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. Eerdekens, (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, Eerdekens, 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 or 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 or 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 bipoar disorder and ADHD: What are we treating? – Gabrielle Carlson, MD; (4) Evidence-based treatment of target symptoms associated with pervasive developmental disorders (PDD) – Christopher McDougle, 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 An American Association of Psychiatrics 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 McDougle, 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 Subaverge 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." [JJREv07498316, 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. Puszkarski 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." [JJNJJNSE00000045]

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." [JJNJJNSE00000056]

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 fashoin [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 Seroqeul [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 Seroqeul'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 symtoms?"[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 staging[5]. [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-41in 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