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 serotoninergic 5-HT_2 and dopaminergic D_2 receptors. The drug binds to alpha$_1$ –adrenergic receptors, with lower affinity to H_2 histaminergic and alpha$_2$ –adrenergic receptors. Risperdal is a potent dopamine D_2 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%." [JJREv 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 PMEs [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