

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.]

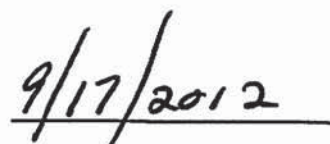
386. Excerpta Medica stated “Strategic Publication Planning for Risperdal (risperidone) Child & Adolescent Use. Submitted to: Magali Reyes-Harde, MD, PhD Janssen Pharmaceutica, Inc. Submitted by: Excerpta Medica November 2, 2001.” [EMRISP0131382]

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.



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Date