . . This should go out with the April issue and correspond with Donna Kessel’s ACOG issue. Timing is everything. Please provide me Dr. Dinger’s comments, if any, and I will pass them on to Susan Cook at MedPro Communications.” (BHCPYAZ009191804-807 at 804, PL-22). In a February 28, 2003 email Bayer’s Dave Vilushis, Field Support Manager, wrote to numerous Bayer colleagues, “Item #1 is a powerful letter which was crafted by a number of national opinion leaders which supports the safety of Yasmin with their endorsement. Remind physicians when this is brought up in offices that this is coming from a third party and not from Berlex Laboratories.” (BHCPYAZ009096664-666 at 664, Foegh-46). Attached to that email is a memo addressed to FHC sales representatives, DMs, FSDs which stated, “National Opinion Leader letter of support about safety Conference call held on Monday February 24th to discuss content and signatures with Key Opinion Leaders (Lee Shulman, Patricia Sulak and Joseph Goldzieher). This letter will be distributed to every SC to dismiss concerns brought up by competitors as well as patients.” (BHCPYAZ009096664-666 at 665, Foegh-46). On March 11, 2003, Bayer’s sales manager, Rusty Thomas (FHC District E-7) wrote to his team, attaching a letter “We have approval to get this Thought Leader Support Letter out to you. Feel free to print it out and give to/use with your customers as needed. You may want to laminate a copy to have in your binder as well.” (BHCPYAZ010527167-170 at 167). On April 16, 2003, Bayer Field Support Manager Dave Vilushis wrote to numerous Bayer colleagues . . . “the Key Opinion Leader’s letter that you and your SCs recently received, has

been published on the website of the Journal of Reproductive Medicine . . .”

(BHCPYAZ008972286-289 at 286). In an attached email, Bayer’s Barry Lee writes: “Hi Everyone, Look what just appeared on the JRM Website: Happy Sales, Remember this is taking the ‘High Road.’ Enjoy the reading . . . make sure the Field Sales Group is aware of this valuable resource. Marketing will also be making JRM Hard Copy (Jacketed Cover) available to the field. We will also have these pieces for ACOG.” (BHCPYAZ008972286-289 at 287).

Attached to those emails is a version of the letter titled, “Oral Contraceptives and Venous Thromboembolic Events.” At the end of the letter is the sentence “Financial Disclosure: The authors have no connection to any companies or products mentioned in this letter. . . .” (J Reprod Med 2003; 48:3060, 0307). (BHCPYAZ008972286-289 at 288). On or about April 14, 2003, Bayer’s Dr. Marie Foegh wrote to Bayer’s Barry Lee and colleagues, “Re: JRM Letters to the Editors. htm”, the following: “It is a great letter. However, one little ? mark. Why did the authors state ‘no connections to any companies or any product mentioned in this letter’?”

(BHCPYAZ015495361-364 at 361). In an April 17, 2003 email from Bayer Dr. Marie Foegh to Bayer colleagues, Dr. Foegh states, “It is a great letter but the spoils are at the bottom of the page under financial disclosure where it is stated that the authors have ‘no connections to any companies or any products mentioned in this letter.’ The competition may pick-up on this.”

(BHCPYAZ015493165-168 at 165, Frick-60A). A letter to the editor signed by Lee P. Shulman, MD, Joseph W. Goldzieher, MD, Mary Jane Minkin, MD, Patricia J. Sulak, MD, and Ian Thorneycroft, MD, Ph.D. appeared in the Journal of Reproductive Medicine, Vol. 48, No. 4, April 2003 and contained financial disclosures that stated, “Dr. Shulman is a consultant and speaker for and receives research support from Berlex Laboratories, Ortho-McNeil and Pharmacia. Dr. Goldzieher is on the safety review board overseeing the European phase IV trial

of Yasmin® vs. other oral contraceptives in 30,000 subjects. Dr. Minkin is on the speakers' bureau of Berlex Laboratories, Eli Lilly, Pfizer and Organon. Dr. Sulak is on the speakers' bureau of Berlex, Barr, Wyeth and Organon and is a consultant to Barr. Dr. Thorneycroft is on the speaker's bureaus of and gives lectures for Berlex Laboratories, Merck, Solvay and Wyeth." (BSPYAZ015728968-969 at 969). On May 12, 2003, Bayer's Jonathan Alexander wrote to Bayer employees, "Cease and desist from using copies of the opinions leaders letter. I think we got some good mileage out of this, and we can always reference the original article published in the April journal." (BHCPSR001093039-40 at 39). On that same day, Bayer's David Sullivan wrote to colleagues, "I received a call late today (05/12/03) from the Journal of Reproductive Medicine urgently asking that we comply with a number of requests...the Journal's editor has requested that we not distribute photocopies, PDF versions or other facsimiles of the letter. Furthermore, they've requested that Berlex destroy all copies of the letter that are not an original part of the April edition....Berlex respects the integrity of the Journal...." (BHCPYAZ001093039-40 at 40).

432. According to Bayer, payments to Dr. Shulman in 2002 included a JRM Supplement for \$1500; in 2003 a publication forum for \$6000, two JRM Supplements for \$2000 and \$1500, an advisory board meeting on YAZ for \$2000, a lunch and learn video for \$1500; in 2004 a speaker training session for \$1500, a forum editorial board meeting for \$8000, a pri-med symposium for \$1500, two publication forums for \$2000 each, a symposium for \$1500, a monograph for a symposium for \$1000, an advisory board meeting for YAZ for \$2000; in 2005 a forum editorial meeting for \$8000, a publication forum editorial meeting for \$3000, a symposium for \$1500, a poster presentation for \$1500, a monograph for a symposium for \$1500; in 2006 a forum editorial board meeting for \$8000, a symposium for \$1500, in 2007 for a YAZ

podcast for \$1500, two NP update meetings for \$2000 each, a speaker training telecom for \$1500, a leadership advisory board meeting for \$2000, an advisory board meeting for \$2000; and in 2009, a short-term hormonal advisory board for \$2500, and a speaker training meeting for \$1000. According to Bayer, payments to Goldzieher included in 2003 for a JRM Supplement for \$3000, and in 2005 a publication forum for \$1500. According to Bayer, payments to Minkin included in 2004 two symposia for \$1500 each, two symposia for \$1000 each, in 2005 a pri-med update for \$1500, a pri-med update for \$3000; in 2006 two symposia for \$1500 each, a symposium for \$2000; and in 2009 a short-term hormonal advisory board for \$2500, a speaker training telecon for \$500, and a symposium for \$2500. According to Bayer, payments to Sulak in 2003 included for a symposium for \$1500, a symposium for \$1000, a symposium for \$2000, female patient article on Yasmin for \$4000, an advisory board meeting on YAZ for \$2000, a POA video for \$1000, a lunch and learn video for \$1000; in 2004 a speaker training session for \$1500, another speaking training session for \$1500, a meet the experts session for \$1500, a slide kit for Yasmin for \$1500, for a pri-med symposium for \$1500, a publication forum for \$2000, an ACOG symposium for \$1500, an advisory board meeting for YAZ for \$2000, a “worth the wait” meeting for \$1500, in accord with the ISS budget in 2004-05, \$67,095.50 with a balance owed of \$143,417.50 related to a YAZ efficacy manuscript (BHCPYAZ014190683, BHCPYAZ014424878-911, BHCPYAZ008567017-19); in 2005 an ACOG symposium for \$1500, a monograph for an ACOG symposium for \$1000, a slide development meeting for \$1500; in 2006 a forum editorial board meeting for \$2000, a publication forum for \$1000, and in 2009, a speaker training telecon for \$500. According to Bayer, payments to Thorneycroft in 2001 included a symposium for \$1750; in 2002 a symposium for \$1750, an audio for \$1500, a JRM Supplement for \$1500; in 2003 a publication forum for \$4000, a JRM Supplement for

\$1500; in 2004 a speaker training session for \$500, a forum editorial board meeting for \$2000, a publication forum for \$2000; in 2005 a pri-med update for \$1500, a forum editorial board meeting for \$2000, a publication forum for \$1500; in 2006 a forum editorial board meeting for \$2000, a publication forum for \$1000; in 2007 a regional advisory board speaker training session for \$4000, a speaker training meeting for \$1000; and in 2009, a speaker training meeting for \$1000. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs' Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010).

433. According to a Bayer Publication Report Q4 2009, an article involving "Response to different pharmacological treatments for PMS/PMDD (background paper)" was "Published in Full." (BHCPYAZ017985839-885 at 847, Lezzaiq-49).

434. In my opinion, Bayer attempted to influence the practice of medicine and increase the prescribing of Yasmin and YAZ by preparing articles that physicians could author and which were published in medical journals.

J. Bayer Had A Medical Publication Strategy To Influence How PMDD And PMS Were Defined

435. A March 31, 2008 draft Marketing Plan, discussed above, stated under the heading, "Publications *Focus of Effort*" that the goal was to: "Provide common international definition of PMS/PMDD with supporting guidelines from third party professional organization to diagnosis and treat, include the definition in the ICD-11;" "convey our key messages (esp. on PMS/PMDD and acne)"; and "Create/Raise awareness to PMS/PMDD." (BHCYPAZ006141556-627 at 607, PL-195).

436. In a draft article, written with Bayer's Dr. Paul Korner's involvement, Bayer highlighted the view that the diagnostic criteria of PMDD were too restrictive. (BHCPYAZ006126622-634 at 627 and 634).

437. Bayer planned a PMS/PMDD Consensus Group meeting on October 24, 2005 in Amsterdam. (BSPYAZ005174841-010 at 878; Lezzaiq-10, p. 38).

438. One of the "main goals" of the meeting was to "arrive at recommendations for diagnostic criteria for Premenstrual Syndrome with the ICD-10 as the departure point." Bayer also had as its goal to "negotiate endorsement of our proposed criteria by International and Major National Professional Organizations, mainly the fields of Ob/Gyn and Psychiatry." The goal was also to "negotiate endorsement of our proposed criteria by WHO and WPA Committees for the ICD-11 – as replacement of the current ICD-10 entity of PMS." Twenty experts were invited to the meeting. One to 2 observers from Schering who were not actively participating in the content of the consensus attended. (BSPYAZ005174841-010 at 878-880; Lezzaiq-10, pgs. 38-40, Bates numbers are absent from the document).

439. In an article that was part of Bayer's Global Marketing Substrategies and Action Plans, "a PMS Consensus Paper" was published titled, "Clinical diagnostic criteria for premenstrual syndrome and guidelines for their quantification for research studies," which stated that "furthermore, the issue of PMDD being a separate diagnostic entity independent of PMS is still unresolved." (BHCPYAZ007738212; BSPYAZ004306033 and PL-195).

440. In a Global Brand Marketing Plan for Yasmin LCM, a Global Marketing Effort Priority was identified to "Lead the development and agreement of a common international definition of severe PMS/PMDD with supporting guidelines to diagnose and treat - possibly

through the creation of an international professional PMS physician society.”

(BSPYAZ001540805-884 at 830, Lezzaiq-18; BSPYAZ004306340-419 at 365, Lezzaiq-16).

441. Bayer carried out a “PMDD Indication Campaign for YAZ” that included “Work with PMS/PMDD guidelines committee, third party groups.” (BHCPYAZ026054360-408 at 392, PL-422).

442. A “Focus of Effort” of Bayer’s global opinion leader development was to “Establish consensus for the definition of PMS/PMDD including treatment guidelines.” (BSPYAZ001540805-884 at 842, Lezzaiq-18; BSPYAZ004306340-419 at 377, Lezzaiq-16).

443. Part of the “PMDD Indication Campaign for YAZ” included pursuing a “Lifestyle program for consumer/lifestyle media.” (BHCPYAZ026054360-408 at 392, PL-422).

444. Part of the “PMDD Indication Campaign” involved “Strategically leverage SSRI safety concerns, side effects.” (BHCPYAZ026054360-408 at 392, PL-422).

445. In my opinion Bayer’s efforts to influence the diagnostic criteria of PMS and PMDD was consistent with their stated goals of expanding the market potential for YAZ and Yasmin beyond the approved indications.

K. Bayer Sponsored CME Activities, Which Apparently Were Not Independent, At Which Off-Label Uses Of Yasmin Were Promoted

446. Medical education that is not independently developed and organized may not promote non-approved use. Such non-independent “educational” efforts are no more permissible than having sales representatives promote such use. (*Guidance on Industry Supported Scientific and Educational Activities*, 62 Fed. Reg. 64093 (Dec. 3, 1997)).

447. Bayer had a strategy in 2004 to “Saturate DRSP clinical differentiation through CME initiatives.” No clinical differentiation due to DRSP was approved to allow such claims to be made for Yasmin. (BHCPYAZ009460069-213 at 119, PL-423).

448. One of the company’s corporate objectives was “support off-label promotion of Yasmin via publications, symposia.” (Lezzaiq-14, p. 65)

449. A Bayer transcript of a CME meeting in New Orleans involving Dr. Daniel Mishell and Dr. Patricia Sulak as speakers began with Dr Mishell stating: “we’re going to have a very interesting symposium this morning entitled, ‘Understanding Contraceptive Choice: The Patient’s Perspective.’ It’s a CME program, and it’s jointly sponsored by the Dave Miller Memorial Educational Foundation [sic] and MedPro Communications. And you’ll receive two hours of credit for attending this symposium.” (BHCPYAZ019186868-911 at 868).

450. The transcript demonstrates that off-label indications were discussed for Bayer’s DRSP containing Yasmin oral contraceptives. (BHCPYAZ019186868-911).

451. For example, Dr. Mishell stated, “Just to summarize the effect of this agent, there’s the antiandrogenic effect, which leads to acne improvement, antiminerlocorticoid effect, which decreases the ethinyl estradiol bloating and water retention. And probably both these effects lead to this feeling of well being.” (BHCPYAZ019186868-911 at 878).

452. Dr. Sulak stated: “if we could take just 60 seconds just to tell her a lot of these benefits, maybe when she has a few side effects, maybe she’s going to be, ‘Wait a minute. I really need to continue these, because there’s--it’s more than contraception.’ The menstrual cycle symptom control, less bleeding, less cramps, less PMS type symptoms, the beneficial effects on the breasts, less fiber cystic changes, less fibroadenomas.” (BHCPYAZ019186868-911 at 880).

453. Dr. Sulak also stated: “The antiminerlocorticoid effects--I mean, it is a diuretic. And like I said, with spironolactone, it has been shown to help the negative mood that can occur and help with these physical symptoms--the bloating and the weight gain that you get during that time. Improvements in emotional versus physical symptoms--in limited data with drospirenone--but there is some data coming out, which is kind of exciting, because if we use spironolactone for these symptoms, and it’s been shown to work, can we give these analogue, which is a lower dose, and would it be effective in helping some of these symptoms that women get when we start oral contraceptives? And this was just one study that was published in contraception. Looking at all of these variables from impaired concentration, negative affect, water retention, increased appetite, hair change, feelings of well being. And what was statistically significant was from baseline to cycle 6, a decrease in the negative affect and a decrease in water retention and increased appetite. These were statistically significant from baseline and then measuring at Cycle 6. And then another study here published--if you see, these are negative numbers. And if you look at all of these factors that they were studying in COPE[?], because COPE studies all of these, patients are really--it’s pretty incredible that they actually fill out all these diaries. But as you can see here, with drospirenone, YASMIN, there’s a greater reduction in almost all of these parameters that they studied. But what was significant was this--there was a greater decrease in patients feeling that they want to be alone. A lot of times patients isolate themselves. And these women were more apt to want to get out. They didn’t want to feel so isolated. And also they didn’t have this great increase in appetite. This was--even though this is a negative number, it looks like their appetite was greater. What it was was there was less appetite changes.” (BHCPYAZ019186868-911 at 884-885).

454. A Dannemiller Memorial Education Foundation “Application for CME Activity” for a symposium/meeting on “Understanding Contraceptive Choice: The Patient’s Perspective” that for which recommended faculty included Dr. Daniel Mishell and Dr. Patricia Sulak, among others, documented an anticipated budget of \$135,000 for the symposium and \$134,000 for a monograph with Bayer’s David Sullivan as the potential source of funds.(BHCPYAZ019226137-141). The budget included payment for faculty honoraria. A Yasmin “Marketing Analysis Spending Report” documented numerous payments to Dannemiller and Dannemiller/MedPro. (BHCPYAZ016296677-703 at 683, 689,700-701 and 703).

455. Both Dr. Mishell and Sulak coauthored articles that were supported by the company. Also, Dr. Sulak and Mishell both reported that they received financial remuneration for grant/research/consultant activities and in the case of Dr. Sulak also for the speakers’ bureau. (<http://www.ajmc.com/publications/supplement/2005/2005-12-vol11-n16Suppl/Dec05-2233pS470>).

456. According to the Company, Dr. Mishell attended, and/or spoke at various medical conferences and events where Yasmin and YAZ were referred to including continuing medical education (CME) in 2003, 2004, 2005, 2006, 2007, 2008, 2009, and 2010. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). According to Bayer, Dr. Mishell was a member of the company’s contraceptive advisory board in 2003 and 2008; a member of the 2004 VTE review board that provided consultation to the company; a member of the 2004 advisory board to provide consultation to the company; a member of the working group for publication known as the Forum in 2004, 2005 and 2006; a member of the medical review Board that provided

consultation to the company in 2006 and 2007; a member of the 2008 women's healthcare regional advisory board that provided consultation to the company; was a member of the company speaker panels and/or attended speaker training meetings related to Yasmin and or YAZ in 2004 and 2008; and received PMDD speaker training for YAZ. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs' Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). Dr. Mishell received the following payments from Bayer: In 2003, \$1500, \$1500, and \$1500 for symposiums; \$1000 and \$1000 for monographs from a symposium; \$3000, \$3000, and \$4500 for an advisory board meeting on YAZ; in 2004 \$3000, \$5000, \$3000, \$3000, \$3000, and \$3000, for speaker training; \$1500 and \$1500 for slides for YAZ and Women's Health; \$4500 for Ask the Experts session at an ACOG meeting; in 2005, \$2500 for a position paper on YAZ, payments for slides of \$4500; \$1000 for PMDD(YAZ); \$1000 for monographs on PMDD (YAZ); \$1500 for an audio program on PMDD(YAZ);\$3000 and \$1000 for meetings on PMDD (YAZ), \$7500 for speaker training teleconferences on PMDD (YAZ), \$2000 for attending a district meeting about PMDD (YAZ), and \$1000 for "reaccreditation of slides" on PMDD(YAZ); in 2006, \$2000 and \$2000 for symposiums on PMDD(YAZ), \$4500 for an advisory board meeting,\$4000 for a regional advisory board meeting/speaker training on YAZ,\$1500, \$1500, \$1500 and \$1500 for speaker training teleconferences on YAZ,\$2000 for district meeting on YAZ, \$1500 and \$1500 for speaker training teleconference on YAZ, \$4000 and \$1500 for a lunch and learn DVD on YAZ, \$3000 for a leadership advisory board meeting, \$2500 and \$2500 for speaker training meetings on YAZ,\$2000 for a speaker training teleconference on YAZ, \$4000 for regional advisory board meeting on YAZ/Mirena, and \$2500 for an advisory board meeting on YAZ; in 2008, \$2500 for a Journal supplement on YAZ, \$1500

for speaker training teleconference on YAZ, \$4000 for a regional advisory board meeting on YAZ/Mirena, and payments of \$2000 and \$2500 for slide creation for a presentation on YAZ at a medical meeting; in 2009, \$3000 for a short-term hormonal advisory board on YAZ, and \$2500 for ACOG societal symposium. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs' Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). Bayer has identified Dr. Sulak as having "provided presentations relating to Yasmin and/or YAZ at various healthcare provider organization conferences." According to Bayer she made presentations for the company in 2009; 2005, 2004, and 2003. She attended meetings and, or provided CME's in 2003, 2004 2005 and 2008 where YAZ or Yasmin were discussed; was a member of the YAZ advisory board in 2004; was a member of the working group on women's healthcare called the Forum in 2004, 2005 and 2006; was a member of the company's speaker panels and/or attended speaker training meetings relating to Yasmin and or YAZ in 2004 and 2009; and received PMDD speaker training on YAZ. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs' Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). Payments from Bayer to Dr. Sulak in 2003 included \$1500, and \$2000 for a symposium; \$1000 for a monograph, \$4000 for a female patient article on Yasmin. \$2000 for an advisory board meeting on YAZ, and \$1000 for a video on women's health. In 2004, she received \$1500 and \$1500 for speaker training, payment of \$1500 for a slide kit on Yasmin, payment of \$1500 for "meet the experts," payment of \$1500 for a Pri-Med symposium, \$2000 for a publication forum, \$1500 for an ACOG symposium on contraception, \$2000 for an advisory board meeting on YAZ, and \$1500 for a "worth the wait" meeting at Berlex. In 2005, she received \$1500 for an ACOG symposium, \$1,000 for a

monograph on PMDD (YAZ), and \$1500 for a meeting on PMDD (YAZ). In 2006, she received \$2000 for a forum editorial board meeting, and \$1000 for a publication – Forum. (Objections and Response of Bayer Healthcare Pharmaceuticals Inc., and Bayer Schering Pharma AG to Plaintiffs’ Interrogatories to Defendant, Set 6, Court of Common Pleas, Philadelphia County, served on August 27, 2010). Thus, both Drs. Sulak and Mishell’s presentations at the CME meeting were not independent of the Company.

457. In discussing Yasmin, a Bayer document that was attached to an email from Beth Bell to Heike Prinz and titled, “Yasmin for Newsletter 12.7.ZIP” stated: “Given the unique opportunities and challenges of the product, Continuing Medical Education (CME) was a key ingredient in gaining early and widespread acceptance for the product. Thought leader support and exposure at key professional symposia assisted in early differentiation and acceptance.” (BHCPYAZ008393865; BHCPYAZ008393866-867 at 866, LP-102).

458. In my opinion Bayer’s promotion of off-label uses of Yasmin at CME activities was in violation of the Federal Food and Drug Act and its duty of care.

459. Bayer also asked its KOLs to assist in eliminating concerns about Yasmin VTE risk at a CME meeting. On March 21, 2003, Bayer’s Senior Project Manager Barry Lee wrote Bayer consultant Dr. Lee Schuman, “I have been thinking about the VTE Issue. I would like to Kill Any Concern That Any Attending Physician has about this issue during your talk at the Update Training Meeting in Vegas. This must be handled during your didactic presentation. If this issue comes up at the closure of the meeting, I feel the speakers will not be willing or capable of handling this on their own. Just Looking For A Little Reassurance On A Friday Before The Meeting.” (BHCPYAZ009016036).

L. Bayer's Off-Label Promotion Of Yasmin And YAZ Was Not Permissible Under The Regulations Governing The Dissemination Of Clinical Information

460. In a deposition, Donald Atkinson, Vice President of Marketing for Female Healthcare at Berlex beginning in late 2000, testified:

00040

24 Q. You were promoting Yasmin as

00041

1 being effective to prevent the symptoms
2 of PMS?

3 MR. STRAIN: Objection form.

4 MR. HOURIHAN: Join.

5 THE WITNESS: Within the
6 definition of promotion, no we
7 weren't. In the definition of
8 medical and scientific exchange we
9 are allowed to provide, we are
10 encouraged to provide all clinical
11 data on our products to physicians
12 and we did so.

13 BY MR. ROBINSON:

14 Q. Including PMS?

15 A. Including PMS.

16 Q. And you did it for Yasmin,
17 correct?

18 A. We provided physicians with
19 all published clinical data on our
20 products.

461. Mr. Atkinson further testified:

1 BY MR. ROBINSON:

2 Q. Now, in spite of that
3 yesterday in the deposition you took the
4 position that you were allowed, on behalf
5 of Berlex, to make a claim that Yasmin is
6 indicated to reduce the symptoms of PMS,
7 correct?

8 MR. STRAIN: Object to form.

9 THE WITNESS: I don't believe
10 so. As I recollect the point that
11 I tried to make was that within
12 the context of scientific exchange
13 and medical education, the

14 regulations allow, it is
15 appropriate for within the
16 regulations, for companies to
17 provide physicians with
18 information on clinical studies
19 that we have conducted.
20

462. As documented in Appendix A, companies may provide scientific and clinical information about off-label or non-approved uses in the form of journal articles at the specific request of physicians.

463. As documented in Appendix A, companies may also provide scientific and clinical information in the form of journal articles about off-label articles if, as FDA has stated, the articles are independent of the company's involvement. That means that the company did not write, edit or significantly influence the publication of the data.

464. The sharing of "medical information" as part of "educational efforts" that are not independently developed, written, edited and organized may not be used to promote non-approved use. Such non-independent "educational" efforts are no more permissible than "promotion" of such use non-approved uses. (*See generally, Guidance on Industry Supported Scientific and Educational Activities*, 62 Fed. Reg. 64093 (Dec. 3, 1997)).

465. From 1997 to September 30, 2006, under Section 401 of the Food and Drug Administration Modernization Act, manufacturers were permitted to disseminate medical and scientific information discussing non-approved uses if certain conditions were met. These conditions required that the manufacturer has 1) submitted an application to the Agency seeking approval of the off-label use; and 2) submitted the materials to the FDA prior to dissemination. Such materials must not be in an abridged form or false or misleading. (21 USC §360aaa). For a

discussion of the legal challenges to these provisions of the Food and Drug Administration Modernization Act see Appendix A.

466. In my opinion, Mr. Atkinson's statement that under the regulations Bayer was permitted to distribute clinical information about non-approved uses is incorrect unless the information was independent of the company or 1) from the period 1997-2006 when Bayer submitted an application to the Agency seeking approval of the off-label use; and 2) Bayer submitted the materials to the FDA prior to dissemination.

467. Based on my review of the FDA reviews of Yasmin and YAZ, I am not aware of any Bayer application submitted to the FDA seeking approval of either drug for PMS.

468. As noted *supra*, Bayer had a publication strategy that included publication of articles about the use of Yasmin and YAZ for non-approved uses.

469. In my opinion, it was not permissible for Bayer to share medical and scientific information about off-label and non-approved uses without having filed an application for such uses with the agency or assuring that the information was developed independent of the company.

M. Public Health Implications Of Off-Label Marketing Of YAZ And Yasmin

470. Promoting a drug for non-approved uses, where FDA has expressly stated that the drug has not been evaluated in condition, and where there is concern about potential serious adverse events, exposes patients to serious risks.

471. Even though the risks and benefits of a drug for non-approved uses have not been reviewed by the FDA, the Agency generally allows a physician to use the drug for those non-approved uses because it believes that the independent judgment of a physician can responsibly assure patient safety and interests. Such judgment is especially key in the case of non-approved uses because the Agency has not performed any assessment of the risks and

benefits of the particular use. Since the goal of drug promotion is to influence the judgment of a physician, such promotion of non-approved uses to physicians is especially problematic in cases where no FDA review has been performed.

472. In those cases where a safety “signal” is picked up involving potentially serious adverse events, there is a special need to guard against non-approved use. Even when there are no safety signals that are seen during a drug testing stages, broadening of a drug’s market, once it is approved, to non-approved uses, may subject those additional patients taking the drug for the non-approved use to harm, if a safety signal was missed or a safety issue later arises.

473. Marketing a drug for a non-approved use increases the number of patients who receive the drug.

474. In my opinion, by marketing and promoting YAZ and Yasmin for non-approved uses, Bayer needlessly exposed a significant number of people to the risk of thrombotic events.

VIII. CONCLUSIONS

In my opinion:

475. The two systems involving consumer protection, the state system and federal food and drug regulation, should and do operate in a complementary but independent manner.

476. Bayer engaged in a pattern and practice of failure to disclose important information about thromboembolic risk to FDA, physicians and consumers, from pre-marketing to the present, including:

- failure to inform FDA about the number and rate of VTEs in the Jenapharm study prior to approval of Yasmin on May 11, 2001.
- failure to report the “famous case” of VTE in April 2001.

- deciding in advance of the analysis, in 2003, that there was no signal of increased VTE reporting rates.
- resisting FDA's request for a stronger warning of VTE risk in 2003, after FDA informed Bayer of the higher reporting rate of fatal VTEs with Yasmin than with other OCs.
- failing to disclose that Bayer's own analysis revealed an increased reporting rate of VTEs compared to other OC's in 2004.
- presenting a selective view of the data, and that representation obscured the potential risks associated with Yasmin and YAZ.
- engaging in a plan to “offset risk” by “leverag[ing] the safety data from EURAS and INGENIX study” and “continu[ing] to build the positive risk/benefit profile of ‘drsp’” represents a bias that impaired its ability to give credence to contrary data about the risks of Yasmin and YAZ.
- failure to disclose the data in the draft Lidegaard manuscript which documented statistically significant excess VTE risk of drospirenone OC's compared to levonorgestrel OC's, from April 2008 to August 2009.
- failure to disclose the Jick U.S. study results which documented statistically significant excess VTE risk of drospirenone OC's compared to levonorgestrel OC's, from January 2010 to 2011, including violation of the duty to disclose results of investigations in connection with the April 2010 supplemental approval of VTE warning information in the label.

477. Bayer engaged in extensive, systematic off-label promotion of Yasmin and YAZ for PMS, in violation of FDA law and regulations, thereby unnecessarily exposing large numbers of women to risk of thromboembolic events, in violation of state law duties. These actions included:

- targeting the large market for PMS, to increase market share and profitability.
- broadcasting TV advertisements that warranted an FDA Warning Letter, the sanction reserved for egregious violations that threaten public health.
- marketing through large budget Direct-to-Consumer promotion, including lifestyle campaigns and print advertisements that overstated benefits and downplayed risks, and which altered the traditional role of physicians as learned intermediaries.

- engaging in misleading advertisements in professional journals.
- retaining paid physicians to promote Yasmin and YAZ for treatment of PMS and acne, in violation of FDA regulations.
- achieving economic success by marketing Yasmin and YAZ off-label
- employing sales representatives who promoted Yasmin and YAZ for off-label uses and made superiority claims in violation of the Food Drug and Cosmetic Act.
- sharing of medical and scientific information about off-label uses of Yasmin and YAZ, without having filed an application for such uses with FDA, and without assuring that the information was developed independent of the company.

478. If I had become aware when I was at the FDA, of the adverse events that had occurred in the ongoing Jenapharm Postmarketing Surveillance Study prior to Yasmin's approval, I would have sought to investigate what was known or knowable about the incidence of serious adverse events, and would not have moved forward on a decision on NDA approval until such time as the results of the investigation were completed.

479. Bayer's spontaneous reporting analyses demonstrated a safety signal about Yasmin and VTE risk.


480. Had Bayer disclosed its internal analyses of increased VTE reporting rates of VTE in 2004, such information would have affected FDA's decisions as to appropriate actions to be taken regarding VTE risk.

481. Bayer viewed the regulatory environment regarding Yasmin and YAZ' safety as a "threat"; had Bayer disclosed the above-referenced information about VTE risk, doctors and consumers would have had more information to guide their decisions regarding medication choices.

482. By failing to disclose all thromboembolic risk information and marketing Yasmin and YAZ off-label, Bayer needlessly exposed large numbers of women to risks of serious or fatal thromboembolic events.

I reserve the opportunity to revise this report based on new information.

Dated: July ^{29th}, 2011



David A. Kessler, M.D.

APPENDIX A

I. THE FDA'S MISSION

483. The Food and Drug Administration (FDA) is one of the nation's most important consumer protection agencies. It is responsible for implementing the nation's food and drug laws. In 1962, as a result of the thalidomide tragedy where a drug that was marketed abroad, but not in the United States, was responsible for thousands of babies born with abnormal limbs, the United States Congress passed the Kefauver-Harris Amendments, which for the first time required the preclearance of all new drugs. Those Amendments required that before a drug company (called the "sponsor") could introduce in interstate commerce a new drug, the sponsor was required to scientifically establish that the drug was "safe and effective." The 1962 Amendments significantly changed how the FDA regulated new drugs.¹ First, they required a positive act on the part of the FDA—prior to the Amendments, drugs were allowed to go on the market unless the FDA disapproved their use. Second, the Amendments added the requirement that new drugs must be proven to be "effective" as well as safe.² Third, they required that effectiveness be established by "substantial evidence" that demonstrates that the drug will have the effects it purports to have under the conditions of use set out in the drug's labeling.³ And fourth, they defined "substantial evidence" as evidence consisting of "adequate and well-controlled investigations, including clinical investigations...."⁴ The 1962 Amendments ushered in the modern era of drug development and evaluation. The statutory requirement of "adequate and well-controlled investigations" shifted drug development and testing to a scientifically based

¹ Drug Efficacy and the 1962 Drug Amendments, 60 Geo. L. J 185, (1965)

² 21 U.S.C. § 355(d)

³ 21 U.S.C. § 355(d)(5)

⁴ 21 U.S.C. § 355(d)

framework that has resulted in significant medical advances. Those Amendments helped shape the FDA requirements into the “gold standard” for the world.

II. THE FDA STANDARDS FOR APPROVAL

484. Under the nation’s food and drug laws, a drug may not be introduced into interstate commerce unless its sponsor has shown that the drug is safe and effective for the intended conditions of use.⁵

485. The law requires that “adequate and well-controlled investigations” be used to demonstrate a drug’s safety and effectiveness.⁶

486. The FDA approves a drug if there are “adequate and well-controlled clinical trials” that demonstrate a drug’s safety and effectiveness for its “intended conditions” of use.⁷

487. The “intended conditions” for use of a drug are listed in the drug’s labeling which is reviewed and approved by the FDA.⁸

488. Indications for use that are not listed in a drug’s labeling have not been approved by the FDA.⁹

III. THE FDA’S SCIENTIFIC STANDARDS TO ESTABLISH SAFETY AND EFFECTIVENESS

489. The standards that govern the FDA safety and effectiveness requirements are contained in statutes, regulations, notices, and guidance documents.

490. The statutory requirement that a drug’s effectiveness be demonstrated by “adequate and well-controlled clinical investigations” has been interpreted to mean a clinical

⁵ 21 U.S.C. § 321

⁶ 21 U.S.C. § 355(d)

⁷ 21 U.S.C. § 355(d)(5)

⁸ 21 U.S.C. § 355(d)(1) &(2)

⁹ “The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information, which the supplier of the drug is required to develop from accumulated clinical experience and systemic drug trials of preclinical investigations and adequate, well-controlled clinical investigations that demonstrate the drug’s safety and the effectiveness it purports or is represented to possess.” (37 Fed. Reg. 16,503 (1972)).

study with 1) clear objectives; 2) adequate design to permit a valid comparison with a control group; 3) adequate selection of study subjects; 4) adequate measures to minimize bias; and 5) well defined and reliable methods of assessing subjects responses to treatment.¹⁰

491. The FDA has published a notice that set forth general principles for the conduct and performance of clinical trials. These principles have been adopted not only by the agency, but also by the International Conference on Harmonisation, which includes the world's leading medicine control agencies.¹¹ Those principles include the following standards for the conduct of clinical trials to support an Agency decision that a drug is safe and effective for its intended conditions for use:

a. The need for trials to be controlled: "Trials should have an adequate control group. Comparisons may be made with placebo, no treatment, active controls, or of different doses of the drug under investigation. The choice of the comparator depends on, among other things, the objective of the trial Historical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."

b. The need for trials to be randomized: "In conducting a controlled trial, randomized allocation is the preferred means of assuring comparability of test groups and minimizing the possibility of selection bias."

c. The need for trials to be blinded: "Blinding is an important means of reducing or minimizing the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant because of the use of placebo or other methods of masking the intervention is referred to as a single blind study. When the investigator and

¹⁰ 21 C.F.R. § 314.26

¹¹ International Conference on Harmonisation : Guidance on General Considerations for Clinical Trials 62 Fed. Reg. 66113 (December 17, 1997)

sponsor staff who are involved in the treatment or clinical evaluation of the subjects and analysis of data are also unaware of the treatment assignments, the study is double blind.”

d. The need for objective and prospectively determined trial endpoints: A drug’s effectiveness is determined if the drug has an effect on an “endpoint.” That endpoint can be a clinical benefit, such as survival or a reduction of pain as measured on a validated pain scale; a clinical measurement, such as blood pressure; and, in some cases, a laboratory measurement, such as the amount of virus in the blood stream. All endpoints need to reflect clinical benefit. An endpoint that indirectly reflects a clinical benefit, such as a laboratory measurement, is known as a “surrogate endpoint. Endpoints should be defined prospectively (i.e., before the trial begins), giving descriptions of methods of observation and quantification. Objective methods of observation should be used where possible and when appropriate. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analyses should be prospectively specified in the protocol. The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

492. The FDA has addressed the need for reproducibility and reliability of clinical data in the trials that support a drug’s approval. The FDA generally requires two pivotal adequate and well-controlled trials to support approval, except in certain circumstances. As

stated by the FDA in the 1998 *Guidance to the Industry*,¹² “it has been FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. v. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA’s position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase “adequate and well-controlled investigations” was designed not only to describe the quality of the required data but the “quantum” of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962)). Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency

¹² U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*, May 1998

may consider ‘data from one adequate and well-controlled clinical investigation and confirmatory evidence’ to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA’s interpretation of the statutory requirements for approval and acknowledged the Agency’s position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.”

493. The FDA usually considers one clinical trial insufficient to support approval.¹³ The cases where the FDA has approved a drug on the basis of one clinical trial plus confirmatory evidence are rare. They include instances of large, independently conducted multicenter trials with strong empirical results, with internal consistency across multiple outcomes, such that “sponsors faced ethical boundaries” in conducting a second placebo-based trial.

494. Clinical trials that are not controlled, blinded, randomized and whose endpoints are not prospectively and objectively determined and measured may be used in early stage drug development phases, but are exceptionally unlikely to qualify as “adequate and well-controlled” clinical trials needed to support FDA approval.

IV. DRUGS ARE REGULATED BASED ON THEIR INTENDED CONDITIONS OF USE AND MAY NOT BE PROMOTED OR MARKETED FOR NON-APPROVED OR OFF-LABEL USES.

495. It is not a drug that is regulated, by itself, that receives approval. It is a drug for an “intended use” that is reviewed and approved by the FDA. Thus it is not a chemical compound that is approved, but a chemical compound for a specific disease or condition at a specific dose that FDA reviews and approves.

¹³ Peck CA, and Wechsler MA Report of a Workshop on Confirmatory Evidence to Support a Single Clinical Trial as a basis for New Drug Approval, *Drug Information Journal*, Vol. 36, pp. 517–534, 2002

496. The Federal Food Drug and Cosmetic Act requires that the New Drug Application include proposed labeling for the intended uses of the drug which include, among other things, the conditions for therapeutic use. (21 U.S.C. § 355(b)(1)).

497. The drug company must submit data in the New Drug Application based on adequate and well controlled clinical trials that demonstrate that the drug is safe and effective when used in accordance with the proposed labeling. (*Id.*)

498. A drug manufacturer must demonstrate its drug works for each intended use before it markets or promotes the drug for that “intended use.” (21 U.S.C. § 355(a), (d)).

499. Federal law specifically prohibits a drug manufacturer from obtaining approval of a drug for one use, then marketing or promoting the drug for unapproved uses. (*See* S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (statement of Senators Kefauver, Carroll, Dodd, Hart & Long, explaining reasons for changing definition of “new drug”)).

500. The requirement that a manufacturer may not market a drug for a condition, disease, dose, or claim that has not been approved by the FDA flows from the following “new drug” statutory provisions:

a. The Act prohibits the introduction or delivery for introduction into interstate commerce of a “new drug” that has not been approved by the FDA. (21 U.S.C. §§ 331(d), 355(a)).

b. A drug is a new drug if it is not generally recognized as “safe and effective” for its intended uses. (§ 321(p)).

c. A new intended use renders an approved drug a “new drug” with respect to the new use, and the manufacturer cannot distribute the drug in interstate commerce for that

use without first obtaining FDA's approval of an application that demonstrates the drug's safety and effectiveness for the new use.

d. Thus, a manufacturer may not introduce a drug into interstate commerce with the intent that it be used for a purpose that has not been approved by the FDA.

501. The requirement that a manufacturer may not market a drug for a condition, disease, dose, or claim that has not been approved by the FDA also flows from misbranding provisions of the Act.

502. As Senator Kefauver, explained at the time of enactment: “[T]he considerations which would warrant examination and approval of the initial claim would be just as appropriate and compelling for successive claims.” If a manufacturer were not required to demonstrate safety and effectiveness for new intended uses, “[t]he expectation would be that the initial claims would tend to be quite limited”; once the drug was approved for one use, “[t] hereafter ‘the sky would be the limit’ and extreme claims of any kind could be made” (*See* S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (statement of Senators Kefauver, Carroll, Dodd, Hart & Long, explaining reasons for changing definition of “new drug”)).

503. FDA's evaluation of a new drug requires an assessment of the safety of a drug for each intended condition of use. The data in a new drug application for a drug for one intended condition may support a finding by the Agency that the risks are acceptable in light of the benefits, but the same drug for a different intended use may not support such a finding. For example, a drug that is used in a narrowly defined disease condition may have an acceptable risk benefit condition compared to the same drug in a much broader, less serious disease. Thus, a drug that has cardiovascular adverse reactions may be found to be safe in a life-threatening

disease such as leukemia, but the same drug with cardiovascular side effects may not be acceptable for acute pain conditions.

504. A drug manufacturer is not required to seek approval for unapproved uses that are not intended.

505. Thus, the requirement that a manufacturer submit an NDA for a particular use turns on whether particular unapproved uses are intended uses.

506. In determining a product's intended use, FDA is not limited to examining the product label. Instead, "it is well established that the 'intended use' of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." (*Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980)).

507. FDA's regulations provide that intended use "refer[s] to the objective intent of the persons legally responsible for the labeling of drugs," and "is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article." (21 C.F.R. § 201.128). The manufacturer's objective intent "may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives." (*Id.*)

508. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for purpose for which it is neither labeled nor advertised.

509. The Act defines "labeling" as "written, printed, or graphic matter" (1) upon a drug itself, its immediate or other "containers or wrappers," or (2) "accompanying such article."

(21 U.S. C. § 321(m), (k)). Materials “accompan[y an] article” or a drug if they are sent from the same origin to the same destination as part of an “integrated . . . transactio[n]” and the two have a “textual relationship.” (*Kordel v. United States*, 335 U.S. 345, 348–50 (1948)).

510. “Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ‘Physician’s Desk Reference’) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor, are hereby determined to be labeling” (21 C.F.R. § 202.1(l)(2)).

511. As I have written previously, the types of medical education activities that a drug manufacturer may engage in depends on whether such activities are considered “educational” or “promotional.” The FDA’s drug regulations draw a critical distinction between “scientific change” and “promotional activities.” While the promoting or advertising of investigational drug is prohibited, the Agency recognizes that educational exchanges among scientists regarding preapproved drugs for non-approved uses of approved drugs must be permitted. When a pharmaceutical firm supports these educational activities, however, the line between “education” and “promotion” becomes harder to draw. The distinction is obviously important to pharmaceutical firms because the FDA regulates promotional activities under its prescription drug labeling and advertising regulations. Although educational activities sponsored by the manufacturer may be considered by the FDA as labeling, the FDA has generally exercised its discretion not to enforce that authority with respect to purely educational activities. (The

Federal Regulation of Prescription *Drug Advertising and Promotion*. David A. Kessler, MD, Wayne L. Pines, *Journal of the American Medical Association* 1990; 264(18):2409-2415.)

512. The criteria to distinguish educational from promotional activities include the degree to which a program is “independent” of the drug company. The more directly involved the company is, the more concerned the FDA becomes about its promotional dimensions. Financial relationships between the speakers and the company will tilt the FDA’s judgment for the category of promotional activities. Furthermore, it is becoming less important to the FDA whether a symposium is set up by a third party or by the company itself. Arranging with a university or another third-party to run a symposium does not automatically ensure its safety from FDA scrutiny. What is important is who controls the agenda, who selects the speakers and the audience and what is said. An audience made up of experts who can engage in a scientific exchange lends more weight to the view that the symposium is educational than one that is by “open invitation.” Specifically, the FDA will examine whether the symposium provides participants with educational information primarily or as an adjunct to promotional activities. In addition, noneducational inducements such as meals, travel, and entertainment make the presentation more likely to be viewed as promotional. The FDA also distinguishes between a single scientific symposium and a road show series; multiple symposiums on the same subject are likely to be viewed as more promotional than scientific. If a speaker makes a promotional statement at a symposium, the FDA expects the sponsoring drug manufacturer to caution the speaker against repeating such statements at subsequent meetings. Employees of the pharmaceutical firm may participate in a symposium but their presentations need to be limited to data they alone can present. (*Id.*)

513. In 1997, the FDA published guidance for the industry on the proper limits of sponsorship of continuing medical education (CME) activities. (62 Fed Reg 64,074). This guidance document stresses that CME programs must be independent of influence of the drug manufacturer.

514. The Federal Food and Drug Act was amended in 1997 (FDA Modernization Act [FDAMA]) to clarify that a manufacturer may disseminate information regarding non-approved and off-label uses only in response to unsolicited requests from a health care practitioner. 21 U.S.C. §360aaa-6. In other instances, the manufacturer is permitted to disseminate information not contained in the approved labeling only after the manufacturer has 1) submitted an application to the Agency seeking approval of the off-label use; and 2) submitted the materials to the FDA prior to dissemination. Such materials must not be in an abridged form or false or misleading. 21 U.S.C. §360aaa. The Washington Legal Foundation (WLF) challenged the restrictions on manufacturers' dissemination of off-label, peer-reviewed scientific articles and on support for continuing medical education (CME). The district court issued an injunction limiting certain aspects of FDA's restrictions on off-label speech and finding certain provisions of the Food Drug and Cosmetic Act as amended FDAMA unconstitutional. *Washington Legal Foundation v. Friedman*, 13 F Supp. 2d 51 (D.D.C. 1998) ("WLF II") and *Washington Legal Foundation v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999) ("WLF III"). However, the U.S. Court of Appeals for the District of Columbia Circuit found the case moot after FDA argued that the FDAMA provisions regarding off-label promotion operate only as a "safe harbor" and do not create any new or independent enforcement rights. *Washington Legal Foundation v. Henney*, 202 F. 3d 331 (D.C. Cir. 2000) ("WLF IV").

515. In certain specific circumstances, FDA has permitted the dissemination of reprints of medical publications. The ability to disseminate articles may only be done when the medical publication 1) was not written, edited, excerpted, or published specifically for, or at the request of, the drug manufacturer; 2) was not edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer; 3) does not focus on any particular drug or device of a manufacturer that disseminates information under this part and does not have a primary focus on new uses of drugs or devices that are marketed or are under investigation by a manufacturer supporting the dissemination of information; and 4) is not false or misleading.

516. The Act, and its implementing regulations, require that in order to label or promote a drug for a use different than the conditions for use specified in the approved labeling, the sponsor is required to file a new NDA, or amend the existing NDA.

517. Labeling, including promotional materials and activities, must not be misleading or fraudulent and must be consistent with the product label that has been approved by the FDA.

518. The manufacturer is required to submit evidence, in the form of randomized and well-controlled clinical studies, sufficient to demonstrate that the drug was safe and effective for the newly proposed therapeutic use or uses.

519. Intended use is also important in determining whether the misbranding prohibitions of the Act apply, because the obligation to provide adequate directions for use extends to all uses that are intended. (*See* 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5, 201.100(c)(1)).

520. A physician, in contrast, may prescribe a drug for an indication not contained in the approved label. Such use is commonly called an off-label use.

521. While a physician may prescribe a drug for an off-label use, the physician is not permitted to promote a drug for an off-label use.

522. Drug manufacturers may not use medical educational or advisory committee forums to promote non approved or off-label uses.

523. Medical education activities that are not independent of the drug manufacturer are not permissible.

524. The Act provides that, unless otherwise exempted, a drug is misbranded if, among other things, the labeling does not contain adequate directions for use. (21 U.S.C. § 352(f)).

525. Not providing adequate directions for use makes the risk of taking the drug greater and certainly increases the liability of the company selling a drug for a non-approved use.

526. Physicians are aware that when they prescribe a drug “off-label,” they are at an increased risk for liability because they do not have the approved FDA labeling upon which to rely as a defense that they acted within the standard of care.

527. Drugs that are promoted for uses that have not been approved by the FDA are misbranded under the Act. (21 U.S.C. § 352(f)(1)). The Act prohibits the delivery for introduction and causing the delivery for introduction into interstate commerce of a misbranded drug. (21 U.S.C. § 331(a)). A person who misbrands a drug with the intent to defraud or mislead is guilty of a felony offense. (21 U.S.C. § 333(a)(2)).

528. FDA has voiced serious concerns regarding the promotion of drugs non-approved uses. These concerns stem from the fact that the Agency has not reviewed and

approved the indications for which the drug is being used. (*See* statement of William B. Schutlz *supra*).

529. In summary:

a. Manufacturers have the responsibility to study a drug for its intended uses and subject that data to FDA review before they promote and market a drug for non-intended uses.

b. A drug company may only market or promote a drug for those indications that are approved in the drug's labeling by the FDA.

c. All major pharmaceutical manufacturers are well aware of the prohibitions on the marketing and promotion of non-approved uses.

d. FDA's prohibitions and policies against marketing and promotion of non-approved uses have been in force for decades.

e. Physicians who are independent of the company may prescribe a drug for a non-approved use if such prescribing is, in the opinion of the physician, in the best interests of the patient.

f. Physicians may not promote a drug for non-approved uses.

g. The promotion and or marketing of a drug for non-approved uses by a manufacturer subjects the public to additional risks of adverse events and harm.

V. **FDA'S ADVERTISING REGULATIONS PROHIBIT ADVERTISEMENT OF DRUGS FOR OFF-LABEL USES AND PROHIBIT A REPRESENTATION OR SUGGESTION, NOT APPROVED OR PERMITTED FOR USE IN THE LABELING, THAT A DRUG IS BETTER, MORE EFFECTIVE, OR USEFUL IN A BROADER RANGE OF CONDITIONS.**

530. FDA advertising regulations state:

§ 202.1 (e)(4) *Substance of information to be included in brief summary* .(i)(a) An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the

act after October 10, 1962, or a prescription drug covered by a new animal drug application approved pursuant to section 512 of the act after August 1, 1969, or any approved supplement thereto, or for a prescription drug listed in the index pursuant to section 572 of the act, or any granted modification thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement, new animal drug application or supplement, or new animal drug index listing or modification. The advertisement shall present information from labeling required, approved, permitted, or granted in a new-drug or new animal drug application or new animal drug index listing relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.[Emphasis added]

531. FDA advertising regulations further state:

§ 202.1(e)(6) “An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it:

(i) Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients (as used in this section *patients* means humans and in the case of veterinary drugs, other animals), safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience (as described in paragraphs (e)(4)(ii) (*b*) and (*c*) of this section) whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

(ii) Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience. [Emphasis added]

532. FDA advertising regulations further state:

§ 202.1(e)(6)(ii) Represents or suggests that a prescription drug is safer or more effective than another drug in some particular when the difference has not been demonstrated by substantial evidence.

An advertisement for a prescription drug may not, either directly or by implication, e.g., by use of comparative test data or reference to published reports, represent that the drug is safer or more effective than another drug, nor may an advertisement contain a quantitative statement of safety or effectiveness (*a*) unless the representation has been approved as part of the labeling in a new drug application or biologic license, or (*b*) if the drug is not a new drug or biologic, unless the representation of safety or effectiveness is supported by substantial evidence derived from adequate and well-controlled studies as defined in §314.111(a)(5)(ii) of this chapter, or unless the requirement for adequate and well-controlled studies is waived as provided in §314.111(a)(5)(ii) of this chapter.

533. FDA’s advertising regulations define advertisements as:

§ 202.1(l)(1) Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.

VI. STATUTORY AND REGULATORY MISBRANDING PROVISIONS OF THE FEDERAL FOOD DRUG AND COSMETIC ACT THAT MAKE OFF-LABEL PROMOTION MISBRANDING

534. The FDCA prohibits the introduction, or causing the introduction, into interstate commerce of misbranded drugs. (21 U.S.C. § 331(a)).

535. A drug is misbranded unless its labeling bears adequate directions for use. (21 U.S.C. § 352(f)(1)). “Adequate directions for use” means directions under which the layman can use a drug safely and for the purposes for which it is intended. (21 C.F.R. § 201.5).

536. Yasmin and YAZ are prescription drugs. They are drugs because they are intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man (*i.e.* in treating cancer). (21 U.S.C. § 321(g)(1)(B)). They are prescription drugs because of their toxicity or other potentiality for harmful effect, or the method of their use, or the collateral measures necessary to their use, they are not safe for use except under the supervision of a

licensed practitioner. (21 U.S.C. § 353(b)(1)(A)). Drugs limited by an approved application for use only under licensed supervision are prescription drugs. (21 U.S.C. § 353(b)(1)(B)).

537. Adequate directions for use, or directions under which a layperson can use a drug safely, cannot be written for a prescription drug. Prescription drugs can only be used safely at the direction, and under the supervision, of a physician.¹⁴

538. Since prescription drugs manufactured by a company cannot bear adequate directions for use—in order for them not to be misbranded an exception for them is required. In other words, all prescription drugs are misbranded unless they qualify for an exemption.

539. 21 U.S.C. § 353(b) grants an exception to prescription drugs but applies “only at the point at which the drug is actually prescribed and dispensed.” *U.S. v. Evers*, 643 F.2d 1043, 1051 (5th Cir. 1981) (citing *U.S. v. Articles of Drug*, 625 F.2d 665, 674 (5th Cir. 1980) and *U.S. v. An Article of Drug . . . Amodril Spancap*, 1975 Food Drug Cos.L.Rep 39,009 at 38,035 (S.D. Fla.. 1974). Thus, the *Evers* Court found that 21 U.S.C § 353(b)(2) provides a much narrower protection for the distributor of the drug, for it exempts the provisions of 21 U.S.C. § 352.

¹⁴ See *United States v. Articles of Drug . . . Rucker*, 625 F.2d 665, 673-75 (5th Cir. 1980) (“Since a prescription drug by definition can be used only under a physician’s supervision, and is unsuitable for self-medication, such a drug must qualify for a regulatory exemption created by FDA, pursuant to the authority of section 352(f). . . .”); *United States v. Baxter*, 712 F. Supp. 1352, 1359 (N.D. Ill. 1989) (“[t]hese products are not exempt from the labeling requirements of section 352(f)(1). This section requires labels to bear ‘adequate directions for use,’ which the FDA defines as ‘directions under which the layman can use a drug safely and for the purposes for which it is intended.’ 21 C.F.R. 201.5. Since Baxter restricted distribution of these products to prescription use only, perforce its labels are not ‘adequate’ for use. The FDA has regulations providing exemptions from section 352(f)(1), see, for example, 21 C.F.R. 201.100, but Baxter has not shown that it has complied with them. As a result, these chemotherapeutic TRC products are misbranded under section 352(f)(1), and hence Baxter’s sales of them violated sections 331(a) and (k) of the Act.”); *United States v. Article of Drug . . . “Mykocert”*, 345 F. Supp. 571, 573 (N.D. Ill. 1972) (“There are five conceivable defenses that claimant could have raised to the Government’s section 352(f)(1) grounds . . . It could have claimed that Mykocert indeed bore adequate instructions for lay use as required by section 352(f)(1) and 21 C.F.R. 1.106(a) but was foreclosed from doing so since Mykocert is a prescription drug and by its very nature cannot bear such instructions.”); See *United States v. 675 Cases, Etc., “Damason-P,”* [1989-1992 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 38,156, at 38,344 (C.D. Cal. 1990) (“By definition, a prescription drug cannot bear adequate directions”).

540. 21 C.F.R. 201.100 provides an exemption for prescription drugs so that they are not misbranded from the time they enter into interstate commerce. To qualify for the exemption in 21 CFR 201.100 the prescription drugs must meet *all* of the conditions set forth in the regulation. Those conditions, in relevant part, are:

- C.F.R. 201.100(c)(1) requires “labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented...”
- C.F.R. 201.100(d) requires that “Any labeling,...contains: (1) Adequate information for such use... including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 505 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted, under the provisions of section 505, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and (2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed.

541. Drugs that are promoted for off-label uses do not satisfy a number of the required conditions.

542. In such a case of a prescription drug promoted for off-label uses, the drug is subject to section 505 of the FDCA, 21 U.S.C. §355, and labeling (off-label promotion) was not the labeling authorized by the approved new drug application.

543. A drug that fails to satisfy the conditions in 21 C.F.R. 201.100 is not entitled to an exemption from the adequate directions for use requirement and is, thus, misbranded.

544. 21 C.F.R. 200.115 provides an exemption from 502(f)(1) for a new drug when such an exemption is claimed in a new drug application. There are no exemptions for new drugs for new intended uses that go beyond the approved labeling.

VII. PHARMACEUTICAL MANUFACTURERS KNEW THAT OFF-LABEL PROMOTION RENDERED A DRUG MISBRANDED IN LIGHT OF THE WARNINGS AND ACTIONS BY THE FDA, THE UNITED STATES CONGRESS, AND THE COURTS.

545. On November 19, 1992, the United States House of Representatives Committee on Government Operations, Committee of the Whole House on the State of the Union, submitted the following statement: “Under the Food, Drug, and Cosmetic Act, manufacturers may promote a drug or device for uses that the FDA has determined are safe and effective. ‘Off-label’ uses are those that the FDA has not determined to be safe or effective, either because the manufacturer did not submit an application requesting approval for such uses, or because the FDA did not approve an application that was submitted in support for such uses. Promotion for off-label uses is considered misbranding, and is therefore illegal under section 502(a), 502(f)(1) and 505.” (House Report 102-1084 (citing memorandum from Acting Director of Division of Drug Advertising and Labeling to the Director of Office of Drug Standards, May 6, 1990, p. 3; in subcommittee files)).

546. In 1993, in the law journal published by the Food Drug and Cosmetic Law Institute, a legal scholar publicly wrote, “the FDA... clearly may exercise control over

manufacturers that promote off-label uses for their products. The off-label use is then intended by the manufacturer, and regulations enacted pursuant to the Federal Food Drug and Cosmetic Act require a drug's labeling to contain information on all intended uses of the drug." (William L. Christopher, Off-Label Drug Prescription: Filling the Regulatory Vacuum Food Drug Cosmetic Law Journal 48:247 (1993), citing as authority 21 C.F.R. §§201.5 and 201.128)).

547. The law review article also stated, "the FDA recently announced a crackdown on manufacturers that promote off-label use..." and cited an article in the *Journal of the American Medical Association* by Terry Randall titled, "FDA scrutinizes 'Off-Label' Promotions." (*Id.*)

548. In 1994, in language that was unambiguous, FDA set out in the public domain what at the time was its longstanding policy on Promotion of Unapproved Uses. In detail that no pharmaceutical manufacturer could have missed, the Agency stated in most relevant part: Information disseminated by companies in contexts such as scientific and educational meetings, symposia, books, and articles may provide evidence of a regulated product's intended use. If these formats include statements promoting a use that is inconsistent with the product's approved labeling, the product is misbranded for failure to bear labeling with adequate directions for use. (59 Federal Register 59820).

549. On September 12, 1996, Dr. Michael Friedman, Deputy Commissioner for Operations of the Agency, in testimony before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, United States House of Representatives, stated, "unlike with the practice of medicine, the food drug and cosmetic act specifically directs FDA to regulate the promotion of drugs. Promotional materials are considered unlawful if they promote an unapproved use for the product ... Were companies

allowed to promote uses of drugs that have not been proven effective, they might promote uses that do not work or are dangerous.” (*Testimony of Supplemental Indications for Approved Prescription Drugs*, Michael Friedman, Before the House Committee Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations, September 12, 1996. <http://www.hhs.gov/asl/testify/t960912a.html>).

550. Pharmaceutical firms were aware that the United States Congress in 1997 permitted a narrow exception to allow the use of certain independent peer-reviewed medical publications. (*FDA Background on FDAMA*, November 21, 1997, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm089179.htm>).

551. In 1999, Genentech pleaded guilty to illegal promotion of a drug for unapproved uses and paid a \$30 million criminal fine. (*Big Pharma’s Crime Spree*, David Evans, Bloomberg Markets, December, 2009, p72-86).

552. Bayer, in a document titled, “Advertising and Promotion: Do’s and Don’ts” cited 13 examples of cases involving off-label promotion where pharmaceutical companies paid settlements with the Department of Justice ranging from 8 million to 2.8 billion. (BHCPYAZ006135260-344 at 269).

553. Bayer knew that “communications about products under the sponsorship and control of Bayer are considered promotional activities,” [Emphasis in original] and are “subject to FDA regulations.” (BHCPYAZ006135260-344 at 326).

554. Bayer knew that “exhibit booths and all individuals who work them are regulated as promotion,” [Emphasis in original] and “subject to regulation.” (BHCPYAZ006135260-344 at 326).

APPENDIX B

I. ACOG DIAGNOSTIC CRITERIA FOR PMS

American College of Obstetricians and Gynecologists. Premenstrual Syndrome. ACOG Practice Bulletin No. 15. Washington, DC: American College of Obstetricians and Gynecologists, 2000, Reaffirmed 2010 (www.acog.org/from_home/publications/green_journal/PBListOfTitles.pdf).

Patient reports at least **one** of each of the following affective and somatic symptoms during the 5 days before menses. Symptoms must appear in three consecutive menstrual cycles:

Affective: Depression, angry outbursts, irritability, anxiety, confusion, social withdrawal

Somatic: Breast tenderness, abdominal bloating, headache, swelling of extremities

Symptoms must also meet the following criteria:

- Be relieved within 4 days of the onset of menses, without recurrence until at least cycle day 13
- Be present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use
- Be causing identifiable dysfunction in social or economic performance
- Occur reproducibly during two cycles of prospective recording

II. PREMENSTRUAL DYSPHORIC DISORDER

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision. Washington, DC: American Psychiatric Association, 2000.

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being 1, 2, 3, or 4:

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feelings of being “keyed up” or “on the edge”
3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. Persistent and marked anger or irritability or increased interpersonal conflicts
5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings

9. Hypersomnia or insomnia
10. A subjective sense of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of “bloating,” weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive somatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

EXPERT REPORT OF DAVID M. KESSLER - APPENDIX C

DAVID A. KESSLER

- 1969-1973 AMHERST COLLEGE, Amherst, Massachusetts
Bachelor of Arts, *magna cum laude* (B.A. Independent Scholar, 1973)
- 1973-1979 HARVARD MEDICAL SCHOOL, Boston, Massachusetts
Doctor of Medicine (M.D. 1979)
- 1975-1977 UNIVERSITY OF CHICAGO LAW SCHOOL, Chicago, Illinois
Doctor of Law (J.D., 1978), Harvard Law School, 1977-1978
- 1984-1986 NEW YORK UNIVERSITY GRADUATE SCHOOL OF BUSINESS
ADMINISTRATION (Manhattanville), Purchase, New York
Advanced Professional Certificate in Management

EMPLOYMENT

- UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
- 2003-present Professor of Pediatrics, Epidemiology and Biostatistics
- 2003-2007 Dean, School of Medicine
Vice Chancellor of Medical Affairs
- 1997-2003 YALE UNIVERSITY SCHOOL OF MEDICINE
Dean
Professor of Pediatrics, Internal Medicine, and Public Health
- 1990-1997 UNITED STATES FOOD AND DRUG ADMINISTRATION
Commissioner
- 1984-1990 THE HOSPITAL OF THE ALBERT EINSTEIN COLLEGE OF
MEDICINE
Medical Director
- 1986-1990 COLUMBIA UNIVERSITY
Julius Silver Program in Law, Science and Technology
Lecturer on Law
- 1982-1984 MONTEFIORE MEDICAL CENTER
Special Assistant to the President
- 1981-1984 UNITED STATES SENATE COMMITTEE ON LABOR AND HUMAN
RESOURCES, Consultant to the Chairman

HONORARY DEGREES

- 1992 AMHERST COLLEGE, Amherst, Massachusetts
Doctor of Science *honoris causa*
- 1992 GEORGE WASHINGTON UNIVERSITY, Washington, D.C.
Doctor of Science *honoris causa*
- 1993 PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE, Philadelphia,
Pennsylvania, Doctor of Science *honoris causa*
- 1993 DICKINSON COLLEGE OF LAW, Carlisle, Pennsylvania
Doctor of Laws *honoris causa*
- 1995 ALBANY MEDICAL COLLEGE, Albany, New York
Doctor of Science *honoris causa*
- 1997 NORTHEASTERN UNIVERSITY, Boston, Massachusetts
Doctor of Science *honoris causa*
- 1998 MOUNT SINAI SCHOOL OF MEDICINE, New York, New York
Doctor of Humane Letters *honoris causa*
- 1998 COLGATE UNIVERSITY, Hamilton, New York
Doctor of Science *honoris causa*
- 1998 YALE UNIVERSITY, New Haven, Connecticut
Master of Arts *privatio*
- 1999 CONNECTICUT COLLEGE, New London, Connecticut
Doctor of Humane Letters *honoris causa*
- 2001 DICKINSON COLLEGE, Carlisle, Pennsylvania
Doctor of Science, *honoris causa*
- 2001 UNION COLLEGE, Schenectady, New York
Doctor of Laws, *honoris causa*
- 2002 UNIVERSITY OF LOUISVILLE, Louisville, Kentucky
Doctor of Public Service, *honoris causa*
- 2005 STATE UNIVERSITY OF NEW YORK, Syracuse, NY
Doctor of Science, *honoris causa*

HONORS

NATIONAL ACADEMY OF SCIENCES, Public Welfare Medal,
Honorary Member

INSTITUTE OF MEDICINE, Member

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
Distinguished Service Award for Scientific Achievement

AMERICAN ACADEMY OF ARTS AND SCIENCES, Fellow

PHI BETA KAPPA, Amherst College

UNIVERSITY OF CHICAGO LAW REVIEW, Associate Editor

2008 PUBLIC HEALTH HERO AWARD, UC Berkeley

SIGMA XI, The Scientific Research Society of North America

BARNARD COLLEGE Barnard
Medal of Distinction

CASPAR PLATT AWARD, The University of Chicago Law School

HARVARD BLODGETT AWARD IN BIOLOGY, Amherst College

WHITING FOUNDATION GRANT-IN-AID for research at
Sloan-Kettering Institute

NATIONAL SCIENCE FOUNDATION FELLOWSHIP (declined)

JOHN WOODRUFF SIMPSON FELLOWSHIP, awarded by Amherst
College for the study of medicine

ALVAN T.--VIOLA D. FULLER AMERICAN CANCER SOCIETY
JUNIOR RESEARCH FELLOW (declined)

NATIONAL INSTITUTES OF HEALTH TRAINING FELLOWSHIP
RECIPIENT for physiology research at the Marine Biological Laboratory,
Woods Hole, Massachusetts

PHI DELTA THETA SCHOLARSHIP
DISTINGUISHED PUBLIC SERVICE AWARD
The George Washington University School of Medicine and Health Sciences

UNITED STATES DEPARTMENT OF JUSTICE, CIVIL DIVISION
Special Citation

AMERICAN SOCIETY OF PUBLIC ADMINISTRATION
National Capitol Area Chapter
President's Award for Outstanding Achievement

AMERICAN FEDERATION FOR AIDS RESEARCH (AmFAR)
Sheldon W. Andelson Public Policy Achievement Award

THE WOODROW WILSON AWARD FOR DISTINGUISHED
GOVERNMENT SERVICE Johns Hopkins University

HAL OGDEN AWARD
Association of State and Territorial Directors of Health Promotion and
Public Health Education and the U. S. Centers for Disease Control

NATIONAL ORGANIZATION FOR RARE DISEASES (NORD)
Outstanding Service to the Public Health Award

MARCH OF DIMES
Franklin Delano Roosevelt Leadership Award

CHILDREN'S HOSPITAL NATIONAL MEDICAL CENTER
Children's Research Institute Award of Academic Excellence

AMERICAN HEART ASSOCIATION
National Public Affairs Special Recognition Award for Food Labeling

ISRAEL CANCER RESEARCH FOUNDATION
President's Award

INSTITUTE FOR ADVANCED STUDIES IN IMMUNOLOGY AND AGING
Lifetime Public Service Award

AMERICAN LUNG ASSOCIATION
Special Recognition Award

UNIVERSITY OF CHICAGO ALUMNI ASSOCIATION
Professional Achievement Award (Washington, D.C. Chapter)

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Secretary's Award for Excellence in Public Service

NATIONAL KIDNEY CANCER ASSOCIATION
Progressive Leadership Award

JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH
Dean's Medal

AMERICAN CANCER SOCIETY
Medal of Honor

AMERICAN HEART ASSOCIATION
Meritorious Achievement Award

WORLD HEALTH ORGANIZATION Pan
American World Health Organization World
No Tobacco Day Award

AMERICAN HEART ASSOCIATION
National Public Affairs Special Recognition Award for Tobacco

PROFESSIONAL ACHIEVEMENT CITATION, University of
Chicago Alumni Association

PENNSYLVANIA HOSPITAL Molly
and Sidney N. Zubrow Award

AMERICAN LUNG ASSOCIATION OF CONNECTICUT
Humanitarian Award

AMERICAN COLLEGE OF PREVENTIVE MEDICINE
Special Recognition Award

ASSOCIATION OF AMERICAN MEDICAL COLLEGES AND THE ROBERT
WOOD JOHNSON FOUNDATION
David E. Rogers Award for Improving Health and Healthcare of the American
People

JACOBS INSTITUTE OF WOMEN'S HEALTH
Excellence in Women's Health Award

NARAL PRO-CHOICE AMERICA
Lifetime Achievement Award

THE ASSOCIATION OF STATE AND TERRITORIAL CHRONIC DISEASE
PROGRAM DIRECTORS
Joseph W. Cullen Award for Outstanding Contributions to Chronic Disease
Prevention and Control

THE COLLEGE OF WILLIAM & MARY LAW SCHOOL
2005 Benjamin Rush Medal

INTERNSHIP & RESIDENCY

- 1981-1982 SENIOR ASSISTANT RESIDENT, Department of Pediatrics,
The Johns Hopkins Hospital
- 1980-1981 ASSISTANT RESIDENT, Department of Pediatrics,
The Johns Hopkins Hospital
- 1979-1980 INTERN, Department of Pediatrics,
The Johns Hopkins Hospital

ACADEMIC APPOINTMENTS

- 2003- present UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Professor of Pediatrics
Professor of Epidemiology and Biostatistics
- 1997- 2003 YALE UNIVERSITY
Professor of Pediatrics
Professor of Internal Medicine
Professor of Public Health
- 1990- 1997 ALBERT EINSTEIN COLLEGE OF MEDICINE
Department of Pediatrics
Department of Epidemiology and Social Medicine
Associate Professor of Pediatrics
Associate Professor of Epidemiology and Social Medicine
- 1988- 1990 ALBERT EINSTEIN COLLEGE OF MEDICINE
Department of Epidemiology and Social Medicine
Assistant Professor
- 1986- 1990 COLUMBIA UNIVERSITY SCHOOL OF LAW
Julius Silver Program in Law, Science and Technology
Lecturer on Law
- 1982- 1990 ALBERT EINSTEIN COLLEGE OF MEDICINE
Department of Pediatrics
Assistant Professor

SPECIAL STUDY

June 1987 JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH
Graduate Summer Program in Epidemiology - Pharmacoepidemiology

June 1985 YALE SCHOOL OF ORGANIZATION AND MANAGEMENT
Advanced Management Studies in Health Care Management

1977-1978 HARVARD LAW SCHOOL, Special Student

RESEARCH EXPERIENCE

Summers 1970-1972 SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
Division of Drug Resistance, New York, New York Research Asst

Summer 1972 MARINE BIOLOGICAL LABORATORY, Woods Hole, Massachusetts
Physiology course

1974-1975 CHILDREN'S HOSPITAL MEDICAL CENTER
Department of Surgical Research, Boston, Massachusetts
Research Associate

Summer 1976 DEPARTMENT OF HEALTH, EDUCATION and WELFARE
Office of the General Counsel, Chicago, Illinois
Law Clerk

VISITING COMMITTEE

1992-1994 UNIVERSITY OF CHICAGO LAW SCHOOL

UNIVERSITY ACCREDITATION

2008- WESTERN ASSOCIATION OF SCHOOLS AND COLLEGES,
Chair of LLU Accreditation Committee

SPECIAL PROJECTS

1982-1988 THE ROBERT WOOD JOHNSON FOUNDATION
Program for Hospital Initiatives in Long-Term Care,

1989-1990 THE PEW CHARITABLE TRUSTS
THE ROBERT WOOD JOHNSON FOUNDATION
Program to Strengthen Hospital Nursing Co-Director

CORPORATE ADVISORY POSITIONS AND COMMITTEES

- 2008 - TPG,
Senior Advisor
- 2007 GOOGLE HEALTH ADVISORY COUNCIL
- 2007 REVOLUTION HEALTH GROUP
Medical Advisory Board
- 2007 PERSEUS LLC
Advisory Board
- 2003 - FLEISHMAN HILLARD INTERNATIONAL COMMUNICATIONS
International Advisory Board
- 2000 – 2003 PERSEUS-SOROS BIOTECHNOLOGY FUND Scientific Advisory Board

ADVISORY COMMITTEES

- 2007 THE RHODES TRUST, THE RHODES SCHOLARSHIPS
Chair, California Selection Committee
- 2006 CENTER FOR THE ADVANCED STUDIES ON AGING, UNIVERSITY OF
MIAMI External Advisory
Group
- 2005 - BROAD MEDICAL RESEARCH PROGRAM
Advisory Board
- 2005 - CLINTON SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES
National Advisory Board
- 2003 HEINZ AWARDS (HEINZ FAMILY FOUNDATION)
Awards Juror
- 2003 MARCH OF DIMES
Chair, Prematurity Campaign in Northern California
- 2002 – 2004 CENTER ON ALCOHOL MARKETING AND YOUTH AT GEORGETOWN
UNIVERSITY Advisory Board

- 2001 - UNIVERSITY OF CHICAGO LAW REVIEW
Editorial Advisory Board
- 2000 – 2005 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
Oversight Committee
- 2000 GOVERNOR'S BLUE RIBBON COMMISSION ON MENTAL HEALTH,
STATE OF CONNECTICUT
Honorary Chair
- 2000 - FILM AID INTERNATIONAL, INTERNATIONAL RESCUE COMMITTEE
Advisory Board
- 1999 WORLD HEALTH ORGANIZATION
Expert Panel on Tobacco
- 1997 ADVISORY COMMITTEE ON TOBACCO AND PUBLIC HEALTH
(Co-Chairman with C. Everett Koop)
- 1993 GOVERNMENT UNIVERSITY INDUSTRY ROUNDTABLE
National Academy of Sciences
- 1990 ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION
Chairman, Drugs and Biologics Subcommittee
- 1988 – 1989 NATIONAL ADVISORY COUNCIL ON HEALTH CARE TECHNOLOGY
ASSESSMENT, Department of Health and Human Services, Washington, D.C.
Chairman, Patient Outcomes Subcommittee

PRIOR FEDERAL COMMITTEE MEMBERSHIPS

WHITE HOUSE COMMISSION ON PRESIDENTIAL SCHOLARS

NATIONAL COUNCIL ON SCIENCE AND TECHNOLOGY
Committee on Health, Safety and Food R&D, Vice Chair

INSTITUTE OF MEDICINE
Forum On Drug Development and Regulation

INSTITUTE OF MEDICINE
AIDS Roundtable

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

OFFICE OF SCIENCE AND TECHNOLOGY POLICY Federal Coordinating
Council for Science, Engineering and Technology Committee on Life Science
and Health Biotechnology Research Subcommittee, Member ex officio

BOARDS OF DIRECTORS

Current:

AMHERST COLLEGE BOARD OF TRUSTEES

ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION
Chairman, Board of Directors

NATIONAL CENTER FOR ADDICTION AND SUBSTANCE ABUSE
COLUMBIA UNIVERSITY

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES INDEPENDENT
CITIZENS OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE
FOR REGENERATIVE MEDICINE

Past:

1999-2007 HENRY J. KAISER FAMILY FOUNDATION

2003-2006 DOCTORS OF THE WORLD

1997-2003 YALE-NEW HAVEN HOSPITAL

1999-2003 CONSUMERS UNION

2000-2002 NATIONAL COMMITTEE FOR QUALITY ASSURANCE

2000-2003 NEW YORK COUNTY HEALTH SERVICE REVIEW ORGANIZATION

1985-1986 COMPREHENSIVE MEDICAL REVIEW ORGANIZATION

FELLOWSHIP

YALE COLLEGE Fellow,
Calhoun College

LECTURESHIPS

THE REGIS J. FALLON LECTURE SERIES ON HEALTH AND LAW
University of Chicago

GRAYSON DISTINGUISHED LECTURE
Southern Illinois University School of Law

WEINBERG SYMPOSIUM LECTURE
Harvard Medical School

THE THOMAS B. FERGUSON LECTURE
Society of Thoracic Surgeons

GEORGE E. ALTMAN, M.D. LECTURE
Beth Israel Hospital

BETH AND RICHARD SACKLER LECTURE
University of Pennsylvania

MARTIN W. WITTE LECTURE
Newport Beach Public Library and Newport Beach Public Library Foundation

HERBERT L. ABRAMS LECTURE
Harvard Medical School

GEORGE GOODMAN LECTURE
State University of New York at Stony Brook

EVNIN LECTURE
Princeton University, Woodrow Wilson School

BOYARSKY LECTURE
Law, Medicine, and Ethics, Kenan Ethics Program, Duke University

CHARTER LECTURE
The University of Georgia

GARDERE & WYNNE LECTURE
Health Law and Policy Institute, University of Houston

DISTINGUISHED LECTURE IN NATIONAL SERVICE
University of Miami

TENTH ANNUAL JOHN O. VIETA, MD LECTURE
Lenox Hill Hospital

HARPER FELLOWSHIP LECTURE
Yale Law School

DR. JAMES STEWART KAUFMAN MEMORIAL LECTURE
The Mt. Sinai Health Care Foundation

DULCY B. MILLER MEMORIAL LECTURE
Smith College

JEAN MAYER LECTURE IN NUTRITION AND FOOD POLICY
Tufts University

HENRY BARNETT DISTINGUISHED LECTURESHIP
Albert Einstein College of Medicine

MARTIN A. CHERKASKY DISTINGUISHED LECTURESHIP
Robert Wagner Graduate School of Public Service New York
University

ALPHA OMEGA ALPHA DISTINGUISHED LECTURESHIP
Cornell Medical School--New York Hospital

ST. GEORGE SOCIETY LECTURESHIP
Johns Hopkins Medical School

GOVERNOR WINTHROP ROCKEFELLER DISTINGUISHED LECTURESHIP
University of Arkansas Medical School

MOLLY AND SIDNEY N. ZUBROW LECTURE
Pennsylvania Hospital

LEROY HOECK M.D. DISTINGUISHED LECTURESHIP
Children's Hospital National Medical Center

JULES AND JANE HIRSH HEALTH POLICY ADDRESS
George Washington University

JOHN S. LATTA LECTURESHIP
University of Nebraska Medical School

PAUL K. SMITH MEMORIAL LECTURE
George Washington University

WOLK HEART FOUNDATION LECTURE
Colgate University

HASTINGS LECTURE

Association for the Advancement of Medical Instrumentation
National Heart, Lung and Blood Institute

INSTITUTE OF MEDICINE 25TH DISTINGUISHED LECTURESHIP University
of Washington

RALPH CAZORT LECTURESHIP

Meharry Medical School

DAVID M. IFSHIN MEMORIAL LECTURE

Potomac, Maryland

CHARLES C. LEIGHTON MEMORIAL LECTURE

Leonard David Institute of Health Economics
University of Pennsylvania

D. W. HARRINGTON LECTURE

State University of New York At Buffalo School of
Medicine and Biomedical Sciences

SAMUEL RUBIN LECTURE FOR THE ADVANCEMENT OF LIBERTY

Columbia University

LEO S. WEIL MEMORIAL LECTURE

Tulane Medical Center, Touro Infirmary,
and Louisiana State University School of Medicine

THOMAS PARRIN LECTURE

University of Pittsburgh School of Public Health

DAVID PACKARD LECTURE

Uniformed Services University of the Health Sciences

NORMAN E. ZINBERG LECTURE

Harvard Medical School

JOHN H. ERSKINE LECTURE

St. Jude's Children's Research Hospital

MARTIN V. BONVENTRE MEMORIAL LECTURE

The Brooklyn Hospital Center

PURVES LECTURE

Woodbridge Library, Woodbridge, Connecticut

VISITING SCHOLAR LECTURE University of
Oklahoma - Board of Regents Oklahoma Scholar
Leadership Extension Program

J. ROSWELL GALLAGHER LECTURER
Society of Adolescent Medicine

KATHERINE BOUCOT STURGIS LECTURESHIP
American College of Preventive Medicine

HELMUT SCHUMANN LECTURE
Dartmouth-Hitchcock Medical Center

50TH ANNIVERSARY COMMUNICATION LECTURE
Centers for Disease Control and Prevention

5TH JAMES BORDLEY III MEMORIAL LECTURE
Mary Imogene Bassett Hospital

TURNER LECTURE
University of California

MARIE SHULSKY MEMORIAL LECTURE ON HEALTH AND
SOCIAL RESPONSIBILITY
Fifth Avenue Synagogue, New York, New York

GERTRUDE AND G.D. CRAIN, JR. LECTURE SERIES
Medill School of Journalism, Northwestern University

GEORGE ARMSTRONG LECTURE
Ambulatory Pediatric Society

ARCO FORUM OF PUBLIC AFFAIRS
Institute of Politics, John F. Kennedy School of Government
Harvard University

PAUL LEVINGER LECTURE AND PROFESSORSHIP PRO TEM IN THE
ECONOMICS OF HEALTH CARE Brown University

ARNOLD J. SCHWARTZ MEMORIAL HEALTH LECTURE
Robert F. Wagner Graduate School of Public Service New York
University

RONALD ALTMAN MEMORIAL LECTURE
Festival of Arts, Books and Culture, Cherry Hills, New Jersey

SAMUEL MARTIN, M.D. III MEMORIAL LECTURE Division of
General Internal Medicine and Leonard Davis Institute University of
Pennsylvania

CARL J. MARTINSON, M.D. MEMORIAL LECTURESHIP ON HEALTH
PROMOTION AND DISEASE PREVENTION University of Minnesota

LEONARD SILK MEMORIAL LECTURE Mt.
Desert Island Biological Laboratories

CALDWELL LECTURE
American Roentgen Ray Society

RICHARD H. DENT LECTURE St.
George's School

ROBERT T. WONG DISTINGUISHED PROFESSORSHIP
University of Hawaii, Manoa

COMMUNITY/PUBLIC SERVICE AWARDS

NATIONAL ASSOCIATION FOR THE ADVANCEMENT OF COLORED
PEOPLE
Montgomery County Chapter
Person of the Year

LEAGUE OF WOMEN VOTERS, NEW YORK
Carrie Chapman Catt Award

COMMON CAUSE
Public Service Achievement Award

AMERICAN ACADEMY OF PEDIATRICS
Excellence in Public Service

BUSINESS WEEK
Best in Public Service

GEORGE ORWELL AWARD FOR HONESTY AND CLARITY
IN PUBLIC LANGUAGE
National Conference of Teachers of English

ANTI-DEFAMATION LEAGUE OF B'NAI BRITH
Man of Achievement Five Towns, New York

GOLDEN SLIPPER CLUB OF PHILADELPHIA
Golden Slipper Award

NATIONAL FATHER'S DAY COMMITTEE
Father of the Year Award

UNITED SENIORS HEALTH COOPERATIVE
Seniors Advocate Award

NATIONAL ASSOCIATION OF GOVERNMENT COMMUNICATORS
Communicator of the Year Award

NATIONAL CONSUMERS LEAGUE
Trumpeter Award

THE INTERNATIONAL PLATFORM ASSOCIATION
George Crile Award

AMERICAN LUNG ASSOCIATION of New York
Life and Breath Award in Public Health

CONSUMER FEDERATION OF AMERICA
Philip Hart Public Service Award

CAMPAIGN FOR TOBACCO FREE KIDS
Distinguished Service Award

MEDICAL SOCIETY OF NEW YORK, 1st District Branch
Public Service Award

ONCOLOGY NURSING SOCIETY
Public Service Award

PUBLIC VOICE FOR FOOD & HEALTH POLICY
Special Recognition Award for Advancing the Consumer Interest in Food and
Agriculture Policy

ATTENDING PEDIATRICIAN

2003-present UNIVERSITY OF CALIFORNIA, SAN FRANCISCO MEDICAL CENTER

1997-2003 YALE-NEW HAVEN HOSPITAL

1982-1990 BRONX MUNICIPAL HOSPITAL CENTER

1982-1990 NORTH CENTRAL BRONX HOSPITAL

1982-1990 MONTEFIORE MEDICAL CENTER

1982-1990 HOSPITAL OF THE ALBERT EINSTEIN COLLEGE OF MEDICINE

COMMUNITY ACTIVITIES

SCARSDALE SCHOOL DISTRICT, Scarsdale, New York

1986-1990 Legislative Affairs Advisory Committee

1988-1990 Buildings and Facilities Advisory Committee

1990 SCARSDALE STUDENT TRANSFER EDUCATION PLAN, Board of Trustees

CERTIFICATIONS

NATIONAL BOARD OF MEDICAL EXAMINERS AMERICAN BOARD OF PEDIATRICS (Recertified 1997, 2002)

GENERAL INFORMATION

Address:
2715 Steiner Street
San Francisco, CA 94123

Office Phone:
(415) 929 1121

Married:
Paulette Kessler

Two children – Elise and Ben

Born:
May 31, 1951

MEDICAL LICENSURE

California
Connecticut (non-active)
Maryland (non-active)
New York (non-active)

PUBLICATIONS

Books

Kessler, David A., A QUESTION OF INTENT: A GREAT AMERICAN BATTLE WITH A DEADLY INDUSTRY, Public Affairs (Hardcover 2001) (Paperback 2002)

Kessler, David A. THE END OF OVEREATING: TAKING CONTROL OF THE INSATIABLE AMERICAN APPETITE, Rodale, 2009 (pub in 10 countries)

Edited Books

Eisdorfer, Carl, Kessler, David A., Spector, Abby (eds.), CARING FOR THE ELDERLY: RESHAPING HEALTH POLICY, Johns Hopkins University Press, 1989. Includes chapter by Coombs, C., Eisdorfer, C., Feiden, K., and Kessler, D.A. "Lessons from the Program for Hospital Initiatives in Long-Term Care."

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Kessler, David A., "Nicotine Addiction in Young People," NEW ENGLAND JOURNAL OF MEDICINE, 333:186-189 (July 20, 1995)

Kessler, David A., "Accelerating the Approval of Drugs for Life-Threatening and Serious Diseases," SCIENTIFIC AMERICAN, 272:48-52 (March 1995)

Kessler, David A., Rose, Janet L., Temple, Robert J., Schapiro, Renie and Griffin, Joseph, "Therapeutic Class Wars: Drug Promotion in a Competitive Marketplace," NEW ENGLAND JOURNAL OF MEDICINE, 331:1350 (November 17, 1994)

Kessler, David A., Merkatz, Ruth B., Schapiro, Renie, "A Call for Higher Standards for Breast Implants," JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 270:2607-2608 (December 1, 1993)

Kessler, David A., Siegel, Jay P., Noguchi, Philip D., Zoon, Kathryn C., Feiden, Karyn L., and Woodcock, Janet, "Regulation of Somatic Cell Therapy and Gene Therapy by the Food and Drug Administration," NEW ENGLAND JOURNAL OF MEDICINE, 329:1169-1173 (October 14, 1993)

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Kessler, David A. for the Working Group, "A New Approach to Reporting Medication and Device Adverse Effects and Product Problems," JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 269:2765-2768 (June 2, 1993)

Kessler, David A., Taylor, Michael A., Maryanski, James H., Flamm, Eric L., and Kahl, Linda S., "The Safety of Foods Developed by Biotechnology," SCIENCE, 256:1747-1749 (June 26, 1992)

Kessler, David A., "The Basis for the FDA's Decision on Breast Implants," NEW ENGLAND JOURNAL OF MEDICINE, 326:1713-1715 (June 18, 1992)

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Kessler, David A., "Drug Promotion and Scientific Exchange," NEW ENGLAND JOURNAL OF MEDICINE, 325:201-203 (July 18, 1991)

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Kessler, David A., Myers, Matthew, "Beyond the Tobacco Settlement," NEW ENGLAND JOURNAL OF MEDICINE, 345:535-537 (August 16, 2001) (editorial)

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Koop, C. Everett, Kessler, David A., Lundberg, George D., "Reinventing American Tobacco Policy - Sounding the Medical Community's Voice," JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 279:550-552 (February 18, 1998) (editorial)

Kessler, David A., "Addressing the Problem of Misleading Advertising," ANNALS OF INTERNAL MEDICINE, 116:950-951 (June 1, 1992) (editorial)

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Kessler, David A., "Remarks by the Commissioner of Food and Drugs," FOOD AND DRUG LAW JOURNAL, 52:1-5, presented at the Food and Drug Law Institute's 39th Annual Educational Conference, Washington, D.C. (December 10-11, 1996)

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Kessler, David A. "The Academic/Industry Interface: The Risks of Scientists Becoming Entrepreneurs," HOPKINS MEDICAL NEWS, Fall 1993:58

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Kessler, David A., "Remarks--1991 Annual DIA Meeting," DRUG INFORMATION JOURNAL (October 1991)

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EXPERT REPORT OF DAVID M. KESSLER - APPENDIX D

APPENDIX D

DR. DAVID KESSLER TESTIFIED AT TRIAL OR DEPOSITION IN THE FOLLOWING CASES INCLUDING THE LAST FIVE YEARS:

FOR THE UNITED STATES:

UNITED STATES OF AMERICA, Plaintiff,
v. PHILIP MORRIS USA INC. f/k/a PHILIP MORRIS INC., *et al.*,
Civil No. 99-CV-02496 (GK)

FOR THE STATE OF CALIFORNIA:

PEOPLE'S ADVOCATE AND NATIONAL TAX LIMITATION
FOUNDATION
V. INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
(ALAMEDA COUNTY SUPERIOR COURT, STATE OF CALIFORNIA
(case # HG05206766)

IN RE: NEURONTIN MARKETING, SALES, PRACTICES AND PRODUCTS
LIABILITY LITIGATION
UNITED STATES DISTRICT COURT, DISTRICT OF MASSACHUSETTS,
MDL DOCKET 1629

IN RE: VIOXX® STATE OF LOUISIANA,
EX REL. JAMES D. CALDWELL,
ATTORNEY GENERAL, *PLAINTIFF*, V.
MERCK SHARPE & DOHME CORP., *DEFENDANT*.
UNITED STATES DISTRICT COURT, EASTERN DISTRICT OF
LOUISIANA CASE NO. 05-3700

PHARMATHENE, INC, PLAINTIFF V.
SIGA TECHNOLOGIES INC, DEFENDANT
IN THE COURT OF CHANCERY OF THE STATE OF DELAWARE
CIVIL ACTION NO. 2627-VCP

BROWN et al. v. AMERICAN TOBACCO et al
SAN DIEGO SUPERIOR COURT, CALIFORNIA

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF TENNESSEE
SMITH & NEPHEW, INC., VS NEW HAMPSHIRE INSURANCE COMPANY, ALLIED
WORLD ASSURANCE COMPANY, LTD., ZURICH INSURANCE COMPANY, GERLING
KONZERN ALLGEMEINE VERSICHERUNGS AG, and ASSICURAZIONI GENERALI
S.p.A. (UK Branch), Cause No. 04-3027-B/V

Hourly Rate: \$1,000/hour