EXHIBIT F

EXPERT REPORT

DAVID A. KESSLER, M.D.

TABLE OF CONTENTS

I. QUALIFICATIONS 3

II. FDA'S REGULATION OF NEW DRUGS 5

A. FDA's Standards For Approval 5

B. The FDA's Scientific Standards to Establish Effectiveness 6

C. Drugs Are Regulated Based On Their Intended Conditions Of Use and May Not Be Promoted Or Marketed for Non-Approved Or Off Label Uses 10

III. FDA REGULATIONS AND STATE TORT LIABILITY USUALLY OPERATE INDEPENDENTLY, EACH PROVIDING A SIGNIFICANT YET DISTINCT LAYER OF CONSUMER PROTECTION 18

IV. THE REGULATORY STATUS OF RISPERDAL 22

A. Risperdal's Regulatory History in Adults 22

B. Risperdal's Regulatory History in Children and Adolescents 25

V. JOHNSON AND JOHNSON TARGETED CHILDREN AND ADOLESCENTS WITH CONDUCT DISORDER AND OTHER UNAPPROVED INDICATIONS IN THEIR MARKETING OF RISPERDAL 33

A. Johnson and Johnson Developed Sophisticated Strategies to Promote Risperdal Use in Children 33

B. Johnson and Johnson Marketed and Promoted Risperdal by Supporting and Drafting Publications in Medical Journals 43

C. Johnson and Johnson Engaged In Other Activities That Promoted Off-Label Uses 52

D. Johnson and Johnson's Sales Force Promoted Risperdal for Use in Children 58

VI. WHILE PROMOTING RISPERDAL FOR NON-APPROVED USES IN CHILDREN, JOHNSON AND JOHNSON DENIED PHYSICIANS THE OPPORTUNITY TO KNOW THAT RISPERDAL WAS ASSOCIATED WITH ENDOCRINE ABNORMALITIES THAT WERE GREATER THAN DISCLOSED IN THE DRUG'S LABEL 63

VII. JANSSEN FAILED TO PRESENT THE DATA ABOUT ELEVATED PROLACTIN LEVELS IN AN OBJECTIVE FASHION 68

VIII. CONCLUSIONS 71

IX. SCHEDULES 78

Schedule 1 – Statutory and Regulatory Misbranding Provisions of the Federal Food, Drug, and Cosmetic Act That Make Off-Label Promotion Illegal 78

Schedule 2 – Pharmaceutical Manufacturers Knew Off-Label Promotion Rendered a Drug Misbranded in Light of the Warnings and Actions by the FDA, U.S. Congress and the Courts 81

Schedule 3: The FDCA and FDA's Regulations Do Not Prohibit Manufacturers from Disseminating Truthful, Non-misleading Information about Risks Associated with Unapproved Uses 84

Schedule 4: Excerpta Medica's Communication Plans for Risperdal 86

APPENDIX A 93

APPENDIX B 115

APPENDIX C 116

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 ("FDA") 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.

4. I have held professorships in pediatrics, epidemiology and biostatistics at Yale University, Albert Einstein College of Medicine, and the University of California at San Francisco. I have served as an attending pediatrician on the hospital staffs of these universities. In my role as attending, I have been involved in assessing treatment options in children and the weighing of the risks and benefits of their care.

5. My resume, including a list of my published books and articles, is included in Appendix A. Cases in which I have testified in the last several years are listed in Appendix B.

6. As Commissioner of the FDA, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act (the "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, 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 to investigate suspected criminal violations of the Act, FDA regulations and other related laws.

7. I am a senior advisor to TPG Capital, a leading global private equity firm that 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.

8. 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 C to this report. At my request, Appendix C 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.

9. I refer interchangeably in this report to Janssen Pharmaceutica Inc. and Ortho-McNeil Janssen (both as "Janssen") and Johnson and Johnson.

II. FDA'S REGULATION OF NEW DRUGS

A. FDA's Standards For Approval

10. Under United States 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. (21 U.S.C. § 321).

11. The law requires that "adequate and well-controlled investigations" be used to demonstrate a drug's safety and effectiveness. (Id. at § 355(d)).

12. 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. (Id. at § 355(d)(5)).

13. The "intended conditions" for use of a drug are listed in the drug's labeling which is reviewed and approved by the FDA. (Id. at §§ 355(d)(1), (2)).

14. Indications for use that are not listed in a drug's labeling have not been approved by the FDA.[1]

15. In my opinion, one of the reasons why we have a system that imposes the responsibility on the purveyor of a drug to test and establish the safe doses of a drug and to submit such data to the FDA for review and approval prior to marketing, is to obviate situations where individual physicians are experimenting in an effort to determine the effectiveness of powerful and potentially dangerous drugs.

---

[1] "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)).

16. In my opinion, physicians are rarely in the position to determine whether a drug is safe and effective. That is the responsibility of a manufacturer.

B. The FDA's Scientific Standards to Establish Effectiveness

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

18. The statutory requirement that a drug's effectiveness be demonstrated by "adequate and well-controlled clinical investigations" has been interpreted to mean a clinical 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. (21 C.F.R. § 314.26).

19. The FDA has published a notice that sets 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. (International Conference on Harmonisation: Guidance on General Considerations for Clinical Trials 62 Fed. Reg. 66113-02 (December 17, 1997)). 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 --

20. "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 --

21. "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 --

22. "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 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 --

23. 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). (Id. at 66117-66118).

24. 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, "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 of the Act 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 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." (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, 3-4 (May 1998) (footnote omitted)).

25. The FDA usually considers one clinical trial insufficient to support approval. (Peck C & Wechsler J, 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). 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 barriers" in conducting a second placebo-based trial. (Id. at 523).

26. 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.

C. Drugs Are Regulated Based On Their Intended Conditions Of Use and May Not Be Promoted Or Marketed for Non-Approved Or Off Label Uses

27. It is not a drug, by itself, that is regulated or 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.

28. The 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)).

29. 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.*)

30. 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)).

31. 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")).

32. 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. (*Id.* at § 321(p)).

33. 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. 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.

34. 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.

35. As Senator Kefauver explained at the time of enactment: "The 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 . . . ." (S. Rep. No.

87-1744, *supra*, at 2901-2903 (statement of Senators Kefauver, Carroll, Dodd, Hart & Long, explaining reasons for changing definition of "new drug")).

36. 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.

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

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

39. 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)).

40. 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.*)

41. 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 a purpose for which it is neither labeled nor advertised.

42. 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 accompany 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)).

43. "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)).

44. 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 exchange" and "promotional activities." While the promoting or advertising of investigational drugs 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. (*See generally* Kessler DA & Pines WL. The Federal Regulation of Prescription Drug Advertising and Promotion. JAMA 1990; 264(18):2409-2415).

45. The criteria to distinguish educational from promotional activities include the degree to which a program is "independent" of the drug company. (*Id.* at 2411). "The more directly involved the company is, the more concerned FDA becomes about its promotional dimensions. Financial relationships between the speakers and the company may cause FDA to categorize the activity as promotional." (*Id.*).

46. In 1997, FDA published guidance for the industry on the proper limits of sponsorship of continuing medical education (CME) activities. (Department of Health and Human Services, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074-01 (Dec. 3, 1997)). This guidance document stresses that CME programs must be independent of influence of the drug manufacturer. (*Id.* at 64094-64096).

47. The Act was amended in 1997 by the 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; *but see* FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New

Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm (last visited August 24, 2012)). 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).

48. 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. The district court issued an injunction limiting certain aspects of FDA's restrictions on off-label speech and finding certain provisions of the Act as amended by 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")).

49. 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")).

50. In certain specific circumstances, FDA has permitted the dissemination of reprints of medical publications. Articles may be disseminated only 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.

51. 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.

52. 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.

53. 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.

54. 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)).

55. 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.

56. 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.

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

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

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

60. 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.

61. 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.

62. 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)). For additional statutory analysis see Schedule 1 *infra.*

63. FDA has voiced serious concerns regarding the promotion of drugs for 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. (Testimony on Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources, 103rd Cong. 5 (February 22, 1996) (statement of William B. Schultz, FDA Deputy Commissioner for Policy), *available at* http://www.hhs.gov/asl/testify/t960222a.html (last visited August 27, 2012)).

64. 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 its 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. *See* Schedule 2 *infra*.

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.

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

65. The purveyor of a drug 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.

66. 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.

67. 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 operate in a complementary but independent manner.

68. As I have written and testified before the United States Congress, the Act grants FDA substantial authority over the approval, labeling, and promotion of pharmaceutical products. Nothing, however, in the Act 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.

69. 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.

70. 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 that 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)).

71. 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.

72. 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 been definitely established." (21 CFR § 201.57(c)(6); see also 21 C.F.R.§ 314.70 (c)(6)(iii)(A)-(C); see generally, David Kessler & David Vladeck, A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims, 96 Geo. L.J. 461 (2008) (discussion of manufacturers' responsibility to change the label in the face of new safety information.)).

73. 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.

74. Moreover, as the Institute of Medicine and Government Accountability Office have noted, during the 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 (Alina Baciu, et al., eds.) 2007, at 4).

75. The Government Accountability Office stated in its report titled, "Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process" that [t]wo 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