

EXPERT REPORT
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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 (“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 Baciuc, 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

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. (GAO, “Improvement Needed in FDA’s Postmarket Decision-making and Oversight Process,” Highlights of GAO-06-402, March 2006).

76. In sum, what a drug company knows about a drug and what the FDA knows may be different.

77. 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. Johnson & Johnson’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. THE REGULATORY STATUS OF RISPERDAL

A. Risperdal’s Regulatory History in Adults

78. Risperdal, whose generic chemical name is risperidone, is an atypical antipsychotic.

79. Risperdal is a selective monoaminergic antagonist with affinity for serotonergic 5-HT₂ and dopaminergic D₂ receptors. The drug binds to alpha₁–adrenergic receptors, with lower affinity to H₂ histaminergic and alpha₂–adrenergic receptors. Risperdal is a potent dopamine D₂ antagonist. On first-pass metabolism through the liver, Risperdal is hydrolyzed to 9-hydroxy-risperidone.

80. Risperdal is a powerful drug. It is associated with an increased mortality including stroke in some elderly patients, neuroleptic malignant syndrome and tardive dyskinesia. It is associated with a greater than 7 percent weight gain and metabolic changes.

81. In a Janssen 2002 presentation, the incidence in children and adolescents with Risperdal of somnolence was 51 percent; headache 29 percent; vomiting 20 percent; dyspepsia 15 percent; weight increase 15 percent; hyperprolactinemia 13 percent; increased appetite 11 percent; and rhinitis 11 percent. [JJRE08976757]

82. Risperdal's use in child and adolescent psychiatric conditions is controversial. See Sharna Olfman and Brent Dean Robbins (editors), *Drugging Our Children*, Praeger 2012.

83. A May 17, 2010 press release from the National Institute of Mental Health stated, "Effectiveness of Long-term Use of Antipsychotic Medication to Treat Childhood Schizophrenia is Limited. Few youths with early-onset schizophrenia who are treated with antipsychotic medications for up to a year appear to benefit from their initial treatment choice over the long term, according to results from an NIMH-funded study. . . . The NIMH Treatment of Early Onset Schizophrenia Study (TEOSS) included 116 youth between 8 and 19 years old, diagnosed with early onset schizophrenia spectrum disorder (EOSS). The TEOSS Team randomly assigned the children to 8 weeks of either olanzapine (Zyprexa) or risperidone (Risperdal) – both new generation atypical antipsychotics – or to the older convention antipsychotic molindone (Moban). Response rates after eight weeks of treatment were comparable among the three medications. . . . After the initial 8-week trial, 54 of the 116 participants entered the maintenance treatment phase in which they continued their initial medication and were monitored up to 44 more weeks of treatment. Only 14 participants completed the additional 44 weeks of treatment." <http://www.nimh.nih.gov/science-news/2010/effectiveness-of-long-term-use-of-antipsychotic-medication-to-treat-childhood-schizophrenia-is-limited.shtml>.

84. Janssen submitted NDA 20-272 for Risperdal to the FDA on April 15, 1992. On December 29, 1993, FDA approved Risperdal for "management of manifestations of psychotic

disorders” in adults. The antipsychotic efficacy of Risperdal was established in short-term (6-8 weeks) controlled trials of schizophrenic inpatients. As the label then indicated, the effectiveness of Risperdal, in long-term use, that is more than 6-8 weeks, had not been systematically evaluated in control trials. There was a Precaution for hyperprolactinemia with a statement that “although disturbances such as . . . gynecomastia . . . have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.” In the section entitled Adverse Reactions, under the subsection “Other Events Observed During the Pre-Marketing Evaluation of Risperdal,” the label listed “Endocrine Disorders: Rare: gynecomastia”.² The label stated that Risperdal’s “safety and effectiveness in children have not been established”. [Physician’s Desk Reference 1995, p. 1193-1197]

85. In September 2000, the FDA requested a class label change for Risperdal, from being indicated for the “management of the manifestations of psychotic disorders” to being indicated for the “treatment of schizophrenia.” [JJRP 00459722-724] Janssen made the change in February 2002, with an implementation first run date in April 2002, at which time the label stated that Risperdal’s “safety and effectiveness in children have not been established”. [JJRIS 03129537; Risperdal label, February 2002, Part Number 7503220]

86. On March 3, 2002, the FDA approved a supplemental new drug application for Risperdal for the longer term efficacy in the treatment of schizophrenia. [JJRE 06116490] The label stated that Risperdal’s “safety and effectiveness in children have not been established”. [JJRE 06116507]

² According to Janssen’s Risperdal label “rare events are those occurring in fewer than 1/1000 patients.” As the label states, this definition of “rare” adverse events was adopted from the International World Health Organization preferred terms.

87. On December 4, 2003, the FDA approved Risperdal for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder and as adjunctive therapy with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults. [JJRE 07713922] The label stated that Risperdal's "safety and effectiveness in children have not been established." [JJRE 07713941]

B. Risperdal's Regulatory History in Children and Adolescents

88. On August 15, 1996, Janssen submitted a supplemental new drug application for a change in the labeling for Risperdal to include the addition of a new section for pediatric use. In this submission, Janssen provided the FDA with a summary of safety data for all pediatric age groups and efficacy data for children aged 2-12 years and adolescents aged 12-16 years. [JJRIS 01230685]

89. On September 17, 1997, FDA's Dr. Paul Leber, Director, Division of Neuropharmacological Drug Products, Office of Drug Evaluation, Center for Drug Evaluation and Research wrote to Janssen and stated:

"We have completed our review and find the information presented is inadequate, and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Your supplement proposes the expansion of Risperdal use into pediatric patients, however, you never state for what child or adolescent psychiatric disorders Risperdal would be intended. Indeed, you acknowledge that you have not provided substantial evidence from adequate and well-controlled trials to support any pediatric indications nor developed a rationale to extend the results of studies conducted in adults to children. Your rationale for proposing this supplement appears to be simply that, since Risperdal

is being used in pediatric patients, this use should be acknowledged in some way in labeling.” [Id.]

90. The FDA also stated:

“1. Under the Pharmacokinetic subsection of Clinical Pharmacology, you propose acknowledging that no systematically collected PK data are available, but you refer nevertheless to the Dosage and Administration section.

2. Under the Pediatric Use subsection of Precautions, you refer to ‘limited evidence regarding the safety and effectiveness of risperidone in the pediatric population,’ and again refer to the Dosage and Administration section.

3. Finally, in the Dosage and Administration section, you again suggest that there is limited evidence of safety and effectiveness from ‘small clinical studies, literature reports, and spontaneously reported adverse events.’ As noted, you never state in this language what indications are supported by these data. Regarding safety, you simply suggest that the safety profile for Risperdal appears to be similar in pediatric patients to that observed in adults. Nevertheless, you advise caution, i.e., avoidance of prescribing in neonates and infants, and cautious titration, beginning with 0.25 mg/day in children and adolescents.” [Id.]

91. Dr. Leber further stated:

“You have provided very little information to support these proposed labeling changes. You acknowledge that the supplements provide no interpretable efficacy data. The safety data submitted were also very limited, including data for n=14 pediatric patients exposed to Risperdal in Janssen-sponsored studies, n=29 pediatric patients exposed to Risperdal in studies reported in the published literature, and n=186 spontaneous reports involving pediatric patients exposed to Risperdal. None of these

data were suggestive of any unusual or unexpected adverse events occurring specifically in association with the use of Risperdal in the pediatric age group.” [JJRIS 01230686]

92. The FDA concluded:

“Accordingly, we must conclude that there is inadequate support for the changes sought. As noted, you have not identified any pediatric indications for which you believe Risperdal could be approved and you have provided no data from adequate and well controlled trials to support any such approvals. There were no specific safety findings of sufficient concern among the meager safety data submitted to justify adding any information to labeling about the safety experience with this drug in the pediatric age group. To permit the inclusion of the proposed vague references to the safety and effectiveness of Risperdal in pediatric patients and the nonspecific cautionary advice about how to prescribe Risperdal for the unspecified target indications would serve only to promote the use of this drug in pediatric patients without any justification. Consequently, this supplement is not approved.” [Id.]

93. As part of IND 31,931 [Janssen’s ongoing new drug investigation] on January 19, 1999, Janssen submitted to FDA protocol RIS-INT-41, “The long term safety and efficacy of Risperdal in conduct disorder in mild, moderate and borderline mentally retarded children aged 5-14 years.” That study was a long-term open-label extension study of RIS-CAN-19, (submitted 9/8/98, Ser. #192). [JJRIS 01230740].

94. On June 28, 1999, FDA’s Dr. Russell Katz stated that an “assessment of the effects of risperidone on the developmental process is needed” and requested that studies in two animal species be initiated as soon as possible. [JJRIS 00572567] Dr. Katz stated, “Considering the age range of the intended patient population, we recommend dosing from as soon after birth as is feasible through sexual maturity. In addition to routine toxicological

parameters, the evaluation of drug-related effects on growth, and neurological, behavioral, and reproductive development should be included as appropriate.” [Id.]

95. Janssen responded on October 19, 1999, “We do not agree that additional developmental toxicity studies need to be conducted to assess the effects of risperidone on the developmental process to support the above referenced trial. We base our conclusion on the extensive amount of nonclinical and clinical data currently available for Risperdal.” [JJRIS 01230781]

96. On November 24, 1999, Janssen requested a meeting with the FDA to discuss the pediatric development of Risperdal. The objectives of the meeting, according to Janssen, were: (1) to discuss the requirements to obtain an additional six months market exclusivity, and (2) obtain an “agreement on the clinical development plan for an indication in conduct disorder.” [JJRP 00012396]

97. Janssen conducted five trials involving pediatric patients with conduct disorder including two comparative trials (RIS-USA-93, RIS-CAN-19) and three long-term open extension trials (RIS-USA-97, RIS-CAN-20, RIS-INT-41). These were referred to as the DBD (Disruptive Behavioral Disorder) database. More specifically, these protocols involved:

RIS-USA-93 - The safety and efficacy of risperidone versus placebo in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 12 years. Trial ended October 6, 1998. [JJRE 05002596]

RIS-USA-97 – The safety and efficacy of open-label risperidone in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 12 years. Trial period ended September 16, 1999. [JJRE 08413273, at -279]

RIS-CAN-19 – The safety and efficacy of risperidone versus placebo in conduct disorder in mild, moderate and borderline mentally retarded children aged 5 to 12 years. Trial period ended July 1, 1999. [JJRE 05011838]

RIS-CAN-20 – Risperidone in the treatment of disruptive behavior disorders in children with intellectual limitations. One year continuation study. Trial period ended August 14, 2000. [JJRE08400029]

RIS-INT-41 – The long-term safety and efficacy of risperidone in conduct disorder in mild, moderate and borderline mentally retarded children aged 5-14 years. Trial period ended July 10, 2001. [JJRE 08408869, at -871] [RIS-INT-70 is a one year extension of RIS-INT-41. JJRE08398771, at -183. RIS-HUN-4 is a two year extension study of RIS-INT-41. JJRE 01190135, at -146.]

98. In a March 2000 meeting with the FDA, the FDA stated the following, according to Janssen: (1) “FDA questioned the validity of Conduct Disorder (CD) as a diagnosis and even the concept of CD as a disorder”; (2) “Even though CD is in DSM-IV that does not mean it is a disorder warranting an indication in the label”; (3) “FDA felt a public hearing is needed to define how to look at CD” and “FDA main concern is that Risperdal or any other product would be used as a chemical straight jacket. This is the reason the issue needs to be public ally [sic] debated”; (4) “FDA believes aggression is synonymous with CD”; (5) FDA said Janssen “[c]ould proceed with the trials proposed [sic] RIS-USA-161 and RIS-USA-222. However, even if these trials are positive, they [FDA] would want a consensus advisory committee meeting to confirm the disorder exists. This AC [Advisory Committee] meeting would be triggered by the review of our [Janssen’s] supplemental application”; and (6) the Division was “willing to work with us [Janssen] to define scales for CD and would like to

see our [Janssen's] data to show their validity and reliability". [JJRE 01521705, at -707] [*See also* JJRIS 00533590]

99. In response to Janssen's question to the FDA "Are the proposed studies RIS-USA-161 and RIS-USA-222 adequately designed to evaluate the safety and efficacy of risperidone in non-mentally retarded children with conduct spectrum disorder?" FDA stated, among other comments, that "they can not accept the use of the Nisonger Scale as the primary endpoint." [JJRIS 00533590, at -593]

100. Earlier, on December 19, 1996, FDA told Janssen regarding their protocols for conduct disorder in mentally retarded children (CDMR) that "it was this inexactitude that troubles them [FDA] about both [CDMR and dementia] programs." FDA went on to say that the "new indications should be done in a similar manner to what the Agency required for pain, in that new analgesics must be tested in more than one model to gain approval." [JJRIS 00773372]

101. In a letter regarding Janssen's investigational trials for Risperdal in conduct disorder, FDA stated on January 22, 1997 that "[w]e have several comments concerning the objectives of the studies. The program described in this submission is ostensibly focused on the entity conduct disorder, involving aggressive behaviors as target symptoms. . . . There would need to be a reliable and valid means of determining whether subjects entered in the clinical trials have the disorder for which the drug is intended when marketed." [JJRIS 00773373]

102. Janssen continued to do clinical trials in disruptive behavior including RIS-INT-79. [JJRE 01521705, -707]. This protocol involved investigation of Risperdal in children and adolescents aged 5-17 years. RIS-INT-79 was a randomized, double-blind, placebo-controlled trial in children and adolescents with conduct and other disruptive behavior disorders.

103. On December 19, 2003, Janssen submitted a supplemental NDA #20-272/S-036 for use and treatment of autism in children and adolescents. [JJRIS 01239616]

104. On February 18, 2004, Janssen's Vidyasagar Adusumalli stated that he was arranging a meeting "to explore ideas on a possible indication supported by results . . ." [JJRE 01521705, at -707]

105. On February 19, 2004, Janssen's Katie Rielly-Gauvin wrote in an e-mail, "We are exploring whether we could go back at CD [conduct disorder] with FDA." [Id. at -706]

106. On February 19, 2004, Janssen's Gahan Pandina wrote in an email with the subject line "Conduct Disorder", "I have discussed this extensively . . . re: new submission in DBD given the new relapse prevention data from RIS-INT-79. Looks like there is forward motion on exploring this as a possibility to revisit with FDA. I will keep you posted." [JJRE 022431397]

107. In a subsequent email, Janet Vergis, Janssen's PGSM, Worldwide VP, CNS Strategic Marketing, wrote that one of the problems with the prior submission was that Janssen was proposing to use a drug for conduct disorder *in mental retardation*. [JJRE 02243575, emphasis added]

108. A draft publication dated January 21, 2005, co-authored by Gahan Pandina stated, "In recent years converging lines of evidence documented a bi directional and significant overlap between conduct disorder and bipolar disorder in children. Data from clinical samples show that about half of youth with a diagnosis of conduct disorder will also satisfy diagnostic criteria for bipolar disorder, and vice versa." [JJRE 06895957, at -959]

109. On May 19, 2005, Johnson & Johnson PRD received a non-approvable action on the supplemental NDA for risperidone treatment in children and adolescents with Autistic Disorder. FDA had the following concerns: (1) proposed dosing recommendations, (2)

proposed initial dose, (3) that the lowest doses used are associated with an unacceptably high incidence of important adverse events including somnolence, parkinsonism, confusion, fatigue, (4) and may be associated with an unacceptable risk of long-term consequences (e.g. tardive dyskinesia, sequelae of prolonged increased prolactin), and (5) interpretation of cognitive testing. [JJRE 03608580, at -584-85]

110. It appears that Janssen ceased to pursue an indication for children and adolescents with conduct disorder and, rather, pursued indications for monotherapy in bipolar mania in children and adolescents aged 10-17 and irritability associated with autistic disorder in children and adolescents aged 5-16 years.

111. On October 6, 2006, FDA approved Janssen's supplemental new drug application for Risperdal in the treatment of the irritability associated with autistic disorder. [JJRE 12781651]

112. On August 22, 2007, FDA approved Janssen's supplemental new drug application for Risperdal's use in the treatment of Bipolar I Disorder in children and adolescents (ages 10-17) and in the treatment of schizophrenic adolescents (ages 13-17). [JJRE 14293409]

113. The FDA has never approved Risperdal for the treatment of conduct disorder, disruptive behavior disorder, depression, ADHD, tics, or Tourette's syndrome.

114. Johnson and Johnson attempted to develop Risperdal for treatment of disruptive behavior disorders in children and adolescents.

115. Johnson and Johnson did not secure approval from the FDA nor demonstrate to the FDA that Risperdal was safe and effective for treating disruptive behavior disorders in children and adolescents.

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

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

116. Johnson and Johnson knew in December 2000 that “ADHD/conduct disorder is the largest pediatric market, with over twice as many diagnosis visits as the combined pediatric affective disorders.” [JJRIS 02628249]

117. Johnson and Johnson knew the “Risperdal pediatric sales in 2000” was “forecast at \$167MM as compared to \$307MM for the entire pediatric class”. [Id.]

118. Johnson and Johnson knew that Risperdal pediatric prescriptions were “growing at nearly 50% annually . . .” [Id.]

119. Johnson and Johnson knew that the “ADHD/Conduct Disorder total pediatric market is forecast at \$821MM in 2000, of which \$54MM is antipsychotic sales.” [Id.]

120. Johnson and Johnson knew that “autism represents a small pediatric market . . . Antipsychotics account for 30% of Autism drug uses.” [Id.]

121. Johnson and Johnson knew that, as of December 2000, Risperdal had a “58% share of the pediatric APS Affective Disorder Market (Bipolar Disorder, Anxiety and Depression.” [Id.]

122. In a 2001 Risperdal business plan summary, Johnson and Johnson stated, “Growing our base business is a critical area of focus. In 2001 we will also appropriately leverage the data and the business opportunity within the child/adolescent market via medical education.” [JJRE 00579070, at -072] [emphasis added]

123. Janssen further stated in the 2001 business plan “in addition, using appropriate medical education prescribers will understand how to effectively use RISPERDAL in other indications like bipolar disorders . . . and conduct disorders.” [Id. at -073]

124. A 2001 “Risperdal Base Business Plan” stated among its “One Year Marketing Objectives” to “grow and protect share in children/adolescents via medical education initiatives and effective rep-targeting with a year-end exit share of 70%.” [JJRErev 00601258, at -269]

125. The 2001 “Risperdal Base Business Plan” had as one of its key strategies to “protect and expand, reach/partnerships with key customer base . . . child/adolescents.” [Id. at -270]

126. The 2001 “Risperdal Base Business Plan” stated “several medical education and tactical programs will be supported in 2001.” [Id.]

127. The 2001 “Risperdal Base Business Plan” stated as one of its critical success factors “drive pediatric, acute medical education.” [Id. at -271]

128. The 2001 “Risperdal Base Business Plan” stated that it intended to “disseminate key studies under WLF.” [Id.] Janssen was apparently referring to the Washington Legal Foundation case *see supra*. In the case of Risperdal, *see infra*, Janssen established a sophisticated publication plan that controlled and influenced the publication of scientific articles on Risperdal, and thus were not written independently of the company.

129. Thus, Janssen planned to use medical education and sales representatives in 2001 to influence doctors to prescribe Risperdal for non-approved uses in children.

130. While physicians may prescribe medicines for non-approved uses based on their independent judgment, pharmaceutical companies may neither promote drugs for non-approved uses nor use physicians to promote or “educate” other physicians about non-approved uses.

131. In my opinion, Janssen developed a corporate strategy to illegally promote Risperdal for use in conditions such as conduct disorder taking advantage of the fact that Risperdal was on the market for other FDA-approved indications.

132. As discussed *supra*, pharmaceutical companies are prohibited from using third party entities to engage in promotion for which the company itself may not engage.

133. A March/April 2000 document titled “Qualitative Research for Risperdal in Pediatrics,” undertaken by the Resolution Group, Inc. set out market research objectives, which included efforts to “refine the messages included in the Risperdal data monograph, including assessing the accuracy, appeal, and relevance of Risperdal messages among target prescribers.” [JJRE 01526520, at -522] Both telephone and in-person interviews were conducted with child and general psychiatrists for whom more than 20% of their patients were younger than 19. [Id. at -523] These included child psychiatrists who prescribed at least 25 atypical anti-psychotic prescriptions during the past month for children. [Id.] According to the survey, Risperdal was “more likely to cause increased prolactin levels, gynecomastia, lactation”, “causes daytime sedation”, and “more likely to cause extrapyramidal symptoms (EPS), including tremor and stiffness.” [Id. at -540] The document also stated “Risperdal patients can get extrapyramidal rigidity, Parkinsonian side effects like drooling, and sometimes females lactate. This happens in about 3% to 5% of Risperdal recipients. The weight gain with atypicals is the biggest problem. Lactation is also a serious problem; everyone panics and we have to stop the Risperdal.” [Id.]

134. According to this survey, physicians prescribing atypical anti-psychotics in pediatric patients “prefer educational media,” for “receiving new data.” [JJRE 01526543]

135. According to this survey, a monograph shown to the doctors “effectively communicated the availability of clinical evidence to support the efficacy and safety of

Risperdal in children with conduct disorder. Typical take-away messages: ‘Risperdal is safe and effective in conduct disorder, regardless of whether the patient is mentally retarded’, ‘Risperdal is good for conduct disorder in children and adolescents.’, ‘Risperdal is an effective and convenient agent to use in conduct disorder with a low risk of toxicities.’, ‘Risperdal has been tested in younger children and shown to be effective,’ ‘Risperdal works; we are on the right track,’ “Risperdal can control conduct disorder at low doses.” [JJRE 01526546]

136. In the survey, 37% of the physicians who prescribe pediatric anti-psychotics stated that the Risperdal data “will increase use.” [JJRE 01526560]

137. For the 37% of physicians who said they would “change-increase use,” “the data are convincing for Risperdal in children with conduct disorder: ‘I would reconsider Risperdal in these kids. I am open minded. I was initially scared of the risk of TD and other adverse events, but it appears to be useful without significant safety problems at the doses that were used. The availability of small tablet sizes and a liquid makes it easier to consider.’” [JJRE 01526562]

138. Around 2002, Janssen developed a “Risperdal Child and Adolescent Market Segment 2002 Business Plan Summary.” [JJRE 00041039] While the plan stated that it “will reflect the market preparation and drug commercialization efforts necessary to gain a pediatric label,” the plan set out “key business strategies” including efforts to “educate health care providers on therapeutic options for treating mental illness in children.” [Id. at -041, -045]

139. According to this summary, “2002 represents the first year a RISPERDAL child and adolescent business plan has been prepared.” [Id. at -043]

140. The summary acknowledged “LT safety concerns-Prolactin, weight gain.” [Id. at -044]

141. The summary also recognized as a weakness that “clinical data does not meet FDA requirements” and that there was “limited clinical development program ongoing.” [Id.]

142. This summary also recognized “lack of consensus-no diagnostic specificity.” [Id.]

143. This summary stated that “The overall tactical budget for the child and adolescent program is \$6.6 million.” [Id. at -045]

144. The tactics in the plan included “CME deliverables: Psychiatric Centers of Excellence, Case Review Network, Excellence in Education Home Study Kit, Audio Tape Program, and Poster Book.” [Id. at -046]

145. According to Janssen, “the psychiatric centers of excellence program will be a full day CME program in the form of a preceptorship for clinicians at a nationally recognized child and adolescent center. The program will consist of a pediatric psychopharmacology review, case presentations, and actual patient consultations in an interactive format. The cost of this program is \$350,000 in the form of a CME grant to the accrediting organization. The first two programs will be completed by the end of April. The next two programs will be completed by the end of July. The final two programs will be completed by November.” [Id.]

146. Janssen also stated that “The case review network will consist of a CME audio tape series involving nationally recognized academicians discussing difficult case presentations and how to appropriately treat these patients. The series will involve multiple case presenters and multiple patient profiles to create a library of diagnostic and symptomatic case reviews. The cost of the program is \$400,000 in the form of a CME grant to the accrediting organization. This program will be completed by the end of September.” [Id.]

147. Janssen further stated, “The excellence in education home study kit will [sic] a self study based CME program that involves several different CME tools. The centerpiece of

the program will be the development of a CME textbook on pediatric psychopharmacology. The cost of this program will be \$500,000 in the form of a CME grant to the accrediting organization. This program is scheduled to be completed in November.” [Id.]

148. Janssen also stated, “The audio tape program will be an interactive CME program consisting of a pre-recorded presentation combined with a live, interactive question and answer session with the presenter. This program will be offered nationwide at 12-16 predetermined dates and times. All interested clinicians will be welcome to participate. The program cost will be \$300,000 in the form of a CME grant to the accrediting organization. The live programs will be completed in September. . .” [Id.]

149. Janssen stated, “The CME poster book consists of all relevant posters presented at the 2002 APA in the area of pediatric psychopharmacology. The posters will be bound in a book format with a full CME review quiz of each poster. The cost of this program will be \$125,000 in the form of a CME grant to the accrediting organization, using the same CME metrics for success already reviewed. The poster book will be available in October.” [Id. at -046-47]

150. As part of its efforts, Janssen was to “develop educational message for prescribers and caregivers” and “evaluate Risperdal C&A data with prescribers” and was to finish these objectives in the second and first quarters of 2002, respectively. [Id. at -051]

151. Janssen’s 2002 business plan summary stated that “all CME programs will target child and adolescent psychiatrists due to cost constraints. If additional funding becomes available or if programs come in under budget, these programs will be opened up to primary care physicians.” [Id. at -047]

152. The 2002 business plan summary for Risperdal child and adolescent projected market size growth from \$249M in 1999 to \$343M in 2000 and \$437M in 2002, representing a 37.7% and 27.2% increase, respectively. [Id. at -049]

153. The Janssen 2003 Child and Adolescent and Other New Business Plan specifically “targeted medical education to pediatricians and neurologists.” [JJRE 02399406, at -419]

154. The Janssen 2003 Child and Adolescent and Other New Business Plan stated, “Develop educational platform to establish the role of APSs in the treatment of C&A mental illness. Key Tactic#1: ‘Branded’ educational initiative; Description: Multi- medium, comprehensive branded educational campaign on the role of APS in the treatment of C&A mental health: Centers of excellence, Regional CME symposia, monographs; Audience: National and regional key opinion leaders, community based physicians. Key Tactic#2: Academic collaboration (MGH and CAPRI)” [Id. at -421]

155. The Child and Adolescent and Other New Business Plan recognized “limited education and awareness of appropriate use of APSs.” [Id. at -419]

156. The Child and Adolescent and Other New Business Plan also stated “Leverage J&J-MGH Pediatric Psychopathology Center to drive educational needs.” [Id.]

157. The Child and Adolescent and Other New Business Plan, in an effort to establish Risperdal as having a favorable risk-benefit ratio, stated: (1) “Neutralize safety and tolerability concerns”, (2) “Leverage current datasets”, (3) “Develop EMRP plan addressing datagaps: ADHD, bipolar disorder, autism, acute agitation, Tourette’s”, and (4) “Maximize RUPP autism publication.” [Id.]

158. Key tactics of the Child and Adolescent and Other New Business Plan were: “Key Tactic#1: Re-analysis and dissemination of CDMR database addressing: prolactin,

EPS/TD, weight gain, development, PK Key Tactic#2: Conduct selected EMRP studies targeting: Treatment-refractory ADHD, Bipolar disorder, Acute agitation, Autism, Tourette's." [Id. at -422]

159. The July 29, 2002 Child and Adolescent and Other New Business Plan documented that, for 2002, Janssen spent \$3,890,000 in Risperdal C&A [child & adolescent] for "Medical Marketing/Education" which included the following activities: (1) CME Branded Initiative, (2) PsychLink/Teletopics, (3) Symposia (2), (4) Publications, and (5) National Ad Board. [Id. at -426]

160. The July 29, 2002 Child and Adolescent and Other New Business Plan documented that, for 2003, Janssen proposed to spend \$3,300,000 in Risperdal C&A [child & adolescent] for "Medical Marketing/Education". [Id.]

161. The July 29, 2002 Child and Adolescent and Other New Business Plan documented that, for 2002, Janssen spent \$1,800,000 for advisory boards, \$160,000 for grants, \$225,000 for "other" for Risperdal C&A [child & adolescent]. The plan also documented that Janssen proposed to spend, in 2003, \$1,900,000 for advisory boards, \$300,000 for grants, and \$400,000 for "other". In Risperdal C&A, Janssen also spent \$325,000 in 2002 for public relations and proposed to spend \$500,000 in 2003 including \$400,000 for a C&A summit. [Id.]

162. Janssen's total for PME [Product Marketing Expense] for Risperdal C&A in 2002 was \$6,400,000 and a similar amount was proposed to be spent in 2003. [Id.]

163. Janssen's documents are specific that these expenses were "marketing expenses". [PME is referred to in Janssen documents as product marketing expense. See generally for the phrase "PME" JJRE 00762736.]

164. Critical success factors for these efforts included among others, (1) "Maximize existing clinical data including dissemination and re-analyses", (2) "Generate new data in key

diagnostic/symptom areas”, and (3) “Gaining acceptance of the usage of APS in C&A.” [JJRE 02399427]

165. Janssen targeted physicians whose (1) “Majority of practice patient load must be pediatric”, and who were (2) “Local thought leaders in their communities (for HOV and RAB)”, or (3) “National thought leaders with extensive research experience (for National Advisory Board).” [JJRIS 00355756, at -770] These physicians were invited to attend either a home office advisory forum, regional advisory meeting or a national advisory board. [Id.] 433 physicians were targeted. [Id.] Meetings were held in Los Angeles, CA on August 16-18, 2002; Boston, MA on July 12-14, 2002; Charleston, SC on April 19-21, 2002; Miami, FL on September 19, 2003; New York, NY on November 15, 2002; Titusville, NJ on March, 26, 2003. –[Id. at -775] Child and Adolescent home office visit meetings were also held on April 10-11 (North Central), May 15-16 (Mid Atlantic), June 26-27 (South Central)³, July 10-11 (West) and September 25-26 (Northeast). [Id. at -756] [JJRIS 00370138, at -142]

166. Presentations at these advisory committees included the efficacy of “risperidone on affective symptoms” in children. [JJRIS 00355816]

167. On June 27, 2002, Janssen held a CNS/Child and Adolescent Advisory Forum where Janssen obtained “feedback regarding the Risperdal current dataset in pediatrics.” There were two one-and-a-half-hour presentations on Risperdal child and adolescent clinical data overview. [J-TX2515382]

168. Janssen included a slide that stated, “Throughout this advisory meeting, you will encounter information that discusses the use of Risperdal that is outside of currently approved product labeling. This information is presented to you as advisors for Janssen Pharmaceutica

³ Dr. Vernon Johnson of Sherman, TX, was reported to have attended this meeting. Janssen’s records indicate that Dr. Johnson was “called on” and in the 90th APS decile. [JJRE 00755908]

and is not intended to promote or encourage the use of Risperdal in these indications.” [JJRE 08976702, at -704]

169. Janssen’s Peter Dorson, Pharm.D., highlighted that antipsychotics are used to treat common symptoms observed across different diagnoses including, (1) disruptive behavioral disorder, (2) ADHD, (3) conduct disorder, (4) mental retardation, (5) bipolar disorder, (6) autism, (7) schizophrenia, and (8) anxiety. The symptoms Dr. Dorson highlighted included (1) Aggression, (2) Agitation, (3) Hyperactivity, (4) Hallucinations, (5) Delusions, (6) Mania, (7) Self-Injurious Behavior, and (8) Mood Instability. [Id. at -744]

170. Janssen’s Peter Dorson, Pharm.D, presented efficacy data on (1) disruptive behaviors, (2) psychotic symptoms, (3) autistic disorder symptoms (4) mood symptoms, and (5) Tourette’s disorder. [Id. at -743]

171. In his presentation, Dorson stated that, “risperidone 0.02-0.06 mg/kg/day was effective for treating behavioral and adaptive/prosocial symptoms.” [Id. at -749]

172. Data on the children and adolescents with aggression was also presented.

173. Dorson also discussed the use of risperidone in autism and related pervasive developmental disorders. [Id. at -778]

174. According to Dorson, the most responsive symptoms included, among others, aggression, SIB, hyperactivity, repetitive behavior and impaired social behavior. [Id. at -778]

175. Dorson stated that risperidone is an “effective treatment for tics in people with Tourette’s syndrome.” [Id. at -803]

176. None of the indications that Dorson discussed were approved in children and adolescents.

177. In my opinion, Johnson and Johnson, under the guise of medical advisors, promoted the unapproved use of Risperdal in children and adolescents.

178. In light of Johnson and Johnson’s expressed business plans, including statements such as “one year marketing objectives” to “grow and protect share in children/adolescents via medical education initiatives,” it is not, in my opinion, credible to say that Johnson and Johnson’s activities were not promotional.

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

179. In July 2001, Excerpta Medica Inc. prepared for Janssen Pharmaceutica Products a “Strategic Publication Plan for Risperidone Mood Disorders: 2002-2003”. This international publication plan was prepared “at the request of Janssen Pharmaceutica Products.” [JJRIS 00726096] (Janssen executed a Master Agency Agreement on or about October 26, 1999. [JJRIS 00935332]⁴)

180. As stated by Excerpta Medica, “This international publication plan, prepared by Excerpta Medica, Inc. at the request of Janssen Pharmaceutica Products, LP, addresses the publication of clinical data and marketing claim-driven risperidone mood disorder messages. It focuses on an approximate 2-year period beginning in late 2001 in order to aggressively counter competitive activity. Overall, the plan supports risperidone’s market expansion into the treatment of patients with bipolar disorder and, more broadly, into the treatment of patients with mood disorders.” Excerpta Medica further stated, “The publication activities suggested in this plan are intended to maximize risperidone’s advantages while putting disadvantages, real or perceived, into clinical perspective. Timely dissemination of the risperidone mood disorder messages will help establish the position of risperidone in this highly competitive sector and counterbalance the positions and claims of the competition, namely, olanzapine, ziprasidone, quetiapine, and imminently, aripiprazole. Thus, the plan identifies and manages the content, direction and timing of data dissemination to maximum competitive advantage.” It also states,

⁴ See Schedule 4 for more detail concerning Excerpta Medica’s activities including Risperdal.

“The plan presents suggestions for awareness and review articles that reach out to an audience broader than the current psychiatric base as well as topic-driven articles highlighting a diverse range of emerging and current issues of special interest to psychiatrists, and original papers and case reports. Publication of original articles would be based on the availability of clinical data and supporting analyses.” [JJRE 00726098, at -99]

181. The plan targeted publications such as the *Journal of the American Academy of Child and Adolescent Psychiatry*. An example of a major topic was “Bipolar disorder in adolescents: adjunctive, treatment with risperidone.” An example of a message was, “Focus: Safety and efficacy in adolescents with bipolar disorder Core messages: Faster symptom [sic] relief (one week) in mania than olanzapine; effective in mania with or without psychosis; optimal atypical for long-term treatment due to decreased risk of weight gain, hyperglycemia/diabetes, and sedation than other atypicals; predictable and manageable side effect profile at correct dose (vs ziprasidone); optimal dosing in acute mania is 2 mg to 4 mg; no induction of mania.” Work on the article was to begin 3rd quarter 2001 and submitted 4th quarter 2001. [JJRE 00726114]

182. According to the plan, “Major target audiences as identified by Janssen Pharmaceutica Products, LP: Psychiatrists (general, geriatric, pediatric).” [JJRE 00726102]

183. Furthermore, according to the plan, the manuscript developing process included (1) Start-up Meeting – Week 0; (2) Meeting w/author & Excerpta Medica – Week 1; (3) Outline drafted – Week 4; (4) Review by author/Janssen – Week 5; (5) 1st draft – Week 9; (6) Review by Janssen – Week 11; (7) Incorporate comments – Week 14; (8) Review by author – Week 16; (9) 2nd draft – Week 17; (10) Review by Janssen/author – Week 19; (11) Final draft + submission package – Week 20; and (12) Target submission date – 5 Months. [JJRE 00726127]

184. According to the plan, different types of articles would be priced accordingly. The proposed budget included (1) Awareness articles – 15 @ \$22,000 each; (2) Review articles – 4 @ \$22,000 each; (3) Topic awareness articles – 6 @ \$22,000 each; (4) Case series – 7 @ \$9,000 each; (5) Brief reports (posters) – 6 @ \$9,000 each; and Original reports – 24 @ \$22,000 each. [JJRE 00726138]

185. According to an internal Janssen email, “the starting point” for publication planning “will be to consider the following for each product and therapeutic area: message requirements, target audiences, primary data availability, gap identification, secondary (review) requirements, manuscript generation processes, management of databases and reporting and communication. This will obviously be a detailed and time-consuming process. . . . [W]e will be able to redefine how we achieve support for messaging through publication, and thereby achieve even greater commercial success in the marketplace.” [J-TXPandina01965, at -66]

186. On February 14-15, 2002, Johnson and Johnson employees participated in a two-day workshop held in Princeton. According to a document prepared by FSP, International, “the aim of the MERCURA workshop for Risperdal was to review, validate and refine positioning and key messages for Risperdal in . . . disruptive behavioral disorder (all age groups).” [J-TXCID1058268]

187. According to the document, attendees were asked to verify the target audiences. For Risperdal in disruptive behavioral disorders, “This audience includes those who initiate treatment for DBD, i.e. pediatricians and other specialists. Secondary targets, depending on market stage and health system, could include teachers, who are an important target audience for Concerta but may be less so for Risperdal. Regulatory authorities may also be important (such as the State Government in Florida which is responsible both for the treatment of children

in care and for regulating the use of drugs such as Risperdal in children).” [J-TXCID1058270] and [J-TXCID1058271]

188. A gap analysis of different messages was performed for Risperdal in disruptive behavior. Messages were rated according to whether (1) it can be supported, (2) It can be supported by ongoing study activities, and (3) It cannot be supported now or (currently) in the future. [J-TXCID1058301]

189. Janssen employees concluded that the message that Risperdal is available in kid friendly formulations “can be supported now and can be supported by ongoing study activities”.

190. Janssen employees concluded that the message, “The low prolactin elevation sometimes seen with Risperdal treatment is not (directly) linked to clinical abnormalities” “can be supported by ongoing study activities.” [J-TXCID1058301] and [J-TXCID1058308]

191. Janssen employees concluded that the message that “Risperdal treatment leads to improved patient and family function” “cannot be supported now or (currently) in the future.” [J-TXCID1058301] and [J-TXCID1058308]

192. In 2002, a tactical secondary publication plan was developed for Risperdal in Disruptive Behavior Disorders (DBD) by Wells Healthcare—Partners in Communication. “This secondary publication plan for Risperdal in DBDs aims to promote the disease, the product in this indication and to target the key messages to the audience in a logically, comprehensive order.” [JJRE 00644621, at -622] [Emphasis Added]

193. According to this tactical publication plan “publication management is critical in the successful marketing of Risperdal in disruptive behavior disorders [DBDs].” The document “details the tactical implementation of the secondary publication plan for Risperdal in DBDs,

and should be used in conjunction with the primary publication plan for Risperdal in DBDs and the overall strategic plan for Risperdal.” [JJRE 00644624]

194. The tactical plan stated “A number of media will be used to distribute key messages for Risperdal in DBD in secondary publications . . . Symposia: Company-sponsored symposia attract large audiences at international congresses and provide an excellent forum with which to present detailed overviews of the study results. In addition, symposia programs can be planned to give the full story of the product for a general audience, or to focus on a specific aspect of the product for a more specialized audience . . . Journals: All data from primary publications will be recycled into review articles. These will reinforce the clinical messages in the primary publications and add the marketing messages not covered in the primaries. These can be aimed at a variety of journals: specialist child psychiatry, general psychiatry, general pediatrics and publications read by primary care physicians. The usual time between submission and publication is between 6 and 9 months. Appendix II details the journals relevant or possibly relevant to Risperdal DBDs publication plan.” [JJRE 00644625]

195. This tactical plan included “Critical Messages,” including, among others, (1) “Children and adolescents who require treatment, along with their parents, can be confident in the data supporting safety/tolerability of Risperdal in this age group.” (2) “700+ children/adolescents studied for up to 1 year (IQ range – 35-84).” (3) “Tolerability maintained in the long term.” (4) “Low dropout rate due to adverse events.” (5) “Low incidence of extrapyramidal symptoms (EPS), comparable to placebo.” (6) “Low incidence of tardive dyskinesia (TD).” (7) “Modest weight gain.” (8) “Mild, transient hyperprolactinaemia that returns to normal range within 48 weeks and no report of major short- or long-term health consequences.” (9) “Transient somnolence, declining after 2 weeks.” [JJRE 00644630 – 00644631]

196. According to a December 2003 Risperdal publication plan status report that was distributed to several dozen Johnson and Johnson employees, numerous manuscripts involving pediatrics and Risperdal were being managed. [J-TXCIDrev 1511780]

197. Manuscripts being managed included: (1) Pharmacokinetics of ris in treatment of conduct and other disruptive disorders in children, adolescents, and adults with subaverage IQ or mental retardation (Findling, Reed, Vermeulen, Plotroviskij, Mannaert, Remmerle), (2) RIS-USA-97, A Long-Term Open-Label Study of Risperdone in Children with Severe Disruptive Behaviors and Below-average IQ (RL Findling, MG Aman, A. Derivan, Lyons, M. Eerdeken, (3) RIS-INT-41, Risperidone in children with disruptive behavior disorders: a 1-year study open-label study of 504 patients (Croonenberghs, Fegert, Findling, De Smedt), (4) RIS-INT 47/GBR-29 & RIS-INT-39GBR-28: Short and long-term efficacy and safety of risperidone in adults with conduct disorder and other disruptive behavior disorders (Gaglana, Read, Thorpe, Eerdeken, Van Hove), (5) RIS-USA-297 Asperberger disorder as a negative symptom spectrum disorder (Raush, Sinola, Londino, Corley), (6) Treatment of Child and Adolescent Aggression in Patients with Bipolar Disorder: A Case Series (Saxena, Steiner, Change) 10 case reports of children/adolescents with bipolar disorder, (7) Open-label study of risperidone in children with in utero drug exposure (Barnett), (8) RIS-USA-93 sub, RIS and affective symptoms in children with disruptive behavior disorder (DBD) – Biederman, Faraone, Mick, van Patten, Pandina, Gharabawi, (9) Prolactin Levels in Children Treated Long-Term With Risperidone – Findling, Kusumakar, Daneman, Moshang, de Smedt, Binder, (10) RIS-USA-257, 1.8 year Outcomes with Risperidone Treatment in Children – Lan, Rosenquist, Ghaemi, (11) RIS-USA-297b Asperger's Disorder as a Negative Symptom Disorder: An Open Trial of Risperdal –Londino, Raush, (12) RIS-USA-183 Efficacy of Risperidone in preschool children with autism and severe pervasive developmental disorders –NOS – Luby, (13) RIS-

USA-93 sub, RIS and cognitive function in children with DBD – Pandina, Binder, Keefe, Gharabawi, (14) RIS-USA-283 Ris in pediatric patients with epilepsy (Gonzalez-Heydrich, Pandina, Fleisher, Hsin, Raches, Bourgeois, Biederman), (15) Review of clinical trial data on DBD (RIS-USA-93, RIS-USA-97, RIS-INT-41, RIS-CAN-19, RIS-CAN-20) (Summary of data on RIS in DBD, relevance to clinical practice (with children) (Biederman, Jensen, Paulsen, Leventhal, Thacker, all TBD), (16) Atypical antipsychotics [sic] in managing severe behavioral problems in autistic children (L. Scahill, to be confirmed), (17) Concurrent Psychotropic and Atypical Antipsychotic Use in Pediatric Inpatients – Flanders, Findling, Pandina, Youngstrom, Jensik, Rupnow, Carlson, (18) Treatment Outcomes in Pediatric Inpatients Treated with Atypical Antipsychotics – Flander, Findling, Pandina, Youngstrom, Jensik, Rupnow, Carlson, (19) Risperidone and cognitive function in children with disruptive behavior disorders – Pandina, Keefe, Bilder, Harvey, Aman, Zhu, Bossie, Gharabawi, (20) Trends in antipsychotic use in children and adolescents: 1996-2000 – Patel, Sanchez, Johnsrud, Crismon, (21) RIS-CAN-23, RIS in children with pervasive developmental disorders (PDD) – Shea, Turgay, Orlik, Smith, Jones, Dunbar, (22) RIS-USA-297 Asperger’s Disorder as a “Negative Symptom Spectrum Disorder”: A Comparison with Schizophrenia, Schizotypal and Schizoid Personality Disorder, and Assessment of Response to Risperidone – Sirota, Rausch, (23) Negative Symptom Spectrum Disorders Responsive to Pharmacotherapy; The Case for Asperger’s Disorder – Rausch, Sirota, Corley, Londino, Janowsky, (24) RIS-USA-307, Open label study of risperidone in children with bipolar disorder – Biederman, (25) RIS-USA-293, A Prospective Comparison of Risperidone Vs. Mood Stabilizers in Pediatric Bipolar Disorder – Pavuluri, Henry, Carbray, Sampson, Naylor, Janicak, (26) Aggression in Children with Disruptive Behaviour Disorders – Binder, LeBlanc, Wang, Kusumakar, (27) Prosocial and Other Item Changes on a Standardized Rating Scale in Children – Aman, Binder, (28) A Hungarian 2-year

open-label extension study of the long-term safety and efficacy of risperidone in children with conduct disorder and borderline-to-moderate mental retardation, (29) RIS-INT-70 An international, 1-year open-label extension study on the long-term safety and efficacy of risperidone in children with conduct disorder and below average IQ – Reyes-Harde and TBD, (30) Neuropsychological and neuroanatomic concomitants of bipolar disorder in children – Pandina, et al., (31) Meta-analysis of the affective symptoms from DBD trials (a broadening and validation of the previous work presented at AACAP last year.) – Pandina, et al., (32) Meta-analysis of the ESRS data from the broader dataset – Pandina, et al., (33) Diane C. said Magali might want to submit an abstract to APA: combined, 2 parts of trials, ext trial of INT-41 and RIS 70?, (34) RIS-USA-93m RIS in treatment of children with DBD and subavg IQ: a double-blind placebo controlled study – Aman M et al (35) Antipsychotic Drug Treatment in the Prodromal Phase of Schizophrenia – Cannon, Huttonen, Dahlstrom, Larmo, Rasanen, Juriloo, (36) The use of RIS for anorexia nervosa – Carver, Miller, (37) RIS-INT-41, Risperidone in Children and Adolescents with Severe Disruptive Behavior and Subaverage IQ – Croonenberghs, Findling, Fegert, Aman, DeSmedt, (38) Growth and sexual maturation during treatment with RIS – Dunbar, Kusumakar, Daneman, Schulz, (39) RIS-USA-97, Long-term open label study of RIS in children with severe disruptive behaviors and subavg. intelligence – Findling, et al., (40) RIS-CAN-20, Long-term safety and efficacy of low dos RIS in children with subavg IQ and disruptive behavior disorders, (41) Non-Em – Gonzalez-Heydrich, Fleisher, Raches, Biederman, (42) RIS-USA-143, RIS vs. HAL in adolescents with psychosis – Lieberman, Sikich, (42) (RUPP STUDY-not EMRP) A Double-Blind Placebo-Controlled Trial of Risperidone in Autistic Disorder – McDougle, Aman, McCracken, Scahill, Tierney, Vitiello, & the RUPP Autism Network, (43) RIS-USA-93//RIS-CAN-19 pooled analyses, Risperidone

in children with oppositional defiant disorder, conduct disorder, subaverage IQ and comorbid ADHA – Turgay, Aman, Binder, and the Conduct Study Group, and (44) RIS-CAN-19.

198. In August 2000, an email from Excerpta Medical’s Michelle Daniels to Dr. Robert Findling stated, “Excerpta Medica is working with Janssen to prepare a manuscript based on the results of RIS-USA-97. ‘The Safety and Efficacy of Open-Label Risperidone in Conduct Disorder in Mild, Moderate and Borderline Mentally Retarded Children Aged 5 to 12 Years.’ You have been identified as the lead author to this manuscript which is targeted for the American Journal of Psychiatry. A companion manuscript from the RIS-USA-93 study with Dr. Aman, as the lead author is also being prepared. Attached is a preliminary outline for your manuscript. A copy of the outline for Dr. Aman’s manuscript is attached as well, for your information. Your input on the outline for your manuscript is appreciated.”

[EMRISP00035590, at 591-92]

199. Dr. Findling responded and suggested that “some secondary analyses be performed in an attempt to identify risk factors for weight gain and prolactin increase . . .”

[EMRISP00035593]

200. In response to the manuscript submitted by Dr. Aman, the *American Journal of Psychiatry* Deputy Editor wrote: “You need to fix the discussion of adverse events. Do not minimize the possible risks involved. A five-pound weight gain in just six weeks is worrisome, as patients in real life will take medication for much longer. The same must be clearly stated about prolactin increase (we simply do not know the long-term risk of hyperprolactinemia to young children) and somnolence (again, what will happen to cognition after one year?)”

[EMRISP00035005, at -007]

201. A November 19, 2002 teleconference that involved Janssen officials documented a Risperdal DBD Publication Team Teleconference. Among the manuscripts and preparations that were discussed was a manuscript, “Prolactin paper – Findling *et al.*: Incorporate bioactive pro active vs inactive data. CB to send to OM for referencing and to GDS to approve- Action CB. Target Journal JCP. Bioactive/inactive data included. Issue on handling recommendation for monitoring arose. Full disclosure on not including gynecomastia was recommended for handling dose-response issue. Inserted phrase to be deleted and manuscript to be re-circulated (Action CB).” [EMRISP0436866, at -867]

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

202. A Johnson and Johnson budget for 2003 listed budgeted items for “C&A and AAP (American Academy of Pediatrics), MedEd/CME program, AACAP (American Academy of Child and Adolescent Psychology)”. [JJRE 00042145]

203. A Risperdal child and adolescent 2003 budget listed \$525,000 for the following symposiums: APA 2003 Symposia – Findling; AACAP Symposia Oct. 22-27, 2002; AACAP 2003; AACAP 2004; AAP; and APA 2004 Symposium #1 Child Application Fee. [JJRE 00042885]

204. A Risperdal child and adolescent 2003 budget listed \$3,150,000 for the following CME programs: MPE – Psych Centers of Excellence; QED – Excellence in Education Home Study Kit; Design Write – CME Poster Book; Psychiatry Educational Initiative; Psychiatry CME Monograph; Pediatric CME Institute; Psychlink; Teletopics; Publications; AACAP CE Enduring Program; Growing Up Whole, Enduring Newsletter; and Multichannel CE case series. [JJRE 00042885, at -886]

205. A 2003 Risperdal “spend document” showed for C&A (1) \$1,894,139 on CME programs, including: MPE – Psych Centers of Excellence; Psychiatry Educational Initiative; Psychiatry CME Monograph; Teletopics; Publications; AACAP CE Enduring Program; Growing Up Whole, Enduring Newsletter, (2) \$615,253 on Symposia programs, including: APA 2003 Symposia – Findling; AACAP Symposia Oct. 22-27, 2002; AACAP 2003; AACAP 2004; AAP; APA 2004 Symposium #1 Child Application Fee, (3) \$315, 615 on Grants, including: MGH Collaboration – Tot. \$500k/McNeil to fund 200k; CAPRI, Pediatric Bipolar Conference; Other grants and contributions; Baylor College of Medicine – Tourette Conf; Roots of Mental Illness in Children, (4) \$318,230 on Charitable Contributions, including: CHADD; Hillside-Hospital Prodromal Workshop; Reed Academy; Nat’l Alliance for Res on Schiz & Depression; AACAP Annual Meeting Support & Sponsor; CAN WalkNow Event Sponsor; Work Group Support; Children’s Mental Health Summit; Run for Autism. [JJRIS 00284696, at -703]

206. A February 15, 2000 Janssen document on Risperdal under the heading child psychiatry stated the following: (1) Opportunity – Increased Market Share; (2) Dollar Potential: \$300 MM (all uses); (3) Issues: RIS Long-term safety profile, ethics, FDA’s opinion; (4) Strategy: Increase awareness of Risperdal in child psychiatry; and (5) Tactics: Market research, Medical education: CME opportunities, child psych meetings, publications (WLF) and OL development, child psych Home Office, Advisory Forums, CNS Summit, Call plan: 691 child psychs in decile 8-9. [JJRE 00168229, at -237]

207. A Phase V status report on child and adolescent CME projects included an American Academy of Child and Adolescent Application for October 14 2003 in Miami Beach, Florida, faculty and presentation title included, (1) Evolving concept of psychiatric spectrum disorders – Hans Steiner, MD, (2) Expanding uses of psychotropics in child and adolescent

disruptive behavior disorders – Peter Jensen, MD; (3) Challenges in management of bipolar disorder and ADHD: What are we treating? – Gabrielle Carlson, MD; (4) Evidence-based treatment of target symptoms associated with pervasive developmental disorders (PDD) – Christopher McDougale, MD; (5) Appropriate use of psychotropics in children and adolescents for the treatment of psychiatric spectrum disorders: risk/benefit assessment – Robert Findling, MD (Chair). [JJRE 00115909]

208. A Phase V status report on child and adolescent CME projects included an American Association of Psychiatric Meeting – Findling on May 18, 2003 in San Francisco. The faculty and presentation titles included: (1) Understanding the Concept of Spectrum in Child and Adolescent Psychiatric Disorders – Janet Wozniak, MD; (2) Rational management of disruptive behavior disorder and comorbidity – Jeffrey Newcorn, MD; (3) Combined pharmacotherapy in the management of bipolar disorders – Robert Findling, MD (Chair) (presentation received); (4) Recent advances in the pharmacotherapy of pervasive development disorder spectrum – Christopher McDougale, MD; (5) Clinically Relevant Drug-Drug Interactions in Pediatric Psychiatry – Michael Reed, Pharm.D (presentation received). [Id. at - 910]

209. A March 27, 2003 document submitted to Janssen Pharmaceutica Products outlined an AAP 2003 symposium to be held on November 1-5, 2003 in New Orleans, LA. [JJRE 00123970] The targeted audience included pediatricians. The document stated, “Experts and researchers in the field of pediatrics and child and adolescent psychiatry will be able to effectively convey appropriate use of these medications by educating clinicians regarding . . . proper dosing of atypical antipsychotics when managing psychiatric and behavioral disorders.” [Id. at -973] One session to be included involved “efficacy of atypical antipsychotics in juvenile bipolar, DBD and PDD (reinforce the message the [sic] risperidione

is the most widely studied atypical antipsychotic in this population.) [Id. at -975] The speakers list included Robert L. Findling who had participated in Janssen supported symposium at AACAP, 2001 and APA, 2002. Other speakers also participated in prior Janssen supported symposia. [Id. at -978]

210. A May 20, 2002 document signed by Robert Findling outlined the symposium to held during the APA 2002 annual meeting in Philadelphia. [JJRIS rev02356937]

211. Lectures at the APA symposium included “Atypical Antipsychotic Pharmacotherapy in Children and Adolescents: What is the Evidence for Long-term Safety?” By Robert L. Findling. Another lecture was titled, “Evolving Treatments for Psychiatric Disorders in Young Patients With Evidence From Bipolar and Other Conditions”. Another lecture was titled “An Increasing Role for Atypical Antipsychotics in Pediatric Psychiatry: Efficacy in Well Designed Trials.” [JJRISrev02356940, at -941]

212. At this APA symposium organized by Johnson and Johnson, there were presentations that involved risperidone in conduct disorder with and without comorbid mental retardation, autistic disorder as well as use of risperidone and other agents in child-onset schizophrenia, other pervasive developmental disorders, Tourette’s disorder, attention deficit/hyperactivity disorder and bipolar disorder. [Id. at -962]

213. Disclosures of Dr. Findling and other faculty relationships with Janssen were made. [Id. at -945]

214. A draft of the PowerPoint slide presentation titled, “Risperidone in Children and Adolescents With Severe Disruptive Behaviors and Subaverage IQ”, presented at the American College of Neuropsychopharmacology 40th Annual Meeting on December 9-13, 2001 in Waikoloa, Hawaii, revealed approximately 25 comments with revisions, adds and deletes by Janssen employees. An email by a senior account manager at Clinical Connexion in

Lawrenceville, NJ, sent that presentation to Joseph Lin at Janssen on September 20, 2002.

[JJRE00037058, at -059]

215.

216. Dr. Deborah Pearson, in the Department of Psychiatry at the University of Texas Medical School, was an investigator on Janssen clinical trials. [JJRE02078140, at -141]

217. On Friday, July 28, 2000, Deborah Pearson, Ph.D., University of Texas, Houston, wrote to Janssen's Ursula Merriman and stated, "I delivered the RIS-USA-93 paper at the TAMR (Texas Association for Mental Retardation) meeting yesterday in Galveston, and it went really well. When I arrived, I noticed that the paper session had been scheduled into the largest meeting room at the facility—and believe it or not, it was full. I think that there has been alot [sic] of word-of-mouth spreading of information about using risperidone in aggressive kids with MR, and even about this study in particular. The audience was very attentive, and asked lots of questions (friendly questions). The only disappointment for them was that we are no longer enrolling—they wanted to refer their patients. What was really interesting was that in addition to the usual interest by the MR professionals, that we also had some law/juvenile probation types who were there. It seemed that everyone was particularly impressed by the findings that the decreases in aggression were accompanied by increases in prosocial behaviors—AND, that these improvements had not come about at the expense of cognitive functioning (i.e., there were no changes in the CPT or in the modified CVLT that Mike/Ben/I came up with). I think that that was very reassuring to folks, many of whom have wanted to use (or even have gone ahead and prescribed) risperidone "off label" for these dually diagnosed kids." Dr. Pearson further stated, "Bottom line—there is a strong interest out there "in the trenches" for the results of this study,. I don't know where we are in formally writing up the results for publication (maybe awaiting the Canadian results? the open-label results?), but

when the time comes to do this, I would very much like to help in any way that I can. I also know, if the TAMR audience was any indication, that we will have a big audience eagerly awaiting the report of our results. Last, but not least, I want to thank you both for all of your help in getting this talk arranged/approved—I really appreciated it. Take care, and I hope that all is going well for you! –Deborah” [JJRE 01547566, at -569]

218. A March 22, 2002 email from Janssen’s Gahan Pandina to Janssen colleagues stated, “George and I wanted to share some information as a follow-up to the meeting with Dr. Biederman. This feedback came from an attendee of the large 3-day educational seminar (over 1000 physicians, \$700 CME course) in child psychopharmacology and pediatric bipolar disorder that Dr. Biederman and his group conducted. This meeting began the day immediately after our meeting with him at Janssen last week. Dr. Biederman was very well-received by the group. The validity of the diagnosis of Pediatric Mania was completely accepted, and his diagnostic techniques deemed to be excellent. He was very balanced in his approaches to treatment, and not perceived to be aligned with any company in particular. Evidently, he made quite a point regarding the metabolic issues related to olanzapine, to the extent of stating that this drug should not be used in the treatment of children and adolescents, highlighting the issues with published data.” He further stated, “I think this is a clear example of the utility of partnering with a group such as MGH, who has the potential of reaching and having a significant impact upon the field of child and adolescent psychiatry with these types of professional activities in non-sponsored venues.” [JJRE 02267568]

219. Other Risperdal child and adolescent priorities and activities for 2002 included, among others, Media Management Plan, CME Programs for 2002; Meeting with QED to update progress on textbook; discuss opportunities to endure content with pediatricians and/or neurologists; Sponsorship of CME Conference in April 2003 (Washington, D.C.) – discuss with

Rob; determine if interest from McNeil; Endure Centers of Excellence – discuss with Rob, Develop advocacy relationships; CAN (Cure Autism Now), CABF (Child, Adolescent Bipolar Foundation), NMHA (National Mental Health Association), NAMI (National Alliance of Mentally Ill); Follow up with FECA, KOL visits/MSL partnering. [JJRE 00128969]

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

220. A May 22, 2001 Janssen CNS sales training presentation focused on child and adolescent physicians identified “key strategies” for “child & adolescents”. These included, (1) Sell on symptoms not diagnosis, (2) Utilize Medical Services for studies, and (3) Develop relationships now – key for future. The presentation also stated under a heading Child & Adolescents, (1) Position Risperdal as First Line, (2) Gain Switches From Competition, and (3) Be A Resource to the C&A Psychiatrists – Medical Services requests – Samples/Coupons – CME Programs – Teletopics/DLN. [JJRIS 00431761, at -887] [date from metadata employee source of Mike Deieso, DOCDATE May 22, 2001]

221. According to a July 29, 2002 Janssen 2003 business plan, 3,307 of 5,192 child psychiatrists received a “call” during the last 12 months with 1,985 having received more than 12 calls. These child psychiatrists were matched to the amount of antipsychotic prescribing they had done. [JJRE 02399406, at -444]

222. On May 27, 2004, Dave Meek, Janssen's CNS Field Sales Director wrote “Abilify [a competitor antipsychotic] is gaining ground primarily with C&A Psych's and we need to make sure Risperdal is growing with this customer segment. Let's make it happen!” [JJRE 00047801]

223. A Janssen Field Conference Report, dated May 16, 2001, for sales representative Ann Shellswick, stated, “You are using both teletopics and audioconferences. Continue to use

these with correct customers. A dinner Finding teletopics focused on your Child docs might be effective.” [JJRE 05281960, at -962]

224. A Janssen Field Conference Report, dated July 26, 1999, for sales representative Keith Webb, stated, “The Child Psyc. Lunch was very beneficial to gain access to another group of residents. . . . You were able to present off overheads the key aspects of efficacy, safety, and dosing.” [JJRE 05282070, at -071]

225. A Janssen Field Conference Report dated February 6, 2001, for sales representative Cheryl Phillips, stated, “You were also able to uncover Dr. Trans use of Risperdal in children and had Medical Services send him the child information to back up any discussion around use in children.” [JJRE 05288617]

226. A Janssen Field Conference Report dated February 23, 1999, for sales representative Liem Campbell, stated, “Follow up with Dr. Gleason by sending the Risperdal child packet. Both doctors see a lot of non-schizophrenic patients, so the bipolar detail could be key here.” [JJRE 05289648]

227. A Janssen Field Conference Report dated November 1, 2000, also for sales representative Liem Campbell, stated, “You were able to demonstrate your PK around special populations with Dr. Webber who specializes in child psyc. You were able to follow through with your discussion by using Medical Services.” [JJRE 05289670]

228. A Janssen Field Conference Report dated June 10, 2003 for sales representative, Denise Buege, stated, “Not only are you well versed in all of the approved proof sources that Janssen has to offer our customers, but you are also well versed in a number of outside pieces of clinical research. I observed this during your inservice with the child and adolescent staff at John Umstead State Hospital. You were very effective in quoting that data around the use of

Risperdal for autism that was published in the August issue of the New England Journal of Medicine.” [JJRE 10181065]

229. A Janssen call note in January 2005 stated “found out that Pamela Smith of the childrens unit loves RISP and would like coupons to give parents.” [JJRErev07498316, at -500167]

230. A Janssen call note in January 2005 stated, “Continue to promote the Ris M-tab’s for the child to use in the treatment of aggressive behavior as well as Concerta for ADHD.” [Id. at -500638]

231. A Janssen call note in January 2005 stated, “reminded him that patient agitat and irritab being back at school get under control fast 3 days with ris which is reliable and easy to dose.” [Id. at -500715]

232. A Janssen Field Conference Report dated September 2, 1998 for sales representative Keith Ellis stated, “You are using strong feature benefit, openings and closing with a request for commitment to use both Risperdal and Paxil. . . . Look for early opportunities to close. Then expand the business to new areas of potential use. (ex. Geriatrics, Child & Adolescents)”. [JJRE 11463379, at -380]

233. A Janssen Field Conference Report dated February 9, 2004 for sales representative Karen Meyerhoffer stated, “Dr. Puskarski admitted he needed rapid control of irritability, aggression, etc. in his child patient population and you reinforced the symptom control that RISPERDAL oral for Bipolar Mania provides with those specific symptoms.” [JJRE 15581034]

234. On April 30, 2004, in a sales call report, Janssen sales representative Jamie Mariano wrote, “Began to talk about the mtab and the convenience of using for his younger population. For adults or children convenience factor and knowing that it works quickly

(clarifying that it is not any faster than the oral tablet). Shared with doc the placebo sample packet and asked him to try on his agitated patients who needs to help calm down.”

[JJNJNSE00000045]

235. On August 13, 2004, in a sales call report, Janssen sales representative Jamie Mariano wrote, “talked to him about new RC starts. medicaid only to ease back into things. Doc still using risp 1st line for children. Using ser for add on bezo replacement. Switching majority of zyp patients to risp.” [JJNJNSE00000056]

236. A Janssen Field Conference Report dated September 22, 2003 for sales representative, Denise Buege also stated, “The call that provided the best opportunity for evaluation was that with the Child and Adolescent physician at John Umstead State Hospital. I observed you beginning the call in very strong fashion [sic] by asking the open-ended question: “Dr., what symptoms do you treat most often and what symptoms are toughest to treat?”” This elicited the response of: agitation [sic] and anxiety being the most common and toughest to treat symptoms. The next question was also outstanding: “Dr., when you reach for an atypical, which do you choose?” The answer was Seroquel. “The third probe was one that needed to be workshopped to position your customer to talk about Risperdal’s benefits as opposed to those of Seroquel [sic]. Your original question was: “Why do you choose Seroquel?” Although the end result was positive, this question put the doctor in the position of selling herself on Seroquel’s [sic] attributes. We determined that a more appropriate question might be: “Dr., what benefits do you think that Risperdal might provide by controlling these symptoms?”[sic] This question puts Risperdal’s benefits at the forefront and still elicited the information that you need to sell most effectively.” [JJRE 10181083, at -083-84]

237. Not only was Risperdal not approved for any pediatric indications during the time period of these sales representative calls as supervised by District Managers, Risperdal was not approved for any “symptoms” in children and adolescents.

238. In my opinion, physicians are subject to numerous influences by the pharmaceutical industry that can influence their prescribing practice.

239. As a group, we physicians like to believe that our judgment and dedication to our patients is unclouded by pharmaceutical company influences.

240. Drug promotion strongly influences prescribing behavior, but doctors underestimate this influence. “Company funding of doctors, of educational events and of research are important elements in this influence.” (Norris P, et. al. Drug Promotion: what we know, what we have yet to learn. World Health Organization and Health Action International. 2005. at 73. Available: <http://www.who.int/medicinedocs/collect/medicinedocs/pdf/s8109e/s8109e.pdf>. (last visited August 21, 2012)). “Haayer found that reliance on information provided by the pharmaceutical industry was negatively associated with prescribing rationality. That is, doctors who relied on promotional information wrote less rational prescriptions for the case studies than those who reported relying less on promotion”). (*Id.* at 37.; *see generally*, Kessler DA. Drug Promotion and Scientific Exchange — The Role of the Clinical Investigator. *NEJM*. 1991; 325:201-203; Kessler DA & Pines WL. The Federal Regulation of Prescription Drug Advertising and Promotion. *JAMA*. 1990; 264(18):2409-2415.

241. In my opinion, Janssen illegally promoted Risperdal in children and adolescents for non-approved uses in violation of the Federal Food, Drug, and Cosmetic Act.

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

242. From the time of Risperdal's approval on December 29, 1993 until October 2006, the label for Risperdal included a Precaution for hyperprolactinemia with a statement that "although disturbances such as . . . gynecomastia . . . have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.

243. In the section titled Adverse Reactions under the subsection "Other Events Observed During the Pre-Marketing Evaluation of Risperdal", the label listed "Endocrine Disorders: Rare: gynecomastia". The label stated that Risperdal's "safety and effectiveness in children have not been established". [Physician's Desk Reference 1995, p. 1193-1197]

244. According to Janssen's Risperdal label "rare events are those occurring in fewer than 1/1000 patients."

245. Thus, from the period December 29, 1993 to October 2006, Janssen stated that the risk of gynecomastia was less than 1 in a thousand (less than 0.1%).

246. Janssen's study RIS-INT-41 had an interim analysis of 319 patients produced on November 2, 2000. [JJRIS 02562360] It was an open-label one year study. Topline results were available on August 29, 2001. [JJRE 06644585] The final clinical study report was available on October 25, 2001 and amended on November 14, 2003. [JJRE 08408869] According to the protocol's flowchart, physical exam was done at screening, month 3, month 6 and month 12; Tanner staging was done day one of the study, 6 months and 12 months. [Id. at - 904] Under the section titled "Prolactin-related adverse events," the clinical study report stated,

“special attention was also given to AEs that were related to prolactin levels. WHO-preferred terms defined as prolactin-related were: gynecomastia, . . . breast discharge, . . . breast pain male, breast pain female, . . . and breast enlargement.” [Id. at -916] Janssen’s final study report on RIS-INT-41 found 25 patients with gynecomastia including 23 boys and 2 girls. [JJRE 08408950]

247. Janssen’s interim analysis of RIS-INT-41 found 11 patients with gynecomastia including 10 boys and 1 girl. [JJRIS 02562360, at -429] The interim study population included 319 patients [JJRIS 02562360], 266 were male and 53 were female. [Id. at -399].

248. According to Janssen’ analysis of RIS-INT-41, of the 24 events of gynecomastia, 20 were classified as probably, very likely, or possibly related to the drug. [JJRE 08408869 at -952-53]

249. Janssen’s study RIS-USA-93 Topline Results were available on July 20, 1999. [JJRE 06769941] It was a double-blind, placebo-controlled six-week study. The final clinical study report was available on November 2, 2000. [JJRE 05002596] According to the protocol’s flowchart, physical exam was indicated as done but no mention of Tanner staging⁵. [Id. at -624] There is no section titled “Prolactin-related adverse events”. [Id. at -599-602] A search of the study report revealed no mention of gynecomastia. There is a sentence that states, “There were no other AEs related to elevated prolactin levels.” [Id. at -657]

250. Janssen’s study RIS-USA-97 Topline Results were available on April 3, 2000. [JJRE 06769946] It was an open-label one year follow up study to RIS-USA-93. The final clinical study report was available on November 2, 2000 and amended November 19, 2003. [JJRE 08413273] According to the protocol’s flowchart, no physical exam or Tanner staging was indicated as being done. [Id. at -304] There is no section titled “Prolactin-related adverse

⁵ A Tanner sexual maturity rating stage field was included on a Case Report Form with check boxes that included “not done”.

events”. [Id. at -282-83] The report states there was one subject with transient gynecomastia. [Id. at -281]

251. Janssen’s study RIS-CAN-19 Topline Results were available on February 28, 2000. [JJRE 06644617] It was a six week double-blind placebo-controlled trial. The final clinical study report was available on November 2, 2000. [JJRE 05011838] According to the protocol’s flowchart, physical examination was done but there was no mention of Tanner staging. [Id. at -867] There is no section titled “Prolactin-related adverse events”. [Id. at -841-45] A search of the report reveals no mention of gynecomastia.

252. Janssen’s study RIS-CAN-20 Topline results were available on November 14, 2000. [JJRE 06769914] It was a one year open-label study. The final clinical study report was available on July 5, 2001. [JJRE 08400029] According to the protocol’s flowchart, there was no mention of physical examination or Tanner staging. [Id. at -062] There is no section titled “Prolactin-related adverse events”. [Id. at -032-35] The report states no subject had gynecomastia. [Id. at -104]

253. Janssen’s study RIS-INT-79 Topline Results were available on February 6, 2004. [JJRE 00061919] It was a randomized double-blind, placebo-controlled trial in three phases, the phases lasting six weeks, six weeks, and six months respectively. Final clinical study report was available on November 5, 2004. [JJRE 04981776] According to the protocol’s flowchart, there was a physical examination and Tanner staging at screening and at the end of phase three. [Id. at -819] There was a section titled, “Potentially Prolactin-related adverse events”. [Id. at -779] The report states that no subject had gynecomastia. [JJRE 08400104] Janssen’s study RIS-INT-79 found in Phases 1 and 2, six males with gynecomastia and one female with breast pain and one female with lactation. [JJRE 04981776, at -894] The study population included 527 patients in Phase 1 and 436 patients in Phase 2 [Id. at -794]; 457

were male and 70 were female in Phase 1. [Id. at -851] In Phase 3, there were three males with gynecomastia, two females with lactation or breast discharge. [Id. at -898] There were 335 patients in Phase 3. [Id. at -794]

254. Janssen's study RIS-INT-84 Topline Results were available on November 12, 2004. [JJRE 01096362] It was a one year open-label follow up study of RIS-INT-79. The final clinical study report was available on May 23, 2005. [JJRP 00777678] According to the protocol's flowchart, there was a physical examination at the end of the study. No Tanner staging was indicated. [Id. at -853] There was a section titled, "Potentially Prolactin-related adverse events". [Id. at -763] There were a total of 232 patients with 201 males and 31 females. [Id. at -738] The report states that two males in the placebo/Risperdal subjects reported treatment emergent gynecomastia. [Id. at -763]

255. Janssen's study RIS-INT-70 Topline Results were available on September 18, 2002. [JJRE 00061853] It was a one year open-label follow up study to RIS-INT-41. Final clinical study report was available on October 27, 2003. [JJRE 08398771] According to the protocol's flowchart, physical and Tanner stage exam was done at the end of this study. [Id. at -800] There was no section titled "Potentially Prolactin-related adverse events". [Id. at -774] The report states there were three "new or aggravated in severity" cases of gynecomastia. [Id. at -829] There were a total of 48 patients with 42 males. [Id. at -785] The study report states there were "few increases in frequency of individual AE occurrences from RIS-INT-41 to RIS-INT-70; a modest increase in the incidence of the gynecomastia was reported (n=24; 8.3% in RIS-INT-41 versus n=6; 12.5% in RIS-INT-70)." [Id. at -830]

256. Thus, Janssen knew, according to its own study reports, that gynecomastia did occur at 8.3% and 12.5% in two trials. Moreover, RIS-INT-41, for which Janssen calculated the 8.3% of gynecomastia, was the one study that (1) specifically stated "special attention was

also given to AEs that were related to Prolactin levels”; and (2) physical examinations and Tanner staging were comprehensively done.

257. In my opinion, by November 2, 2000, when the interim analysis of study RIS-INT-41 was conducted, Janssen knew that the risk of gynecomastia was significantly higher than the rate it reported in Risperdal’s label.

258. In my opinion, by November 2, 2000, Janssen had an obligation to correct the information concerning the risk of gynecomastia on Risperdal’s label.

259. No FDA statute, regulation or agency policy prevented Janssen from removing the word “rare” that modified the adverse event of gynecomastia on Risperdal’s label. *See* Schedule 3 *infra*.

260. In my opinion, Janssen failed to adequately warn physicians about the risk of gynecomastia.

261. The importance of appropriately warning physicians about the extent of gynecomastia is underscored by the fact that Janssen knew that “gynecomastia does not appear to easily resolve . . .” [JJRE 06455459]

262. In my opinion, Janssen, by failing to correct the label soon after the interim analysis of study RIS-INT-41 in November 2000, misled physicians about Risperdal’s risk.

263. In my opinion, Janssen failed to disclose the frequency of gynecomastia in its clinical studies, in its presentations to its home office advisory board members. Dr. Peter Dorson’s presentation titled, “Risperidone: Child and Adolescent Clinical Data” was misleading. *See supra*. [JJRE 08976702, at -742]

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

264. As noted above, Janssen developed a message concerning Risperdal that stated, “The low prolactin elevation sometimes seen with Risperdal treatment is not (directly) linked to clinical abnormalities”. [J-TXCID1058301] and [J-TXCID1058308]

265. A July 30, 2002 draft manuscript was titled, “Prolactin Levels in Children and Adolescents with Long-Term Risperidone Use”. [JJRE 00115170]

266. In that draft, “The percentage of children with SHAP [Side Effects Hypothetically Attributable to Prolactin] was assessed for patients with prolactin levels above the ULN versus patients with prolactin levels within the normal range at the various analyses time periods. The proportions were all comparable except for Weeks 8 to 12 time period, in which 7.4% of patients who had prolactin above the ULN had SHAP at some point during the trial, while 2.9% of patients with prolactin levels within normal range at Weeks 8 to 12 experienced SHAP at some time during the study (P=0.02)(this may be notable as this could be seen to suggest that patients who show an initial rise during the “peak” period above ULN do have a higher propensity for SHAP. I think we need to discuss this somewhere in the manuscript. Gahan). There was no statistical difference in the percentage of patients who reported SHAP for any other analysis time period, whether or not prolactin levels were normal or above the ULN (range 3.4% to 6.5% with SHAP).” [Id. at -192] [see also JJRE 03892154; JJRE 03895395]

267. The published manuscript stated, “There was no statistical difference in the percentage of patients who reported SHAP for any analysis time period, whether or not prolactin levels were normal or above the ULN (range, 1.8%-3.5% with SHAP).” (Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents – Robert L.

Findling, M.D.; Vivek Kusumakar, M.D., F.R.C.P.C., M.R.C.Psych (UK); Denis Daneman, M.B.B.Ch., F.R.C.P.C.; Thomas Moshang, M.D.; Goedele De Smedt, M.D.; and Carin Binder, M.B.A. – J. Clin Psychiatry 64:11, November 2003, at 1367.

268. Janssen altered the results by doing its analysis on what it subsequently defined as “SHAP B” which ignored all events reported in boys 10 years of age or older. [Id. at 1367] Janssen failed to report the analysis for that 8-12 week period on what it characterized as “SHAP A” [Id.] which included all subjects, as it did in its July 2002 draft.

269. In my opinion, by failing to include the fact that there was a statistically significant increase in the number of patients who had both prolactin levels above the upper limit of normal during the 8-12 week time frame and symptoms associated with hyperprolactinemia, Janssen misled physicians and the scientific community. The results that Janssen omitted were particularly important because the time frame during which the peak occurred was of potential clinical significance for children who were taking the drug for two months or more when adverse events such as gynecomastia can occur.

270. In my opinion, further, Janssen’s published manuscript is misleading because it misleads the reader to assume that in patients 5-15 years the incidents of SHAP was only 2.2% when in fact the incidence of SHAP in these patients was 5.1% based on Table 2. Physicians have limited time to read published papers. That is why the abstract is significant.

271. Janssen significantly misleads the reader in other respects because when it did its calculation of overall SHAP rates it excluded 100% of male events in males 10 years of age or above (80% of the events which occurred among males), but did not exclude males 10 years of age or above or females from the denominator calculation.

272. Proper calculations in Table 3 would reveal gynecomastia in the primary analysis group (“PA”) of 2.0% gynecomastia rather than 0.8% gynecomastia because the

denominator number of males less than 10 is 255, not 592 (*see* statistical document for manuscript support, Table 14). [JJRE 14085087, at -119]

273. Similarly, the proper calculation of SHAP events in females should be 7.8% rather than the 1.4% reproductive disorders reported in Tables 2 and 3 because the total number of females was 103, not 592.

274. Janssen used the Findling publication for CME.

275. Physicians Postgraduate Press, Inc. (“PPP”) submitted an Educational Grant Request and Letter of Agreement to Joseph Lin, Product Director, CNS, Janssen, on August 15, 2003 for a CME “Info ◊ Pack” on the forthcoming publication, “Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents” by Findling, et al.

[JJRIS00293318]

276. The CME materials were comprised of a reprint of the article and commentary from the faculty, from a recorded and transcribed teleconference, condensed into a “newsletter type format.” [JJRIS00293319]

277. The Letter of Agreement stated that the Educational Grant Request for this CME was for \$111,805. [Id.] The Letter of Agreement and Educational Grant Request were signed by Janssen’s David Fabbri on 10/20/03. [Id. at -320, JJRIS 00293321]

278. According to the Educational Grant Request, the targeted audience was psychiatrists. PPP could request that Janssen “assist in the delivery of the enduring materials. This assistance can be in the form of a list of these individuals to target for mailing. . .” because PPP might not be aware of “additional professionals who can benefit from this activity.” [Id. at -324]

279. The Educational Grant Request stated the cost of the 20-page Info ◊ Pack “to be mailed to approximately 34,500 physicians in 2004 is \$111,805. . .” [Id. at -326]

280. In an email dated August 20, 2003, Joseph Lin stated, “If I had to prioritize, I would start with the Hotline and CME Info Pak. . . while the CME Info Pak provides for broad dissemination of positive prolactin data (in children).” [JJRE 14667339]

281. Findling was cited in a subsequent article that Janssen had Excerpta Medica draft [EMRISP0256954] and which was co-authored by Janssen’s Goedele De Smedt. [Croonenberghs, Fegert, Findling, De Smedt, Van Dongen, and the Risperidone Disruptive Behavior Study Group, “Risperidone in Children With Disruptive Behavior Disorders and Subaverage Intelligence: A 1-Year, Open-Label Study of 504 Patients” , J. Am. Acad. Child Adolesc. Psychiatry, 44:1, January 2005]

282. In addition, Janssen misled physicians by omitting from the Croonenberghs article that it had drafted, Janssen’s analysis, as noted *supra*, of RIS-INT-41 of the 24 events of gynecomastia, 20 were classified as probably, very likely, or possibly related to the drug. [JJRE 08408869 at -952-53] Considering the fact that the Croonenberghs article was reporting on “safety”, Janssen should have highlighted the significant incidence of gynecomastia in the abstract, as this is the place where physicians are likely to focus.

283. In my opinion, Janssen’s manuscript titled, “Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents” significantly misled physicians.

VIII. CONCLUSIONS⁶

In my opinion:

284. Janssen promoted Risperdal for non-approved uses in violation of the Federal Food, Drug, and Cosmetic Act.

285. The promotion of non-approved uses by a manufacturer, because it undercuts the system and safeguards of drug regulation, is concerning.

⁶ The following list is not meant to be an all-inclusive list of opinions. Please read the report in its entirety.

286. The promotion of non-approved uses by a manufacturer of powerful drugs is more concerning.

287. The promotion of non-approved uses in the most vulnerable children of powerful drugs is most concerning.

288. Janssen's promotion of Risperdal, a powerful drug, for non-approved uses in the most vulnerable children is deeply troubling.

289. Janssen and Excerpta Medica's tactic of publishing scientific articles by "maximizing" the benefits of a drug compared to its risks in the scientific literature is equally troubling.

290. Patients, doctors, and our system of medical care depend on the scientific literature to be free of promotional content.

291. Janssen and Excerpta Medica's plan and efforts to "manage the content" of scientific literature for "maximum competitive advantage" has profound consequences. Janssen and Excerpta Medica undercut the ability of the medical community to have confidence in the scientific literature.

292. Physicians are subject to numerous influences by the pharmaceutical industry that affect prescribing practice.

293. Janssen used the medical literature to influence doctors to prescribe Risperdal for non-approved uses.

294. Johnson and Johnson targeted children and adolescents with conduct disorder and other unapproved indications in their marketing of Risperdal.

295. The FDA has never approved Risperdal for the treatment of conduct disorder, disruptive behavior disorder, depression, ADHD, tics, or Tourette's syndrome.

296. Johnson and Johnson developed sophisticated strategies to promote Risperdal in children for non-approved uses.

297. Johnson and Johnson marketed and promoted Risperdal by supporting and drafting publications in medical journals.

298. Johnson and Johnson's sales force promoted Risperdal for use in children during the time period when no uses were approved in children by the FDA.

299. Janssen planned to use medical education and sales representatives in 2001 to influence doctors to prescribe Risperdal for the non-approved uses in children.

300. While physicians may prescribe medicines for non-approved uses based on their independent judgment, pharmaceutical companies may neither promote drugs for non-approved uses nor use physicians to promote or "educate" other physicians about non-approved uses.

301. Janssen developed a corporate strategy to illegally promote Risperdal for use in conditions such as conduct disorder, taking advantage of the fact that Risperdal was on the market for other FDA-approved indications.

302. Johnson and Johnson, under the guise of medical advisors, promoted the unapproved use of Risperdal in children and adolescents.

303. In light of Johnson and Johnson's expressed business plans, including statements such as "one year marketing objectives" to "grow and protect share in children/adolescents via medical education initiatives," it is not, in my opinion, credible to say that Johnson and Johnson's activities were not promotional.

304. Drug promotion strongly influences prescribing behavior, but doctors underestimate this influence. Company funding of doctors, of educational events and of research are important elements in this influence.

305. 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.

306. Janssen failed to present the data about elevated prolactin levels in an objective fashion.

307. Janssen had responsibility for the safety of Risperdal and the adequacy of its warnings regardless of what the FDA did or did not do.

308. Janssen knew, according to its own study reports, that gynecomastia did occur at 8.3% and 12.5% in two trials. Moreover, RIS-INT-41, for which Janssen calculated the 8.3% of gynecomastia, was the one study that (1) specifically stated "special attention was also given to AEs that were related to prolactin levels"; and (2) physical examinations and Tanner staging was comprehensively done.

309. By November 2, 2000, when the interim analysis of study RIS-INT-41 was conducted, Janssen knew that the risk of gynecomastia was significantly higher than the rate it reported in Risperdal's label.

310. By November 2, 2000, Janssen had an obligation to correct the information concerning the risk of gynecomastia on Risperdal's label.

311. No FDA statute, regulation or agency policy prevented Janssen from removing the word "rare" that modified the adverse event of gynecomastia on Risperdal's label. *See* Schedule 3 *infra*.

312. Janssen failed to adequately warn physicians about the risk of gynecomastia.

313. The importance of appropriately warning physicians about the extent of gynecomastia is underscored by the fact that Janssen knew that "gynecomastia does not appear to easily resolve . . ." [JJRE 06455459]

314. Janssen, by failing to correct the label soon after the interim analysis of study RIS-INT-41 in November 2000, misled physicians about Risperdal's risk.

315. Janssen failed to disclose the frequency of gynecomastia in its clinical study results in its presentations to its home office advisory board members. Dr. Peter Dorson's presentation titled, "Risperidone Child and Adolescent Clinical Data" was misleading. *See supra.* [JJRE 08976702, at -742]

316. 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.

317. In the published article, "Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents" by Findling, et al. ("Findling"), Janssen altered the results by doing its analysis on what it subsequently defined as "SHAP B" which ignored all events reported in boys 10 years of age or older. Janssen failed to report the analysis for that 8-12 week period on what it characterized as "SHAP A" which included all subjects, as it did in its July 2002 draft.

318. In Findling, by failing to include the fact that there was a statistically significant increase in the number of patients who had both prolactin levels above the upper limit of normal during the 8-12 week time frame and symptoms associated with hyperprolactinemia, Janssen misled physicians and the scientific community. The results that Janssen omitted were particularly important because the time frame during which the peak occurred was of potential clinical significance for children who were taking the drug for two months or more when adverse events such as gynecomastia can occur.

319. Janssen's published Findling manuscript was misleading because it misleads the reader to assume that in patients 5-15 years the incidents of SHAP was only 2.2% when in fact

the incidents of SHAP in these patients was 5.1% based on table 2. Physicians have limited time to read published papers. That is why the abstract is significant.

320. Janssen significantly misled the reader in other respects because when it did its calculation of overall SHAP rates in Findling, it excluded 100% of male events in males 10 years of age or above (80% of the events which occurred among males), but did not exclude males 10 years of age or above or females from the denominator calculation.

321. Proper calculations in Table 3 of Findling would reveal gynecomastia in the primary analysis group (“PA”) of 2.0% gynecomastia rather than 0.8% gynecomastia because the denominator number of males less than 10 is 255, not 592 (*see* statistical document for manuscript support, Table 14). [JJRE 14085087, at -119]

322. The proper calculation of SHAP events in females should be 7.8% rather than the 1.4% reproductive disorders reported in Tables 2 and 3 because the total number of females was 103, not 592.

323. Janssen’s publication titled, “Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents” significantly misled physicians.

324. The two systems of state consumer protection and federal food and drug regulation operate in a complementary but independent manner.

325. Nothing in the Federal Food, Drug, and Cosmetic 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.

326. 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.

327. 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.

328. 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.

329. 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."

330. 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.

331. What a drug company knows about a drug and what the FDA knows may be different.

332. 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.

333. Johnson & Johnson's responsibility for the safety of its product and the adequacy of its warnings exists regardless of what the FDA did or did not do.

334. The FDCA and FDA’s regulations do not prohibit manufacturers from disseminating truthful, non-misleading information about risks associated with unapproved uses.

335. By promoting Risperdal off-label to children, Janssen put children at increased risk.

336. By failing to appropriately disclose the frequency of gynecomastia, beginning in November 2000 on the drug label, and in presentations, yet marketing Risperdal off-label, Janssen needlessly exposed vulnerable children to risks of serious adverse events.

IX. SCHEDULES

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

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

338. 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).

339. Risperdal is a prescription drug. Risperdal is a drug because it is “intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man.” (21 U.S.C. § 321(g)(1)(B)). Risperdal is a prescription drug “because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use” require that it is not safe for use except under the supervision of a licensed practitioner. (*Id.* at § 353(b)(1)(A)). Drugs limited by an approved application for use only under licensed supervision are prescription drugs. (*Id.* at § 353(b)(1)(B)).

340. Adequate directions for use, or directions under which a layperson can use a drug safely, cannot be written for a prescription drug; these drugs can only be used safely at the direction and under the supervision of a physician. (See *United States v. Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980) (“a prescription drug by definition can be used only under a physician’s supervision, and is unsuitable for self-medication.”); *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 for forfeiture. 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.”)).

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

342. 21 U.S.C. § 353(b) grants an exemption 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 *United States v. An Article of Drug . . . Amodril Spancap*, 1975 Food Drug Cos. L. Rep 39,009 at 38,035 (S.D. Fla.. 1974)). 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. (*Id.*).

343. 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 the following:

a. C.F.R. 201.100(c)(1) requires that the “[l]abeling 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.”

b. C.F.R. 201.100(d) requires labeling to contain “(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.”

344. Drugs that are promoted for off-label uses do not satisfy a number of these required conditions to qualify for the exceptions.

345. 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) because the labeling, which is essentially the off-label promotion, is not the labeling authorized by the approved new drug application.

346. 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.

347. 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.

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

348. 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.

(H. Rep. No. 102-1064, at 2 (1992) (*citing* memorandum from Acting Director of Division of Drug Advertising and Labeling to the Director of Office of Drug Standards, May 6, 1990, at 3; in subcommittee files)).

349. 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 [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*, 48 Food & Drug L.J. 247, 250 (1993) (citing 21 C.F.R. §§ 201.5 and 201.128)).

The article also stated that “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.*)

350. In 1994, in unambiguous language, 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.”

(Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59820, 59822 (Nov. 18, 1994)).

351. On September 12, 1996, Dr. Michael Friedman, FDA’s Deputy Commissioner for Operations, in testimony before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, United States House of Representatives, stated that “[u]nlike with the practice of medicine, the [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 on Supplemental Indications for Approved Prescription Drugs Before the House Committee Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations*, 104th Cong. (September 12, 1996) (testimony of Michael Friedman, Deputy Commissioner for Operations at the Food and Drug Administration), *available at* <http://www.hhs.gov/asl/testify/t960912a.html>).

352. 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 Backgrounder on FDAMA (November 21, 1997), *available at* <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAAct/FDAMA/ucm089179.htm>).

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

354. Johnson and Johnson knew that “off-label promotion” was “prohibited.” [JJRE 13237356, at -362]

355. Johnson and Johnson knew that a “business plan should not be premised on driving sales growth targets for off-label uses.” [Id. at -365]

356. Johnson and Johnson knew that “on-label deployment for one product cannot justify off-label deployment for another.” [Id. at -368]

357. Johnson and Johnson knew “where there is a potential for off-label use, redouble sales force training efforts.” [Id.]

358. Johnson and Johnson knew to “examine available data to determine if it is reasonably possible to design commercial field compensation plans to incentivize sales for on-label use and not incentivize for off-label uses.” [Id. at -369]

359. Johnson and Johnson knew that the number of advisors to which it shared off-label information should be “limited to that needed to do the job.” [Id. at -405]

360. Johnson and Johnson knew that “Risperdal calls should never be made on customers who do not treat patients within Risperdal’s approved indications.” [JJRE 14351076, at -080]

361. Johnson and Johnson knew that a “Risperdal compliance question is: - “Doctor, do you treat patients who are age 18 or over for schizophrenia or bipolar mania?” If a customer is a “no” for the qualifying question then the representative should immediately stop detailing Risperdal to them. [Id. at -081]

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

362. FDA has stated that a manufacturer may warn about safety risks and that such warnings are not evidence of intent to market a drug for an unapproved use.

363. Specifically, the agency has stated that drug manufacturers “may communicate information regarding an unapproved use to inform practitioners of risks associated with the use and improve the safety of the drug, as long as it does not promote the unapproved use.” (Defendant’s Memorandum of Points and Authorities In Support of Motion to Dismiss or For Summary Judgment, *Allergan, Inc. v. United States*, Case 1:09-CV-01879-JDB (D.D.C. Jan. 11, 2010), ECF No. 27, at 10 (internal citations omitted)).

364. FDA has further stated that “[a]bsent promotion, the dissemination of safety information relating to an unapproved use would not establish that the use is an intended use, and therefore would not trigger either the new drug approval process or the misbranding provisions of the FDCA. A manufacturer contemplating the distribution of such information

need not submit it to FDA for approval (unless the manufacturer wishes to modify FDA-approved labeling, as distinct from promotional labeling), but the manufacturer may choose to seek FDA's guidance on a voluntary basis." (*Id.* (internal citations omitted))

365. These statements by the agency have come in response to Allergan's arguments that "the Act and regulations make it unlawful for a manufacturer to engage in truthful and non-misleading speech regarding unapproved uses, even if the manufacturer professes to be motivated solely by the desire to protect the public," an argument that the agency called "profoundly wrong." (*Id.* at 18).

366. FDA stated that Allergan's argument "rests on basic mischaracterizations of what the law prohibits and what it permits. The Act and regulations leave ample room for Allergan to disseminate truthful, non-promotional information about dangers associated with unapproved uses of Botox, above and beyond the information that FDA has already directed Allergan to provide." (*Id.*)

367. FDA has stated that "the Act leaves open numerous avenues for manufacturers to provide prescribing physicians with important safety information about unapproved uses. Nothing in § 202.1(e)(4)(i)(a), which is aimed solely at promotional speech rather than the non-promotional dissemination of safety information, stands in the way of that process." (*Id.* at 29. (internal citations omitted)).

368. FDA has concluded that "a manufacturer wishing to warn physicians of serious risks associated with unapproved uses and to offer guidance on how to minimize those risks will not find its path barred by FDA." (*Id.* at 36).

369. According to the Agency, "the FDCA and FDA's regulations do not prohibit manufacturers from disseminating truthful, non-misleading information about risks associated with unapproved uses. FDA does not construe the Act or regulations to prohibit the

communication of non-promotional safety information about unapproved uses. A manufacturer is free to warn about the adverse consequences of an unapproved use as long as the warning does not explicitly or implicitly promote the effectiveness of the drug for that use. If the communication is not promotional, it will not be viewed as evidence of intended use, and therefore will not trigger the obligation either to include adequate directions for use or to submit a new drug application.

Indeed, far from prohibiting manufacturers from disseminating warnings relating to unapproved uses, FDA has affirmatively encouraged them to do so. For example, when a drug manufacturer distributes copies of medical or scientific articles regarding unapproved uses for the manufacturer's drug, FDA's Reprint Guidance urges the manufacturer to attach a prominently displayed statement that discloses all significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not disclosed in the article itself. And on multiple occasions, including this one, FDA has affirmatively required manufacturers to disseminate warning information about risks associated with unapproved uses." (*Id.* at 36-37 (internal citations and internal quotations omitted)).

Schedule 4: Excerpta Medica's Communication Plans for Risperdal

370. A Strategic Medical Communications Program for Risperdal in Conjunction with Reminyl, Topamax, and Concerta was presented by: Excerpta Medica to: Pharmaceutical Group Strategic Marketing, Jansen Pharmaceutica Products, L.P. on February 28, 2003.

[EMRISP0396622]

371. "Providing Proprietary Opportunities: Many services and tactics we suggest cannot be provided by any other medical education company because they are proprietary to us.

Thus, a medical journal like *clinical Cornerstone* or a specific monograph series ensures the client that such an educational program will be innovative and unique.” [Id. at -627]

372. The Program for Risperdal included the following statements:

373. “Leveraging Programs from Maximum Effects and Efficiency: Research shows that exposure to the same material several times and in different formats enhances learning. Therefore, as an example of the ‘rules of threes,’ we try to ensure that various educational programs that are done for clients are leveraged to develop further programs (a total of at least three) that can go to the same audience, thereby enhancing recall, recognition, and awareness. Thus, a journal article may be the basis for a slide kit sent to speaker’s bureau members because the slides are essentially already developed for the original article. The content of the original article can also be included in a newsletter to the same audience to allow repetitive learning. The costs of the latter two programs can be reduced because the original article bore the brunt of the expense. This approach ensures that two critical issues are met: 1) learning is enhanced due to multiple exposures to the same material, and 2) significant cost efficiencies can be realized.” [Id. at -628]

374. “Ensuring Vast Opinion Leader Access: No other medical education company has the tremendous access to top opinion leaders that Excerpta Medica does through our journal editorial boards. Our parent company, Reed Elsevier, is the largest supplier of medical information in the world, publishing over 700 medical journals in almost every conceivable therapeutic area. Each journal has an editorial board composed of renown specialists throughout the world who are available to us as consultants, advisory board members, speakers, and in other capacities. We provide this significant access to all of our clients.” [Id. at -628]

375. “Serving and protecting the client: Because we are a CME-accredited provider, we can accredit our own CME programs and are extremely knowledgeable about all

educational guidelines and regulations. We ensure that every effort is made to achieve our clients' educational program needs while guiding the client through the process. This ensures that the maximum result is achieved while avoiding problems for the programs or jeopardizing the client and the company." [Id. at -628]

376. Excerpta Medica further stated, "In recent years, Excerpta Medica has undertaken a number of highly successful CME programs for Janssen. These have included: Acute Myocardial Infarction; Contemporary Epilepsy, Parts I and II; Ischemic Stroke, Parts I and II; Reperfusion '96; Rethinking Stroke Treatment; Stroke: An Urgent Need; Stroke You Can Treat; Thrombolytic Therapy, Parts I and II." [Id. at 628-629]

377. Excerpta Medica stated "Proprietary Opportunities: Excerpta Medica has a number products of potential benefit to Janssen's CNS/Psychiatry franchise." [Id. at -629]

378. Discussing Excerpta Medica's history with Janssen, Excerpta Medica stated: "Janssen and Excerpta Medica have been involved in a long-standing and successful partnership on a number of major products." [Id. at -639]

379. They continued "Risperdal: Excerpta Medica has been responsible for implementing the strategic publication plan for Risperdal for 11 years and served for 6 years as the company of record for medical communications. We are currently the medical education company of record for BPSD and acute care. Excerpta Medica also prepared the strategic publication plans for Risperdal in Mood Disorders/Bipolar Disorder, BPSD, DBD, and Quicklet in the Acute Care Setting." [EMRISP0396639]

380. They further stated: "In 1992, Excerpta Medica began its work with Janssen on the strategic publications plan for Risperdal. An early milestone in the publication program was the writing, by Tim Coffey, of the original report of the first risperidone clinical trial in the United States (Marder & Meibach, *Am J Psychiatry*, 1994). Excerpta Medica was also

responsible for several other significant publications in the treatment of schizophrenia (e.g., Peuskens et al., *Br J Psychiatry*, 1995; Marder, Davis, & Chouinard, *J Clin Psychiatry*, 1997; Csernansky & Mahmoud, *N Eng J Med*, 2002); dementia in the elderly (e.g., Finkel, *Int Psychogeriatr*, 1996; Katz et al, *J Clin Psychiatr*, 1999; De Deyn et al, *Neurology*, 1999); bipolar disorder (e.g., Sachs et al, *AM J Psychiatry*, 2002; Yatham et al, *Br J Psychiatry*, 2003); psychotic agitation (e.g., Currier & Simpson, *J Clin Psychiatry*, 2001); and behavioral problems in children and adolescents (e.g., Findling et al, *J Am Acad Child Adolesc Psychiatry*, 2000; Aman et al, *Am J Psychiatry*, 2002), among others.” [Id. at -639-640]

381. Excerpta Medica stated: “Another highlight of the Risperdal program was the publication of “Behavioral and Psychological Signs and Symptoms of Dementia,” a 552-page, 1996 supplement to *International Psychogeriatrics* that was based on the proceedings of an international consensus conference sponsored by the International Psychogeriatric Association and supported by Janssen. A follow-up *International Psychgeriatrics* supplement was published in 2000. Both of these major consensus conferences were planned and executed by the Medical Meetings group of Excerpta Medica.” [Id. at -640]

382. Excerpta Medica also stated that it was “responsible for the development of original articles dealing with Risperdal Consta.” [Id.]

383. They further stated that “In addition to the consensus conferences on BPSD mentioned previously, Excerpta Medica partnered with Janssen to initiate the Janssen Psychiatric Forum in 1997. The success of this Forum led to the planning and executing of a larger event, the CNS Summit, in 1998. The CNS Summit served as a major opportunity for key opinion leader development, and additional successful Summits followed in 1999, 2000, and 2001. To neutralize negative perceptions about Risperdal among physicians, Excerpta Medica conceived and executed a highly successful series of Regional Advisory Boards.” [Id.]

384. They continued: “Problem-Solving Strategies: As a few examples will illustrate, creative problem solving has been the hallmark of Excerpta Medica’s approach to the Risperdal program. To dramatically increase awareness of Risperdal and use of atypical antipsychotics, Excerpta Medica conceived a newsletter entitled ‘Advances in Psychosis.’ This newsletter generated so much interest in the psychiatric community that more than 1,800 unsolicited requests for copies were received. As mentioned previously, the CNS Summit served as an invaluable means of key opinion leader development, and Regional Advisory Boards served as an effective means of neutralizing negative perceptions and misinformation on the part of physicians.” [Id. at -640-641]

385. Excerpta Medica stated: “When it became clear that it was important to use efficacy as the cornerstone for the Risperdal growth strategy, Excerpta Medica developed the Efficacy in Schizophrenia platform. Our solution to the need to bolster physician confidence for multiple uses of Risperdal was the development of the Efficacy Slide Kit and a key review article by Robert Conley, MD. In response to the need to focus global opinion to characterize and refine treatment approaches for BPSD, Excerpta Medica partnered with the International Psychogeriatric Association to organize two major consensus conferences and two enduring publications that appeared as supplements to *International Psychogeriatrics*. When the need for better competitive intelligence became obvious, Excerpta Medica initiated an electronic slide library and the *Risperdal Intelligence Scout* newsletter, a real-time, electronically delivered monitoring service.” [Id.]

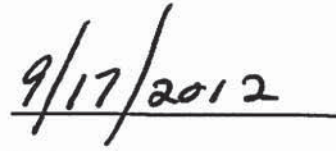
386. Excerpta Medica stated “Strategic Publication Planning for Risperdal (risperidone) Child & Adolescent Use. Submitted to: Magali Reyes-Harde, MD, PhD Janssen Pharmaceutica, Inc. Submitted by: Excerpta Medica November 2, 2001.” [EMRISP0131382]

387. Excerpta Medica stated “Several challenges will be addressed by the suggested publications including the following: Widespread misperception that children and adolescents are not affected by mental illness; Perception that there is widespread inappropriate prescribing of psychotropic drugs in the child and adolescent population; Symptoms of mental illness in children and adolescents do not correspond to mental illness symptom definitions commonly used in adult populations. Moreover, there may be considerable symptom overlap in children that complicates making definitive DSM-IV diagnoses and that can obfuscate the identification of comorbid conditions; Primary care physicians, parents, educators and social workers need to appreciate that the prompt initiation of appropriate treatments substantially reduces the morbidity and improves the social and educational functioning of mentally ill children; Physicians need to be made aware that antipsychotic drugs are an effective component of multimodality therapy for treating symptoms of many childhood mental illness; Risperidone must be differentiated from traditional and other novel antipsychotics that might be used to treat children.” [EMRISP0131384-EMRISP0131385]

I reserve the right to supplement this report based on new information and to correct any proofreading or cite-checking errors.

A handwritten signature in black ink, appearing to read 'D. A. Kessler', written over a horizontal line.

David A. Kessler, M.D.

A handwritten date '9/17/2012' written in black ink over a horizontal line.

Date