IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

Sheller, P.C.
1528 Walnut Street
Philadelphia, PA 19102

Plaintiff,

v.

United States Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201,

United States Food and Drug Administration,
10903 New Hampshire Avenue
Silver Spring, MD 20993,

Sylvia Mathews Burwell, Secretary of the Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201, and

Margaret A. Hamburg, M.D., Commissioner of the Food and Drug Administration.
10903 New Hampshire Avenue
Silver Spring, MD 20993

Defendants.

No. 2:15-CV-00440

Hon. Legrome Davis

FIRST AMENDED COMPLAINT

Plaintiff Sheller, P.C. files this First Amended Complaint for injunctive relief and declaratory judgment pursuant to 5 U.S.C. § 702 and 28 U.S.C. § 2201.

PARTIES

1. Plaintiff Sheller, P.C. ("Sheller") is a professional corporation incorporated under the laws of the Commonwealth of Pennsylvania with a principal place of business in

Philadelphia, Pennsylvania. Sheller is a law firm that represents hundreds of children who have suffered serious injury caused by their ingestion of Risperdal®, generic versions of risperidone, and Invega® (collectively, the "Risperdal Drugs"). Sheller also serves as plaintiffs' liaison counsel for the Risperdal®-related litigation program at the Philadelphia Court of Common Pleas. Sheller represents its clients in Risperdal®-related litigation on a contingency fee basis.

2. Defendant Department of Health and Human Services ("HHS") is a cabinet-level agency of the United States Government. HHS is responsible for enforcing and administering relevant provisions of federal law, in particular, the Food, Drug, and Cosmetics Act.

3. Defendant Sylvia Mathews Burwell ("Burwell") is Secretary of the Department of Health and Human Services. Plaintiff sues Burwell in her official capacity.

4. Defendant United States Food and Drug Administration ("FDA") is an agency within the United States Department of Health and Human Services. FDA is responsible for enforcing and administering relevant provisions of federal law, in particular, the Food, Drug, and Cosmetics Act.

5. Defendant Margaret A. Hamburg, M.D. ("Hamburg") is the Commissioner of the FDA. Plaintiff sues Hamburg in her official capacity.

JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over Sheller's claims pursuant to 28 U.S.C. § 1331 because they arise under federal law, in particular, 5 U.S.C. § 702, 28 U.S.C. § 2201, and 21 U.S.C. § 301, *et. seq.*

7. This Court also has subject matter jurisdiction over Sheller's claims pursuant to 28 U.S.C. § 1346 because the defendants are agencies and officers of the United States.

8. Venue is proper in this District under 28 U.S.C. § 1391(e) because (1) Defendants HHS and FDA are agencies of the United States, and Defendants Burwell and Hamburg are

officers of United States agencies acting in their official capacities and under color of legal authority; (2) a substantial part of the events or omissions giving rise to the claim occurred in the Eastern District of Pennsylvania; and (3) Sheller resides in the Eastern District of Pennsylvania.

RELEVANT FACTUAL BACKGROUND

I. Introduction

9. This action arises from the FDA's decision to deny a citizen petition filed by Sheller. The citizen petition requested the FDA to require a change in the labeling for the Risperdal Drugs, which are second-generation atypical anti-psychotic mediations, and to revoke the Risperdal Drugs' pediatric indication.

10. The citizen petition also requested that the FDA review certain confidential documents that establish the danger of the Risperdal Drugs. Sheller has obtained these confidential documents in the course of representing its clients in other litigation, but was unable to produce them directly to the FDA because they were subject to confidentiality and protective orders in those cases. Sheller's citizen petition requested that the FDA request those confidential documents directly from Johnson & Johnson ("J&J") and its subsidiary Janssen ("Janssen"), the manufacturer of Risperdal®, or instruct J&J and Janssen to release Sheller from the confidentiality orders so that Sheller could submit the confidential documents to the FDA itself.

11. The FDA denied Sheller's citizen petition without a hearing or meeting and without considering all the evidence that Sheller identified.

12. The FDA's denial of the citizen petition was arbitrary, capricious, and an abuse of discretion for the reasons described in this Complaint. In particular, the FDA refused to review the confidential documents cited by Sheller, even though it permitted Janssen to make an *ex*

parte submission of documents that Sheller only learned about through discovery in other litigation.

13. Sheller has represented plaintiffs injured by Risperdal® in two cases that have gone to trial after the FDA denied the Petition, and after Sheller's original Complaint was filed in this case. A number of the confidential documents have only now become public through those trials. Janssen had concealed them from the FDA during the pendency of the Petition. As described below, the now-public information in those documents demonstrates the error in the FDA's decision not to modify the Risperdal Drugs' labeling. Further, testimony in those trials has established that key information about the safety of the Risperdal Drugs was never provided to the FDA.

14. The FDA's denial of the petition also *expressly refused* to consider certain facts Sheller had submitted regarding the inadequate labeling of the Risperdal drugs.

15. The FDA also gave no reason for its decision to deny Sheller's request for a hearing, and its denial of that request suggests that it fundamentally misunderstood the nature of the relief sought by Sheller.

16. The FDA's decision puts at risk numerous pediatric patients who are prescribed the Risperdal Drugs. The Risperdal Drugs cause increased levels of prolactin, which leads to a variety of side effects including the abnormal development of breasts in male patients (gynecomastia) and a variety of adverse effects on sexual development in patients of both sexes. These adverse effects are severe and long-lasting.

II. Statutory Background

17. HHS and FDA are responsible for enforcing the provisions of the Food, Drug, and Cosmetics Act, 21 U.S.C. § 301, *et. seq.* ("FDCA").

18. The FDCA governs, among other things, the approval of applications for new drugs. The FDCA also provides for the withdrawal of the approval for drugs that are subsequently found to be unsafe. In particular, the FDCA provides that the FDA *shall* withdraw approval of a drug application where it "finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; [or] (2) that new evidence of clinical experience . . . shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved." 21 U.S.C. § 355(e).

19. The FDCA also governs the labeling of drugs. Among other things, the FDCA provides that a drug is misbranded "[u]nless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users." 21 U.S.C. § 352(f); *see also* 21 CFR § 201.57(c)(6)(i).

20. Regulations enacted pursuant to the FDCA provide that a "boxed warning" is appropriate to warn of "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury." 21 CFR § 201.57(c)(1).

21. A label must also indicate if specific tests are necessary to monitor the safety of patients on a drug, or if a drug should be limited to certain situations or populations. 21 CFR § 201.57(c)(2); 21 CFR § 201.57(c)(6)(iii).

III. Procedural background

22. On July 27, 2012, Sheller filed a Citizen Petition with the FDA pursuant to 21 CFR § 10.30 requesting that the FDA (a) immediately revoke the pediatric indication for the Risperdal Drugs unless and until the long term safety of those drugs could be demonstrated, or

(b) in the alternative, immediately require that labeling for those drugs include a black box warning based on the lack of sufficient data to prove their safety. The Citizen Petition was docketed at FDA-2012-P-0857 and is attached hereto as Exhibit A.

23. The Petition also requested the FDA to direct Johnson & Johnson ("J&J"), the manufacturer of Risperdal®, to consent to release Sheller from Confidentiality / Protective orders that govern the dissemination of certain confidential documents that Sheller has obtained in the course of its representation of its clients (the "Confidential Documents") so that Sheller can present those documents to the FDA.

24. In the alternative, the Petition requested that the FDA request that J&J submit the Confidential Documents to the FDA directly, including internal communications and litigation material such as deposition transcripts, provided that such material be made available for public review or comment, or at least for Sheller to review *in camera* to determine that the submission was complete.

25. Sheller filed an amended version of the Petition (the "Petition") on August 27, 2012, which provided additional factual background and sought the same relief as the original petition, and is attached hereto as Exhibit B.

26. As described more fully in Section IV.E below, the Confidential Documents describe the risks associated with the Risperdal Drugs and contradict, complicate, and/or substantially call into question safety data provided by J&J and/or Janssen to the FDA. The documents are in J&J and/or Janssen's possession and control, and in many instances were generated by J&J, Janssen and/or J&J's predecessor or subsidiary companies who were involved in the research and development of Risperdal®. Upon information and belief, certain of these

documents have never been given to the FDA, and others were buried within "document dumps" to the FDA to conceal their relevance and significance.

27. On January 29, 2013, the FDA provided Sheller an interim response pursuant to 21 CFR § 10.30(e)(2)(iii), attached hereto as Exhibit C, stating that "FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials."

28. On March 20, 2013, according to a document obtained by Sheller during discovery in separate litigation, the FDA sent an Information Request (the "Information Request") to Janssen that stated:

> We remind you of your obligations pursuant to section 505(k) of the FDCA to submit to FDA "data relating clinical experience and other data and information," as well as those set forth in 21 CFR Part 314, with respect to the drugs that are the subject of the above referenced NDAs. To the extent that you have any data in your possession relevant to the use of risperidone or paliperidone in children and adolescents that you have not previously provided to the Agency, please do so, or otherwise respond to this letter, within 30 days of receiving this letter.

29. The March 20, 2013 Information Request was never sent to Sheller by the FDA and was not made available on the public docket.

30. In response, Janssen submitted certain documents to the FDA on April 19, 2013. Janssen represented that "[w]e have not identified any data that were required to be submitted pursuant to section 505(k) of the FDCA or 21 CFR Part 314 but was not." Janssen further represented that its response was based on "a review of all data in our possession relevant to the use of risperidone or paliperidone in children and adolescents."

31. The FDA allowed Janssen to submit its response *ex parte*, without filing it on the public docket. Sheller was only able to obtain Janssen's response through discovery in other litigation.

32. Meanwhile, on March 26, 2013, Sheller submitted a letter, attached hereto as Exhibit D, requesting that the FDA schedule a hearing on the Petition pursuant to 21 CFR § 10.30(h)(2). Sheller requested a hearing, in part, because of the "unique knowledge/information in [its] possession," including the Confidential Documents that the FDA had not, and still has not, reviewed.

33. The FDA denied Sheller's request for a hearing in a letter dated June 11, 2013, attached hereto as Exhibit E. Fundamentally misunderstanding the relief requested by Sheller, the FDA invited Sheller to submit the Confidential Documents to the FDA by filing them on the public docket.

34. Sheller responded to the FDA's denial of a hearing by letter dated July 2, 2013, attached hereto as Exhibit F. Sheller explained that because of the Confidentiality/Protective Orders, it was unable to submit the Confidential Documents to the FDA as suggested in the FDA's denial of a hearing. As Sheller explained, the FDA "misunderst[ood] both [Sheller's] request and the legal status of those documents."

35. Sheller also explained the importance of certain of the Confidential Documents, in particular, the supporting analyses for a report authored by David Kessler, M.D., former Commissioner of the Food and Drug Administration (the "Kessler Report"). Among other things, the Kessler Report undermines a published study that is frequently cited by J&J, Janssen, and others for the proposition that there is no direct correlation between prolactin elevation and adverse effects including gynecomastia. Although the Kessler Report is publicly available, its supporting analyses were subject to the confidentiality orders referenced above, and were in the control of J&J.

36. Sheller sent its July 2, 2013 letter directly to Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research.

37. The FDA acknowledged Sheller's July 2, 2013 letter in a response dated August 16, 2013, attached hereto as Exhibit G, but gave no reason for its refusal to provide Sheller a hearing. Indeed, the FDA failed to even acknowledge the existence of the Confidential Documents, or the fact that Sheller was unable to submit them to the FDA for review. Instead, the FDA merely noted:

> Your letter addresses issues related to your citizen petition and is being considered as part of that deliberative process. We will issue a response once our review has been completed and a decision has been made. You also requested to meet with the Agency. We do not believe that such a meeting would be beneficial at this time. Therefore, your request is denied.

38. The FDA also requested that Sheller submit its July 2, 2013 letter "to the petition docket" "[f]or reasons of transparency, and in compliance with [FDA] policy." Thus, the FDA refused to allow Sheller to submit documents to the FDA for review *ex parte*, as it had permitted Janssen to do.

39. The FDA decided Sheller's Petition on November 25, 2014, in a decision attached hereto as Exhibit H. The FDA denied Sheller's request to revoke the pediatric indication for the Risperdal Drugs or to require a black box warning. The FDA noted that it had issued the Information Request to Janssen, but otherwise denied Sheller's request to obtain additional information from J&J and Janssen. The FDA did not address Sheller's request for a hearing.

40. Sheller is aggrieved by the FDA's decision because that decision has been used as the basis to assert federal preemption and other arguments against Sheller's clients in Risperdal®-related litigation. As described below, *see infra* Section V, Janssen has already asserted meritless arguments relating to the FDA's denial of the Petition before the Philadelphia

Court of Common Pleas and will almost certainly raise them again in other cases. Sheller has and must continue to spend money defending against such arguments, even though they are without legal merit. In defending against those arguments, Sheller must explain, among other things, that the FDA refused to consider relevant documents and that its decision was based on an incomplete record.

41. Sheller is aggrieved by the FDA's decision because Sheller has a right under 21 CFR § 10.30 to file a citizen's petition and have it be considered by the FDA in light of all relevant information. The FDA's refusal to consider or even accept information relevant to the Petition, and the FDA's express refusal to consider grounds for relief stated in the Petition, effectively deny Sheller that right.

42. Sheller is also aggrieved by the FDA's decision because that decision increases the cost to Sheller of litigating its clients' Risperdal®-related personal injury claims and interferes with Sheller's representation of hundreds of consumers of the Risperdal Drugs and its ability to exercise its responsibilities as liaison counsel for Risperdal®-related litigation at the Philadelphia Court of Common Pleas.

43. Sheller has an obligation as an advocate for its clients to act on the information it has to protect its clients' safety. At the time Sheller filed its Petition, and again when it brought this action, Sheller was in the wholly unique position of having confidential safety information about the Risperdal Drugs that even the FDA did not have. This information relates not only to the safety of Sheller's clients but also to the safety of other consumers of the Risperdal Drugs. At the time Sheller filed its Petition, and again when it brought this action, Sheller was aggrieved by its inability to act on that confidential information for the benefit of its clients and those whose interests it has been charged with protecting.

IV. The Risperdal Drugs are mislabeled, and their pediatric indication should be withdrawn

A. The dangerous effects of the Risperdal Drugs

44. Risperidone and its active metabolite, paliperidone are second-generation atypical anti-psychotic drugs marketed in the United States as Risperdal® and Invega®, respectively, by Janssen Pharmaceuticals, Inc. ("Janssen"), formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Inc., a subsidiary of J&J.

45. By the time Sheller filed its Petition, the FDA had given approval to at least 10 generic manufacturers for the manufacture and distribution of generic risperidone.

46. Risperdal® was approved for adults by the FDA in 1993 as an anti-psychotic therapy for schizophrenia. In 2003 this adult indication was expanded to include use of Risperdal® for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults.

47. In 2006, Risperdal® received its first approval for children, for treatment of the irritability associated with autistic disorder in children between the ages of 5 and 17. In 2007 the adult indications for schizophrenia and for the treatment of acute manic or mixed episodes associated with bipolar I disorder were expanded to include children and adolescents as young as 13 and 10, respectively.

48. At least tens of thousands of children have been prescribed the Risperdal Drugs both on and off-label and are at risk of suffering adverse events if the FDA does not take immediate action.

49. In particular, the Risperdal Drugs cause serious adverse events including gynecomastia, an abnormal enlargement of glandular tissue in male breasts, and other adverse events related to an increase in the hormone prolactin.

50. The Risperdal Drugs are known to cause significant increases in levels of prolactin (hyperprolactinemia). The introduction of the Risperdal Drugs to pre-pubertal or pubertal adolescents enhances the hormonal and endocrinological processes already at work, resulting in permanent conditions such as gynecomastia and adverse events on sexual maturation that would not have been experienced in the absence of the Risperdal Drugs. The Risperdal Drugs can also trigger substantial weight gain, which itself increases the risk of gynecomastia.

51. Between 10% - 25% of cases of gynecomastia are drug-induced. The Risperdal Drugs increase prolactin in adolescents more than nearly all other medications.

52. While J&J and Janssen publicly maintain that conditions such as gynecomastia are "mild" and "transient" or are readily reversible with drug cessation, the experiences of Sheller's clients demonstrate that the condition is chronic and devastating.

53. The development of breasts for even a psychologically healthy adolescent boy or young man can be extremely detrimental. The patient becomes subject to taunts, derision, and even physical bullying by their peers, as well as questions about their sexual and gender identity at the very time those elements of their psyche are starting to manifest. For boys and young men who are already mentally and/or psychologically impaired enough to have been prescribed anti-psychotic medications, the daily horror that often accompanies the abnormal development of breasts can be the last straw.

54. Patients who are otherwise functional describe having to avoid peers, miss school, forego social opportunities and the development of relationships, all due to the shame and fear associated with their abnormal breast growth. Having to change clothes for gym class becomes a regularly scheduled torture session. While their peers are busy enjoying their summers, playing sports and dating, the victims of gynecomastia induced by the Risperdal Drugs are hiding at

home, under multiple layers of clothing, or bound within homemade compression bands in an attempt to hide the abnormal breasts they have developed.

55. Indeed, a study presented at the American Academy of Pediatrics Meeting on April 29, 2012 found that being bullied or ostracized increases special-needs children's risk of depression and other internalizing emotional-behavioral conditions. It should be no surprise that the adolescent, teen, and pre-teen boys whom Sheller represents and who have developed breasts as a result of their ingestion of the Risperdal Drugs uniformly report being bullied (both physically and verbally) and ostracized by their peers.

56. In the course of considering J&J's application for approval of Risperdal® for the treatment of irritability associated with autistic disorder, the FDA in 2006 conducted a review and evaluation of clinical data provided by J&J. Incidents of gynecomastia were included among serious adverse events discussed in the FDA's evaluation.

57. In a one-year, post exclusivity adverse event review for risperidone that was presented to an FDA Advisory Committee in 2008, the FDA included gynecomastia and hyperprolactinemia among "serious adverse event[s]" caused by risperidone.

58. Gynecomastia was again described by the FDA as a "serious" adverse event in a "Pediatric Focused Safety Review" of Invega® at a meeting of the Pediatric Advisory Committee in March 2013.

59. The FDA's claim in its denial of the Petition that ethical concerns make it impossible to conduct controlled studies of the effects of the Risperdal Drugs is false. Indeed, such controlled studies have already been performed. *See* Yvette Roke, *et. al.*, "Risk of Hyperprolactinemia and Sexual Side Effects in Males 10-20 Years Old Diagnosed with Autism

Spectrum Disorders or Disruptive Behavior Disorder and Treated with Risperidone," 22 J. Child and Adolescent Psychopharmacology 432 (2012).

B. Inadequate labeling

60. The long-term safety of the Risperdal Drugs for children has not been established, and current prescribing information does not adequately reflect the true health risks caused by the Risperdal Drugs.

61. The current prescribing information for the Risperdal Drugs actively impedes physicians' ability to comply with the standard of care for the monitoring, diagnosis and treatment of hyperprolactinemia. Adequate warning would result in most, if not all adolescents being switched from the Risperdal Drugs to one of the many other atypical antipsychotics with a safer prolactin profile.

62. The approved indications for the use of the Risperdal Drugs in the pediatric population are unduly vague and lack appropriate guidance for physicians considering prescribing the drugs.

63. The Risperdal Drugs' known effect of causing gynecomastia and adverse effects on sexual maturation is not warned about at all in the "Highlights of Prescribing Information" section of the Prescribing Information, under either the "Warnings and Precautions," "Adverse Reactions," or "Use in Specific Populations" sections. Data about the rates of gynecomastia in child and adolescent trials is buried in Section 8 of the Risperdal® label, consisting of the following language:

> In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

64. That statement is misleading because studies have shown that the rate of gynecomastia can range from 5%- 14% with long term use of Risperdal®, which clinical experience shows is the most typical use of the drug.

65. That statement, combined with the fact that data on the adolescent rates of Risperdal®-induced hyperprolactinemia and its associated disorders of: galactorrhea (discharge from the breast), amennorhea (absence of menstruation), infertility in girls, gynecomastia and diminished libido in boys, and adverse impact on sexual maturation in children of both genders, are buried in the "Use in Special Populations" section of the Prescribing Information, have given physicians and the public a false sense of the safety of the Risperdal Drugs for adolescents.

66. The Invega® label also includes no warning about the risk of gynecomastia or sexual maturation in the "Highlights of Prescribing Information" section. Data on the incidence of gynecomastia in adolescent pages is buried in a table in Section 6 of the Invega® label.

67. The propensity of the Risperdal Drugs to cause weight gain is understated, leading physicians to inaccurately attribute any abnormal breast growth to weight gain itself, and fail to consider the Risperdal Drugs as a potential cause.

68. The Prescribing Information also lacks clear guidance to physicians regarding monitoring their pediatric patients' blood prolactin levels and obtaining complete physical exams, by qualified practitioners, to identify and assess abnormal breast growth or effects of hyperprolactinemia. Indeed, the Invega® label expressly provides that "[n]o specific laboratory tests are recommended."

69. However, as evidenced by certain of the Confidential Documents, elevated prolactin levels during a critical period from 8 to 12 weeks after a patient starts taking risperidone are a predictor of significantly increased risk of adverse effects. Also as evidenced

by the Confidential Documents, senior executives at Janssen advised that this critical safety finding – and a recommendation to conduct blood tests - be omitted from the label because of the potential to negatively impact sales of the Risperdal Drugs.

70. The correlation between increased prolactin levels at 8 to 12 weeks following the start of treatment, and the eventual development of gynecomastia, is detailed in a draft letter by Joseph Glenmullen, M.D. to the FDA, attached hereto as Exhibit I. Dr. Glenmullen is a practicing psychiatrist and clinical professor of psychiatry at Harvard Medical School, and was retained by the State of Texas as an expert witness in Risperdal-related litigation. Although Dr. Glenmullen's letter is not confidential, having been filed on the public docket in connection with litigation in Texas, Sheller did not become aware of it until after the FDA denied its Petition. Upon information and belief, the draft letter was not sent to the FDA, and it was not disclosed to the FDA by J&J and/or Janssen.

71. If physicians were directed to monitor pediatric patients' prolactin levels, few adolescents would remain on the Risperdal Drugs past their first and second blood test.

72. The Risperdal Drugs and other anti-psychotic medications are often prescribed by mental health professionals who are not in the habit of conducting physical examinations of their patients, including assessments of adolescent/teen boys and young men for abnormal breast growth, Tanner staging (an evaluation of the development of puberty), evaluation of testicular development and sexual maturation generally.

73. Young patients who are prescribed the Risperdal Drugs, and their parents, are not instructed to be on the look-out for abnormal breast growth. The adolescent patients themselves who are taking the Risperdal Drugs may not have the mental and/or psychological capacity to

recognize abnormal breast growth as a potential drug adverse event, let alone connect it to the Risperdal Drugs.

74. The standard of care and recommended best practices for diagnosis and treatment of potentially medication-induced hyperprolactinemia is to take the patient off the medication and determine whether the patient's prolactin levels return to normal. If the patient's underlying condition requires continuation of an anti-psychotic medication, the standard of care is to switch to another drug in the same class that does not cause hyperprolactinemia, for instance, olanzapine, clozapine, quetiapine, or aripiprazole. Risperdal Drugs prevent physicians from adhering to this standard of care and recommended best practices.

75. J&J and Janssen have resolutely refused to change the Risperdal Drugs' Prescribing Information to more accurately reflect the risk of weight gain, hyperprolactinemia and their associated disorders, which J&J and/or Janssen is authorized to do.

76. The ability of generic manufacturers to alter the prescribing information for generic medications is narrowly circumscribed, and plaintiffs are generally unable to sue generic manufacturers for defects in a drug's warning label. Thus, the inadequate labeling of generic risperidone will also remain in place unless the FDA takes action.

C. Off-label use

77. J&J's conduct prior to approval of Risperdal® for pediatric use created a robust off-label market for the Risperdal Drugs for conditions far removed from the limited pediatric indication eventually approved by the FDA.

78. Even after Risperdal® was approved for children in very limited circumstances, J&J has aggressively marketed the drug for off-label conditions such as autism generally (even absent "irritability"), attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), oppositional-defiant disorder (ODD), conduct disorder (CD), disruptive

behavior disorder (DBD), Tourette's Syndrome, post-traumatic stress disorder (PTSD) and pervasive developmental disorder (PDD).

79. Thus, J&J has helped fuel an explosion of the anti-psychotic pharmaceutical sector. In 2011, sales of anti-psychotic medications in general totaled $18.2 billion, a 12.7% increase over 2010. Atypical anti-psychotics became one of the fastest growing medication classes in the United States.

80. J&J has repeatedly been found guilty of inappropriate off-label and otherwise fraudulent marketing of Risperdal®.

81. In South Carolina in 2011, J&J was found liable by a judge in a bench trial and ordered to pay a verdict of $327 million (reduced to $136 million on appeal).

82. In 2012, J&J was forced to settle a case by the State of Texas for $158 million.

83. These are cases that were brought by the States' Attorneys General seeking to protect the safety of their citizens from J&J's inappropriate conduct related to Risperdal®.

84. In addition, on November 4, 2013, the Department of Justice announced that J&J agreed to pay more than $1.391 Billion to resolve civil investigations against it relating to off-label promotion of Risperdal® and Invega®.

85. J&J also pleaded guilty to a criminal information on November 4, 2013 in which it admitted that it promoted Risperdal® to health care providers for off-label use. It agreed to a plea agreement under which it would pay a total of $400 million.

86. As part of its settlement with the government, J&J and its subsidiaries also agreed to the imposition of a Corporate Integrity Agreement ("CIA") with the Department of Health and Human Services Office of Inspector General. The CIA is intended to increase accountability and transparency and prevent future fraud and abuse.

D. Concerns raised by FDA's Advisory Committee

87. Members of an FDA Advisory Committee in 2008 expressed concern regarding the Prescribing Information for Risperdal® and issued a series of recommendations to further study off-label use and adverse effects of the Risperdal Drugs.

88. On November 18, 2008, the FDA's Pediatric Advisory Committee met to consider whether or not to maintain the *status quo* with regard to the Risperdal Drugs, or whether a heightened inquiry into the safety of the drug for children was warranted. Specifically, the question posed to the Committee by the FDA was "FDA will continue its standard, ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?"

89. The Committee "discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects" and unanimously concluded that the *status quo* for the Risperdal Drugs was inadequate. Specifically, as part of the Committee Vote and Recommendation, "Twelve (12) committee members unanimously supported more than the standard, ongoing safety monitoring for oral risperidone."

90. The Committee made several very specific recommendations, including:

a. Additional follow-up regarding on-label and off-label product use of [the] class of drug products with specific attention to age and indication for which the product is being used.

b. Additional follow-up regarding metabolic syndrome, growth, sexual maturation, and hyperprolactinemia;

c. Studies, which may be collaboratively developed with NIH, on long-term effects in the pediatric population of [the] class of products;

d. Additional follow-up on extrapyramidal side effects in the pediatric population; and

e. Additional evaluation of [the] class of anti-psychotic medications and concomitant drug use.

91. The report further stated that "[t]welve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee."

92. The Committee also raised concerns about the extensive off-label use of the Risperdal Drugs.

93. Upon information and belief, none of the Committee's recommendations have been implemented by the FDA or completed, and the Prescribing Information for the Risperdal Drugs remains deficient.

94. J&J and Janssen have persistently failed to conduct adequate long-term studies on the safety of the Risperdal Drugs in children and adolescents as specifically requested by the FDA's Pediatric Advisory Committee in 2008.

95. Indeed, J&J summarily dismissed the Advisory Committee's concerns. In a New York Times article on the Advisory Committee meeting, a J&J spokeswoman is quoted as saying "[a]dverse drug reactions associated with Risperdal use in approved indications are accurately reflected in the label."

E. The FDA refused to consider confidential documents that establish the dangers of the Risperdal Drugs and Janssen's efforts to conceal them.

96. Sheller, through its representation of hundreds of children and adults who have been injured as a result of their ingestion of the Risperdal Drugs, has learned of critical documents related to the risks associated with the Risperdal Drugs which contradict, complicate and/or substantially call into question safety data provided by J&J and Janssen to the FDA,

including a statements to the FDA that a review of the safety information did not show a correlation between prolactin levels and adverse events potentially attributable to prolactin

97. Upon information and belief, none of the Confidential Documents described below were considered by the FDA in its consideration of the Petition, and Janssen did not provide them to the FDA even in its *ex parte* response to the FDA's Information Request, which identified the documents that were being provided to the FDA.

98. As described below, some of the Confidential Documents have become public in two jury trials of claims brought by Sheller's clients, only after the Petition was denied and after Sheller filed its original Complaint in this case. However, also as described below, some of the Confidential Documents remain subject to confidentiality orders and, upon information and belief, are still not accessible to the FDA.

99. All of the Confidential Documents are and have been in Janssen and/or J&J's possession and control, and in many instances were generated by J&J, Janssen, and/or J&J's predecessor or subsidiary companies who were involved in the research and development of Risperdal®.

100. The Confidential Documents include but are not limited to the following:

101. ***First***, the Confidential Documents include supporting documents for a report authored by David Kessler, M.D., former Commissioner of the Food and Drug Administration. As described above, Dr. Kessler's report undermines the results of an article ghostwritten by Janssen employees to dispute the correlation between prolactin elevation and symptoms including gynecomastia. The article was based on Janssen's own meta-analysis of trials that Janssen had conducted of Risperdal® on pediatric patients. *See* Robert L. Findling, et. al., *Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents*, J. Clin.

Psychiatry 2003; 64: 1363-69 (the "Findling Article"). The goals of this meta-analysis were to explore any relationship between Risperdal®'s propensity to raise prolactin levels and side effects attributable to prolactin, and conveying a key message that elevated prolactin levels in the bloodstream did not correlate with side effects, namely gynecomastia.

102. The FDA would have relied upon the Findling Article in responding to the Petition. Articles studying the risk of gynecomastia and the Risperdal Drugs have continued to rely on the Findling Article. Indeed, the Findling Article has been cited and relied upon in more than 84 scholarly publications.

103. Although Dr. Kessler's report was publicly available at the time of the FDA's decision, its supporting analyses were subject to the confidentiality orders referenced above, and are in the control of J&J and/or Janssen. Some of those supporting analyses remain subject to confidentiality orders today. The FDA was provided the Findling Article in connection with its review of the supplemental new drug application for its approval of a pediatric indication for Risperdal® in 2006.

104. ***Second***, the Confidential Documents also include a supplemental report that Dr. Kessler subsequently authored in connection with litigation before the Philadelphia Court of Common Pleas in which Sheller represents victims of the Risperdal Drugs which further confirm J&J and Janssen have not provided all relevant information to the FDA, prescribing doctors, and the public. That report and Dr. Kessler's related deposition testimony are in the possession of J&J and/or Janssen and were subject to confidentiality / protective orders that prevented Sheller from providing it to the FDA at the time of the FDA's decision. Dr. Kessler has since testified to his conclusions in the report, but the report itself remains confidential.

105. ***Third***, also included among the Confidential Documents are the original data for the Findling Article and analyses of that data; a draft manuscript of the Findling Article; and correspondence among Janssen employees describing how to manipulate the Findling Article. The Findling Article was co-authored by Janssen employees and disavowed a link between Risperdal® and gynecomastia.

106. Although certain of these documents are now public, having been released during the trial of one of the Risperdal cases in the Philadelphia Court of Common Pleas, they were subject to confidentiality orders at the time the FDA decided the Petition.

107. The original data for the Findling Article showed a statistically significant association between Risperdal ingestion and gynecomastia. A draft of the Findling Article acknowledged this association with the comment that "I think we need to discuss this somewhere in the manuscript." Ultimately, Janssen manipulated the data for the final report by performing a post-hoc analysis on only a subset of the original sample and not subtracting the excluded subset from the calculation of the total number of subjects. One Janssen employee commented that "this exclusion may be questioned, as we get feedback from advisors that they see the most gynecomastia in adolescent boys." The same Janssen employee noted in response to a statement in the manuscript that "[g]ynecomastia is frequently seen in boys going through puberty" that "if I read correctly, gynecomastia was excluded for boys > 9 years".

108. Correspondence among employees of Janssen and affiliated companies demonstrated that the Findling Article was highly manipulated. For instance, one Janssen employee, Carin Binder, emphasized to the "Pediatric Publication Team" that the "Key message" should be "prolactin rise is transient and not related to side effects hypothetically attributed to prolactin." In agreement, Gahan Pandina replied that "[i]f we can demonstrate that the transient

rise in PRL does not result in abnormal maturation or SHAP [Side Effects Hypothetically Attributable to Prolactin], this would be most reassuring to clinicians."

109. Binder criticized a subsequent version of the manuscript because it "now include[s] a nauseating amount of info on SHAP, specifically gynecomastia throughout all ages and a ris [sic] total dose vs. prolactin analysis." She urged that "[t]here's nothing to find people!"

110. Ultimately, and in contradiction to the data and the initial drafts of the article, the published Findling Article stated that "[t]here was no direct correlation between prolactin elevation and SHAP."

111. ***Fourth***, the Confidential Documents include marketing and business plans created by Janssen that reflect its efforts to downplay adverse effects of the Risperdal Drugs in order to increase market share, particularly in the pediatric market. Certain of these documents have become public at trial in the Philadelphia Court of Common Pleas, but like the documents above were subject to confidentiality orders at the time the Petition was decided and the original Complaint in this case was filed.

112. For example, Janssen's business plan for the "RISPERDAL Child and Adolescent Market" indicates the importance of the pediatric market for Janssen, noting that "[c]hild and adolescent patients comprise 21% of Risperdal's overall uses, twice the APS market rate. Half of Risperdal child and adolescent patients are under age 13." The business plan recognized that a "threat" was "FDA Relabeling of Current RISPERDAL PI" and that a "weakness[]" of the drug were its negative "Safety Perceptions (EPS/TD, Prolactin, Weight Gain)." A later business plan stated that a "Critical Success Factor[]" was to "Neutralize misconceptions about RISPERDAL's safety profile."

113. Other previously undisclosed marketing materials include a "poster" distributed to physicians based on misleading data from the Findling Article, and meeting minutes describing Janssen's strategy to "reassur[e]" clinicians by publishing data on Risperdal®.

114. Janssen has repeatedly admitted that it has withheld key Confidential Documents from the FDA.

115. In testimony before the Philadelphia Court of Common Pleas in two separate cases, Janssen Vice President Ivo Caers admitted that the meta-analysis from five clinical trials and an important analysis of this raw data underlying the Findling Article had not been provided to the FDA.

116. In responses to Requests for Admissions propounded upon Janssen in a products liability action in Texas, Janssen admitted that it had not provided several key safety results from original unaltered analyses of five studies conducted in connection with the Findling Article, which stated that there was a statistically significant association between prolactin levels and adverse events potentially attributable to prolactin. These studies were the basis of the Findling Article, and Janssen has submitted the final studies, but not the original unaltered analyses, to the FDA as evidence of the Risperdal Drugs' safety.

117. Although Sheller was aware of the existence of the Confidential Documents from its representation of victims injured by the Risperdal Drugs, Sheller could not submit these documents to the FDA while the Petition was pending because of confidentiality orders under which the documents were provided to Sheller.

118. J&J and Janssen have consistently refused to permit confidentiality to be waived.

119. For instance, when a specially-appointed panel of "discovery masters," including retired judges, in the New Jersey Risperdal litigation (*In re Risperdal / Seroquel / Zyprexa*

Ligitation, No. 274, Middlesex County) agreed over J&J's strenuous objections to lift confidentiality so that Sheller could present the documents to the FDA, J&J responded by successfully appealing that decision to the trial judge and keeping the confidentiality restrictions in place.

120. The FDA was empowered to demand that Janssen provide the Confidential Documents to the FDA so that the FDA can carry out its responsibility of ensuring the safety of the Risperdal Drugs. 21 U.S.C. § 355(k)(1) and (2)

121. Because the FDA refused to allow Sheller to submit the Confidential Documents or to obtain them directly from Janssen, the administrative record is incomplete, preventing adequate review of the FDA's denial of the Petition based only on the documents submitted to the FDA in connection with the Petition. Further, the FDA's refusal to allow the submission of these documents necessarily resulted in its failure to consider factors relevant to its final decision, making it arbitrary and capricious.

V. The Risperdal Trials

122. Two cases brought by Sheller's clients against Janssen for personal injury caused by ingestion of Risperdal have proceeded through trial in the Philadelphia Court of Common Pleas. *See P.P. v. Ortho-McNeil-Janssen Pharma*., April Term 2012, No. 1997 ("Pledger"); *W.C. v Janssen Pharma*., March Term 2013, No. 1803 ("Cirba"). Sheller's clients claimed in those cases and others that Risperdal® is defective because its warnings were inadequate and failed to warn of the risk of gynecomastia.

123. Janssen's counsel has argued before the Philadelphia Court of Common Pleas that the FDA's denial of the Petition establishes that gynecomastia is not a "serious adverse event," that the FDA would have rejected any change to the Risperdal® label, and thus that the failure to warn claims of Sheller's clients are preempted.

124. In the Pledger case, Janssen filed a motion in limine to preclude arguments, evidence, or testimony that gynecomastia is a "serious adverse event" based upon the FDA's denial of the Petition. Janssen also filed a motion in the Pledger case specifically to preclude the testimony of Sheller's expert, Dr. Kessler, that Janssen failed to warn of a serious adverse event. Sheller filed oppositions to these motions and attorneys from Sheller and Sheller's co-counsel presented oral argument against them. The Court denied each of Janssen's motions. In response to Janssen's position, Sheller also filed a motion in the Pledger case to strike a reference to the FDA's denial of the Petition.

125. In the Pledger case, Janssen's counsel repeatedly attempted to elicit testimony from Plaintiff's experts Dr. Kessler and Dr. Mathisen regarding the FDA's denial of the Petition, in particular, its statements regarding whether gynecomastia is a "serious adverse event." Although the Court did not permit testimony directly on the Petition, the questioning by Janssen's counsel did suggest to the jury that the FDA disagreed with the testimony of Plaintiff's experts.

126. After the Plaintiff's presentation of evidence in the Pledger case, Janssen filed a motion for compulsory nonsuit asserting, among other things, the preemptive effect of the FDA's denial of the Petition.

127. On February 26, 2015, the jury returned a verdict in plaintiff's favor in the Pledger case, awarding $2.5 million in compensatory damages. Janssen filed a motion for post-trial relief on March 13, 2015 arguing, among other things, that the Court improperly denied its motion in limine to preclude the testimony of Dr. Kessler and that the Court erroneously precluded testimony by Janssen's witnesses regarding the FDA's denial of the Petition. Sheller is required to expend resources defending this meritless argument. If Janssen's post-trial motion

is denied, Janssen will almost certainly file an appeal to the Superior Court, which Sheller will also be required to defend.

128. In the Cirba case, Janssen filed a motion in limine to preclude arguments, evidence, or testimony that gynecomastia is a "serious adverse event" based upon the FDA's denial of the Petition. The court granted Janssen's motion, and as a result, Sheller was unable to present such evidence.

129. In four other cases, Janssen has filed a letter with the Court, as a supplement to pending motions for summary judgment, referencing the FDA's denial of the Petition. Sheller has had to address that argument in its response to the summary judgment motions. *See* Opposition to M.S.J. at Ex. 30, *J.C. v. Janssen Pharma., Inc.*, Feb. Term 2014, No. 01276 (Filed Dec. 10, 2014).

130. Sheller has expended significant time and resources in opposing Janssen's meritless arguments about the effect of the FDA's denial of the Petition, and will be required to do so in the future. More than 1,200 Risperdal-related cases are pending before the Philadelphia Court of Common Pleas, and more than 700 such suits have been filed in California state court.

COUNT I
VIOLATION OF THE ADMINISTRATIVE PROCEDURES ACT

131. The FDA's denial of the Petition is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

132. In exercising its discretion, the FDA is required to examine the relevant data and articulate a satisfactory explanation for its action. However, the FDA failed to consider important evidence and facts that Sheller introduced into the record.

a. In its decision, the FDA *expressly* declined to "respond to [Sheller's] specific contentions regarding the current labeling of" the Risperdal Drugs.

b. The FDA also gave virtually no consideration to Sheller's substantial evidence of the continued and prevalent off-label use of the Risperdal Drugs.

c. The FDA failed to consider the Confidential Documents, even after Sheller explained their significance to the FDA in connection with its request for a hearing on the Petition.

133. The FDA's statement that gynecomastia is not a "serious adverse event" is directly contradicted by the FDA's own prior statements in FDA safety reviews of Risperdal® and Invega®.

134. The FDA's clear failure to even consider the evidence that Sheller submitted, and its failure to articulate any reason for that failure, makes its decision arbitrary and capricious based on the record that was before it.

135. The FDA's denial of Sheller's request for a hearing was arbitrary and capricious, an abuse of discretion, and otherwise not in accordance with law.

a. The FDA's initial refusal of Sheller's hearing request misapprehended the nature of the relief sought by the Petition. In particular, the FDA suggested that in lieu of a hearing, that Sheller should submit the Confidential Documents to the public docket. But, as Sheller explained, it was constrained from doing so because of the confidentiality orders to which it is subject. Indeed, that is a primary basis of the relief sought in the Petition.

b. The FDA's subsequent refusal of Sheller's hearing request was devoid of any explanation other than the conclusory statement that "[w]e do not believe that such a meeting would be beneficial at this time. Therefore, your request is

denied." Accordingly, the FDA failed to offer any satisfactory explanation for its decision.

136. The FDA's decision to allow Janssen to submit correspondence and evidence *ex parte*, but not to allow Sheller to submit material *ex parte*, was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

137. The FDA's decision had the effect of allowing Janssen to submit only certain confidential documents to the FDA, while ignoring other confidential documents in Sheller's possession that, as described above, were never provided to the FDA by J&J or Janssen.

138. The FDA's decision to allow Janssen to submit *ex parte* material but not to obtain the Confidential Documents cited by Sheller resulted in the compilation of an incomplete and biased record, making it impossible for this Court to review the FDA's decision based solely on the materials in the administrative record.

WHEREFORE, Plaintiff asks this Court:

A. To issue an injunction ordering that the FDA

a. immediately revoke the pediatric indication for the Risperdal Drugs, unless and until the long term safety of those drugs could be demonstrated, or

b. in the alternative, immediately require that labeling for those drugs include a black box warning based on the lack of sufficient data to prove their safety; and

B. To issue an injunction ordering Defendants to either

a. direct J&J and Janssen to consent to release Sheller from any confidentiality / protective orders that govern the dissemination of any confidential documents relating to the Risperdal Drugs that Sheller has obtained in the course of its

representation of its clients so that Sheller can present those documents to the FDA; or

b. in the alternative, request that J&J and Janssen submit directly to the FDA any documents relating to the Risperdal Drugs that it has not previously submitted to the FDA, including internal communications and litigation material such as deposition transcripts, and further provide that such material i) be made available for public review or comment; ii) be made available for Sheller to review *in camera* to determine that the submission was complete; or iii) be examined by a Special Master appointed by the Court to verify its completeness; and

C. To enter judgment declaring the Defendants' denial of the Petition to be arbitrary, capricious, an abuse of discretion, and contrary to law, in violation of the Administrative Procedures Act, 5 U.S.C. § 701, *et. seq.*; and

C. To grant such other and further relief as the Court should find just and proper, including attorneys' fees and costs.

Dated: May 1, 2015

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EXHIBIT

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July 27, 2012

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg,

Sheller, P.C. represents individuals and groups of individuals who have suffered serious physical and mental injuries caused by prescription pharmaceuticals, biologicals and devices. We presently represent hundreds of individuals who have suffered serious harm, including gynecomastia and prolactin-related injuries as a result of their ingestion of the second-generation atypical anti-psychotic medications Risperdal® (risperidone) marketed by Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Janssen Pharmaceutical, Inc., a subsidiary of Johnson & Johnson (hereinafter "J&J").

Requested Action

We hereby petition the Food and Drug Administration (hereinafter "FDA"), pursuant to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§352, 321 and 21 C.F.R. §§10.30 and 7.45 **to immediately revoke the pediatric indication for Risperdal®, all generic version of risperidone, and Invega®[1] (an extended release and injectable medication which includes the same primary active metabolite as Risperdal®) unless and until the long-term safety of the drug can be demonstrated, or in the alternative to immediately require that labeling for Risperdal® and all generic versions of risperidone include a black box warning on the lack of sufficient safety data.** Additionally, the FDA should **direct J&J to consent to release Petitioner from any and all standing Confidentiality/ Protective Orders so that Petitioner[2] can**

[1] Given the pharmacologic similarity between Risperdal® and Invega®, the information set forth in the remainder of this Petition applies equally to both drugs. J&J's conduct with respect to Risperdal® demands that the FDA take the same remedial actions with respect to Invega® in order to protect the public.

[2] In the alternative, the FDA should request that J&J themselves submit all internal documents, including e-mails and correspondence, as well as documents and testimony from the Risperdal® litigation. However, given J&J previous submission of data to the FDA, in a manner likely to bury or gloss over significant adverse event information, it is imperative that any documents produced directly by J&J either be available

FDA-2012-P-0857

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present to the FDA the internal documents and data, as well as an expert analysis thereof which we believe support the foregoing requested actions.

Basis for Action

Interest of the Parties

Petitioner represents hundreds of children who have suffered Risperdal®-induced gynecomastia and prolactin-related adverse events as a result of their ingestion of Risperdal®. Our clients constitute a sample of the tens (if not hundreds) of thousands of children who have been prescribed Risperdal® (both on- and off-label) and who are at risk of suffering adverse events if the FDA does not take immediate action.

Nature of the Problem

Our own investigation has revealed that the long-term safety of Risperdal® for children has not been established, and that the current Prescribing Information does not adequately reflect the true risks posed by Risperdal®.

Specifically, and as explained in more detail below:

* The approved Indications for the use of Risperdal® in the pediatric population are unduly vague and lack appropriate guidance of physicians considering the use of the drug.

    * For example, while Risperdal® is approved for use in children diagnosed with Bipolar I, that condition is never defined or described, leaving the potential for the conflation of that condition with the more common Bipolar II Disorder and therefore the inadvertent expansion of off-label use of Risperdal®.

    * The approval for "irritability" associated with autism is so vague and ambiguous as to practically equate with an approval for treatment of Autism generally, which is something the FDA specifically has refused to do.

    * J&J's conduct prior to pediatric approval by the FDA has created a robust off-label market for Rispderdal for conditions far afield from the limited Pediatric Indication eventually approved by the FDA.

* At the same time, children are particularly susceptible to the significant increases in prolactin-levels which Risperdal® is known to cause. This fact, and its significance, is not adequately conveyed to physicians and patients in the Prescribing Information:

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for public review and comment and/or made available to Petitioner for *in camera* review in order to assure the accuracy and completeness of J&J's document submission.

* The introduction of Risperdal® to pre-pubertal or pubertal adolescents enhances the hormonal and endocrinological processes already at work, resulting in substantially worse and more permanent conditions such as gynecomastia and adverse effects on sexual maturation than would have been experienced in the absence of Risperdal®. This fact is not warned about at all;

* The propensity of Risperdal® to cause weight gain is understated, leading physicians to inaccurately attribute any abnormal breast growth to weight-gain itself, and therefore fail to consider Risperdal® as a potential cause.

* Meanwhile, the Prescribing Information lacks clear guidance to physicians in terms of monitoring their pediatric patients' blood prolactin levels and obtaining complete physical exams, by qualified practitioners, to identify and assess abnormal breast growth or effects of hyperprolactinemia.

As such, our investigation validates the concerns raised by the FDA's own Advisory Committee regarding the safety of Risperdal® as labeled. As discussed in detail below, the Advisory Committee in 2008 found that the current Prescribing Information for Risperdal® was inadequate and issued a series of recommendations aimed at correcting the situation. To date, however, the Prescribing Information for Risperdal® remains unchanged and we have seen no evidence that J&J has provided the FDA with the information which the Advisory Committee found essential to the creation of an adequate prescribing label.

Background

Risperdal® was approved for adults by the FDA in 1993 as an anti-psychotic therapy for schizophrenia. In 2003 this adult indication was expanded to include use of Risperdal® for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults.

In 2006 Risperdal® received its first approval for children, for treatment of the irritability associated with autistic disorder in children between the ages of 5 and 16. In 2007 the adult indications for schizophrenia and bipolar I disorder were expanded to include adolescents as young as 13 and 10, respectively.

The manufacturer of Risperdal® has augmented these FDA-approved indications through aggressive "off-label" marketing, including the marketing of Risperdal® to children prior to the FDA's approval for use of the drug in that population.

Even after Risperdal® was approved for children in very limited circumstances, J&J has aggressively marketed the drug for off-label conditions such as Autism generally (even absent "irritability"), Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), Oppositional-Defiant Disorder (ODD), Conduct

Disorder (CD), Disruptive Behavior Disorder (BDB), Tourette's Syndrome, Post-Traumatic Stress Disorder (PTSD)[3] and Pervasive Developmental Disorder (PDD).

In so doing, J&J largely helped to fuel a veritable explosion of the anti-psychotic pharmaceutical sector. In 2011, sales of anti-psychotic medications in general totaled $18.2 billion, a 12.7% increase over 2010. Atypical anti-psychotics became one of the fastest growing medication classes in the nation.[4]

Risperdal® and Gynecomastia and Prolactin-Related Adverse Events

The current Prescribing Information for Risperdal® **fails** to even mention gynecomastia or hyperprolactinemia in the HIGHLIGHTS OF PRESCRIBING INFORMATION under either the "WARNINGS AND PRECAUTIONS" , "ADVERSE REACTIONS" or "USE IN SPECIFIC POPULATIONS" sections.

In fact, one must search 17 pages into the Prescribing Information to locate data about the rates of gynecomastia in child and adolescent trials. The label reads in relevant part:

> In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.[5]

This statement is misleading in that studies have demonstrated that the rate of gynecomastia is actually 5% with long-term use of RISPERDAL®, which clinical experiences shows is the most typical use of the drug.

Further, the statement, combined with the fact that data on the adolescent rates of Risperdal®-induced hyperprolactinemia and its associated disorders of: galactorrhea, amennorhea, infertility in girls; galactorrhea, gynecomastia and diminished libido in boys; and adverse impact on sexual maturation in children of both genders, are buried in the "USE IN SPECIAL POPULATIONS" section of the Prescribing Information, have given physicians and the public a false sense of the safety of Risperdal® for adolescents and concealed the epidemic of prolactin-related adverse events being inflicted upon children by Risperdal®

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[3] Notably, after a study of risperidone for the treatment of PTSD conducted at Veterans' Administration Medical Centers, the United States Army recently gave Risperidone a "D-level Recommendation", meaning that the "harm outweighs benefit"). See: *Memorandum for Commanders, MEDCOM Regional Medical Commnds dated 4/10/12* at p.9. While this Army study involved adults, it demonstrates that the risk/benefit analysis that supported initial FDA approval of risperidone does not support the myriad off-label uses for which J&J has promoted the drug.

[4] . *See: (http://www.imshealth.com/ims/ Global/ Content /Insights/IMS%20Institute %20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf)*

[5] A copy of the Prescribing Information for Risperdal is attached as Exhibit A.

The role of Risperdal® in triggering the development of gynecomastia in young boys is particularly invidious, as Risperdal® is responsible for multiple adverse events that, individually or in combination, contribute to the development of abnormal breast growth in that patient population. Specifically, Risperdal® causes hyperprolactinemia particularly aggressively in adolescents, a population particularly susceptible to the adverse sequella of that condition, including gynecomatia and impaired sexual mauration. At the same time, Risperdal® can trigger substantial weight gain which itself increases the risk of the gynecomastia. These two Risperdal®-induced mechanisms combine to wreak havoc on an adolescent's endocrine system. The Risperdal®-induced weight gain is particularly serious because the propensity of Risperdal® to cause weight gain is understated in the Prescribing Information, which leads many prescribing physicians to incorrectly attribute the development of gynecomastia to either "over-nutrition" or puberty.

Indeed, the prescription of Risperdal® to children prior to or during puberty is particularly harmful given that the drug can both exacerbate pubertal gynecomastia and turn pubertal gynecomastia (which is typically a short-lived phenomenon) into a chronic condition often requiring surgical repair.

Nevertheless, the Prescribing Information for Risperdal® is silent on these risks, leaving physicians in the position of throwing gasoline on the hormonal and endocrine fire already simmering in their pre-puberty and puberty aged patients.

By contrast, when the anti-depressant EFFEXOR was found to have an increased risk of adverse events in pediatric patients, the following black-box warning was added to the Prescribing Information, **even though EFFEXOR is not even approved by the FDA for use in children**:

Rx only
Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk,

PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

Likewise, the website for EFFEXOR includes this black-box warning displayed prominently in two different locations on the medication's homepage.[6]

Compared to the responsible and prudent way in which a special pediatric risk is conveyed for EFFEXOR, the risk of hyperprolactinemia with Risperdal® is hidden like a needle in a haystack.

It is Petitioner's experience that misinformation such as exists in the Risperdal® prescribing materials results in the failure of physicians and patients to recognize, report and attempt to remedy adverse events such as Risperdal®-induced gynecomastia and prolactin-related conditions.

For example, RISPERDAL® and other anti-psychotic medications are often prescribed by mental health professionals who are not in the habit of conducting physical examinations of their patients, including assessments of adolescent/teen boys and young men for abnormal breast growth, Tanner staging, evaluation of testicular development and sexual maturation generally.. Young patients who are prescribed RISPERDAL® and risperidone (and their parents) are not instructed to be on the look-out for abnormal breast growth. The adolescent patients themselves who are taking RISPERDAL® may not have the mental and/or psychological wherewithal to recognize abnormal breast growth as a potential drug adverse event, let alone connect it to RISPERDAL®. For that matter, most patients and/or their parents have no idea what the term "gynecomastia" means, or that it is in any way related to abnormal breast growth.

Additionally, all atypical anti-psychotic medications carry the risk of weight gain. We believe the Prescribing Information for Risperdal® understates and inaccurately minimizes the propensity of RISPERDAL® to cause weight gain. Therefore, when gynecomastia *is* recognized by a patient and/or their healthcare provider, it is often misattributed to diet or nutrition-based weight gain and/or puberty and incorrectly assumed to be unrelated to the patient's ingestion of RISPERDAL®.

On the contrary, between 10-25% of cases of gynecomastia are drug-induced.[7] RISPERDAL® increases prolactin in adolescents more than nearly all other medications. However these facts are not provided to physicians and patients in the Prescribing Information for RISPERDAL®. Were they provided, physicians confronted with adolescent patients on RISPERDAL® who experience abnormal breast growth would reach the unavoidable conclusion that RISPERDAL® had either caused or substantially contributed to the development of that condition. The physician could then take steps, including discontinuing the use of RISPERDAL®, to remedy the gynecomastia.

All of these factors constitute multiple levels at which adverse events can fall through the cracks and fail to be recognized, reported and remedied, permitting the

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[6] http://www.effexorxr.com/medication-guide.aspx

[7] Braunstein, G.D., Gynecomastia, *N. Engl. J. Med. 1993:328(7); 490-5.*

perpetuation of false safety data, and continued and/or increased sales that result in a vicious cycle of yet more unrecognized and unreported adverse events.

FDA Pediatric Advisory Committee Assessment of the Risperdal® Safety Profile

On November 18, 2008, the FDA's Pediatric Advisory Committee met to consider whether or not to maintain the *status quo* with regard to Risperdal®, or whether a heightened inquiry into the safety of the drug for children was warranted. Specifically, the question posed to the Committee by the FDA was "FDA will continue its standard, ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?"[8]

The Committee "discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects"[9] and unanimously concluded that the *status quo* for Risperdal® was **inadequate**. Specifically, as part of the Committee Vote and Recommendation, "Twelve (12) committee members **unanimously** supported **more than the standard**, ongoing safety monitoring for oral risperidone."[10] Instead, the Committee made several very specific recommendations:

> Twelve (12) committee members recommended the following:
>
> 1. Additional follow-up regarding on-label and **off-label product use** of this class of drug products with specific attention to age and indication for which the product is being used;
>
> 2. Additional follow-up regarding metabolic syndrome, growth, sexual maturation, and **hyperprolactinemia**;
>
> 3. Studies, which may be collaboratively developed with NIH, on **long-term effects in the pediatric population** of this class of products;
>
> 4. Additional follow-up on extrapyramidal side effects in the pediatric population;
>
> 5. Additional evaluation of this class of anti-psychotic medications and concomitant drug use;
>
> 6. Committee is not recommending any public communication before additional discussion which should occur after receipt of data from above recommendations[11]

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8 *See*: Minutes of The Pediatric Advisory Committee, Tuesday, November 18th, 2008 at page 3 (attached hereto as Exhibit B).

9 *Id.*

10 *Id.* (emphasis added).

11 *Id.* at 3-4 (emphasis added).

Ultimately, the Committee **unanimously** refused to grant its *imprimatur* to Risperdal® as presently labeled, concluding that "Twelve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee."[12]

Three-and-a-half years have passed since the Advisory Committee issued its recommendations. Petitioner is unaware of any evidence that any of the Committee's recommendations have been implemented by the FDA or completed within the intervening 42 months, and the Prescribing Information for Risperdal® therefore remains as it was in November 2008.

The concerns raised by Committee members during their meeting on Risperdal® demonstrate the urgent need for FDA action.

Initially, it should be noted that while the Pediatric Advisory Committee considered a total of nine (9) different "Specific Drug Reviews" during the course of that one-day meeting, their consideration of Risperdal® generated, by far, the most discussion and concern. The Committee's consideration of Risperdal® spans 68 transcript pages and constitutes nearly one-quarter of the transcript pages for "Specific Drug Reviews".

On November 18, 2008, the day of the meeting, the Pediatric Advisory Committee was presented with a "one-year, post-exclusivity adverse event review for risperidone."[13]

Committee Member Dr. Keith Kocis, M.D., M.S. voiced the concern that:

> In looking at this drug compared to many of the drugs that we're going to review or have reviewed over the few years that I've been here, this is somewhat unique in that it's being used – 25 percent of its use has been in pediatrics. It's a drug that has many effects, some that are serious, and I would disagree with your assessment that the FDA is passive in this thing in what they can do.
>
> . . .
>
> And then the final comment is on behalf of the sponsor, in the labeling when they talk about the long-term effects of Risperdal on growth and sexual maturation have not been fully evaluated**, I find that lacking** in the sense that we **know it has profound impact on prolactin** and other endocrine things that I believe should **require them** to study this in children who are undergoing sexual maturation.[14]

Discussing what he characterized as "the very high incidence of hyperprolactinemia in the pediatric population", Committee Member Dr. Geoffrey Rosenthal, M.D., Ph.D. concurred with Dr. Kocis:

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12 *Id.*

13 *See:* Transcript of 11/18/08 Pediatric Advisory Committee Meeting at p.44 (attached hereto as Exhibit C).

14 *Id.* at pp.74-76 (emphasis added).

If these medications are used to a significant degree in the pediatric population, and there is information regarding the effects of the medication on the neural endocrine access. Is it reasonable to ask the question of what is the long-term effect on growth and development in these areas?[15]

Dr. Rosenthal specifically noted that this concern should be added to the Prescribing Information:

I'm wondering whether there aren't some mechanisms even through the labeling process where particular attention can be drawn to this point, which might then stimulate research in this area . . . and **maybe if particular attention is drawn to the very high occurrence of hyperprolactinemia in the label**, that will raise enough eyebrows that the studies will get done.[16]

When it came time for the Committee to vote, not a single member supported continuation of the *status quo* "standard ongoing safety monitoring":

CHAIRPERSON RAPPLEY: So the vote will be the FDA will continue its standard ongoing safety monitoring for oral risperidone. How many on the Committee support that?

(No response)

CHAIRPERSON RAPPLEY: **So I am not seeing any hands raised.**

. . .

CHAIRPERSON RAPPLEY: So would you like me to summarize our recommendations first before we vote? Okay.

So a summary then of the recommendations that have arisen from our discussion today is that, one, the Committee would like follow-up information regarding **actual use** in light of **concern for extensive and rapidly increasing off-label use of risperidone**.

Number two, that we would **express concern** and like **further information** and further encouragement of **investigation** of **long-term effects** of this medication, including the metabolic syndrome, the other endocrine effects, **in particular, hyperprolactinemia, effects on growth and sexual maturation**.[17]

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[15] *Id.* at p.79

[16] *Id.* at p.80 (emphasis added).

[17] *Id.* at pp. 93-94 (emphasis added).

FDA Participant Dr. Dianne Murphy, M.D., Director of the Office of Pediatric Therapeutics, OC, reiterated the Committee's concern that the safety profile for RISPERDAL® was lacking:

> You're saying that **we're not finished with looking at adverse effects of these products, particularly this product, in the pediatric population. We have additional concerns**.[18]

Petitioner echoes the Advisory Committee's concern that the current Prescribing Information for RISPERDAL® fails to draw the attention of physicians, patients or the parents of adolescent patients to the "very high occurrence of hyperprolactinemia" in children and the complete absence of safety-data regarding the long-term effects of RISPERDAL® for pediatric patients.

Petitioner's own investigation has revealed that, historically and notoriously, J&J aggressively marketed RISPERDAL® for off-label uses within the pediatric population and took certain steps to affirmatively mislead the medical community and the public at large about the safety of RISPERDAL® for any duration of use. The repercussions of that conduct continue to be manifest in the extensive off-label use of Risperdal® which the Pediatric Advisory Committee raised concerns about in their November 2008 meeting.

Rather than heed the Advisory Committee's recommendation and attempt to assuage their concerns, J&J, through a spokesperson, **summarily dismissed** the Committee's concerns. Specifically, a New York Times article on the Advisory Committee Meeting, headlined Use of Antipsychotics in Children Criticized,[19] quoted a J&J spokeswoman as saying "Adverse drug reactions associated with Risperdal use in approved indications are accurately reflected in the label."

Three-and-a-half years have now passed since the Pediatric Advisory Committee issued its unanimous recommendations and yet the label for RISPERDAL® and the pervasive off-label prescription of the drug remain unchanged. With each passing month thousands of children are exposed to risperidone. Given the explosive growth of the atypical-antipsychotic pediatric market, and the percentages of children with hyperprolactinemia found in the clinical trials as cited in the Prescribing Information, a large number of children have certainly suffered from this serious problem, and many of *those* children have also experienced severe prolactin-related side effects such as gynecomastia

These children could and should have benefited from either another atypical anti-psychotic medication with a better prolactin safety profile, shorter-term use or cycling of their anti-psychotic medication, and/or some other type of intervention.

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[18] *Id.* at p.100 (emphasis added).

[19] http://query.nytimes.com/gst/fullpage.html?res=9405E3DA1539F93AA25752C1A96E9C8B63&ref=gardinerharris

J&J Hiding Behind A Wall of Confidentiality Orders

Petitioner, through our representation of hundreds of children and adults who have been injured as a result of their ingestion of Risperdal®, have learned of critical documents related to the risks associated with Risperdal® which contradict, complicate and/or substantially call into question the safety data provided by J&J to the FDA. These documents are in J&J's possession and control, and in many instances were generated by J&J and/or its predecessor companies who were involved in the research and development of Risperdal®. Petitioner believes that some of these internal documents have never been reviewed by the FDA, and that others were produced to the FDA buried within "document dumps" of thousands of pages intended to conceal their relevance and significance.

As such, the FDA has been deprived on a more fully-informed, *objective* analysis of this data which is *essential* for the FDA to make a full and fair analysis of the safety profile of Risperdal® and risperidone.

However, J&J has tried to ensure that the evidence in question remain hidden from the FDA by insisting upon confidentiality/protective orders from the Courts overseeing litigation arising from Risperdal®-induced injuries.

In fact, when a specially-appointed panel of "discovery masters", including retired judges, in the New Jersey RISPERDAL® litigation *agreed,* over J&J's vicious *ad hominem* attacks on Petitioner and our clients, that Confidentiality should be lifted so that Petitioner could present the data to the FDA J&J responded by appealing that decision to the trial judge who agreed to allow them to continue to hide the evidence from the FDA.

Nevertheless, J&J remains free to *consent* to Petitioner's presentation of these documents, data, and an expert analysis thereof, to the FDA. FDA must insist that J&J authorize Petitioner to do so in order to counterbalance the biased presentation of the data that J&J has foisted upon the FDA to date. Should the FDA instead request that J&J submit these documents (including internal communications and litigation material such as deposition transcripts) directly to the FDA, Petitioner requests that J&J's document submission be made available for public review and comment, or at the very least be made available to Petitioner for *in camera* review in order to ensure its accuracy and completeness

The Effects of Hyperprolactinemia

While J&J publicly maintains that conditions such as gynecomastia are "mild" and "transient", the experiences of our clients demonstrate that the condition is chronic and devastating.

The development of breasts for even a psychologically healthy adolescent boy or young man can be extremely detrimental. The youngster becomes subject to taunts, derision, and even physical bullying by their peers, as well as questions about their sexual

and gender identity at the very time those elements of their psyche are starting to manifest. For boys and young men who are already mentally and/or psychologically impaired enough to have been prescribed anti-psychotic medications, the daily horror that often accompanies the abnormal development of breasts can be the last straw.

Those of our clients who are otherwise quite functional describe having to avoid peers, miss school, forego social opportunities and the development of relationships, all due to the shame and fear associated with their abnormal breast growth. Having to change their clothes for gym class becomes a regularly-scheduled torture session. While their peers are busy enjoying their summers, playing sports and dating, the victims of RISPERDAL®-induced gynecomastia are hiding at home, under multiple layers of clothing, or bound within home-made compression bands in an attempt to hide the abnormal breasts they have developed.

Indeed, a study presented at the American Academy of Pediatrics Meeting on April 29, 2012 found that being bullied or ostracized increases special-needs children's risk of depression and other internalizing emotional-behavioral conditions.[20] It should be no surprise that the adolescent, teen, and pre-teen boys whom we represent and who have developed breasts as a result of their ingestion of RISPERDAL® uniformly report being bullied (both physically and verbally) and ostracized by their peers. This study now demonstrates the far-reaching consequences of that bullying and ostracism, all caused by an avoidable injury.

Had they known the true risks of RISPERDAL®, these individuals would likely never have agreed to take it, and by and large their physicians would not have prescribed it.

The true devastation of gynecomastia can be recognized by viewing photographs of those suffering this serious condition. Photographs of several young boys who developed gynecomastia as a result of their ingestion of RISPERDAL® are attached to this Petition.[21] Photographs of this type, which demonstrate what gynecomastia is, must be included in the Prescribing Information so that physicians and patients are better informed of the side-effects to look for.

Implications of the Continued Marketing of Risperdal With Inadequate Warnings

J&J has resolutely refused to change its Prescribing Information to more accurately reflect the risk of weight gain, hyperprolactinemia and their associated disorders, which they are authorized to do under the "Changes Being Effected" provision of 21 C.F.R. §314.70(c)(2)(ii).

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[20] http://www.abstracts2view.com/pas/view.php?nu=PAS12L1_3158&terms; http://aapnews.aappublications.org/content/early/2012/04/29/aapnews.20120429-2

[21] see: *Exhibit D.*

This is despite the fact that, as judge and jury after jury in civil litigation have heard evidence and reviewed internal J&J documents, the courts have found J&J guilty of inappropriate off-label and otherwise fraudulent marketing of Risperdal®.[22]

Specifically, in 2010 J&J was found liable by a jury in Louisiana and ordered to pay a verdict of **$258 Million**.[23] In South Carolina in 2011 J&J was found liable by a judge in a bench trial and ordered to pay a verdict of **$327 Million**.[24] Most recently in 2012 a jury in Arkansas found J&J liable and ordered them to pay a verdict **in excess of $1.1 BILLION**.[25] Also in 2012 J&J was forced to settle a case by the State of Texas for **$158 Million**.[26] These are cases that were brought by the States' Attorneys General seeking to protect the safety of the citizens of their States from J&J's inappropriate conduct related to Risperdal®.

In addition, J&J has been in negotiations with the United States Department of Justice to settle federal civil litigation over the same issues. According to news reports, J&J has offered to pay **$1.3 BILLION** to settle that case. The Department of Justice, having reviewed all of the evidence of J&J's improper marketing of Risperdal®, is said to be insisting upon at least **$2 BILLION** to settle the matter.[27] Such a settlement would also allow J&J to avoid **felony** charges over its marketing of Risperdal®.

And yet, despite the fact that J&J has been ordered by pay over **$1.84 BILLION**, and is in negotiations to pay as much as **$2 BILLION** more, for its inappropriate marketing of Risperdal® they have refused to correct their Prescribing Information. Clearly, J&J considers the children harmed by Risperdal® to be merely a cost of doing business. Indeed, these unprecedented verdicts and settlements constitute just a fraction of the money that J&J has made from Risperdal®. For example, Risperdal® had at least $2.5 Billion in sales in 2007 *alone* (the last year that it enjoyed patent-protection).

Nor does J&J have an incentive moving forward to ensure that the Prescribing Information for Risperdal® accurately reflects the risks associated with the drug. In its 2012 annual report, J&J reported a 10.6% drop in the sales of Risperdal Consta®, the long-acting form of Risperdal®. Sales data were not provided for the standard Risperdal®, but are believed to have been essentially "wiped out" by the sale of generic

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[22] Petitioner has personally reviewed additional internal J&J documents, that we believe have not yet been either publicly presented in Court or available to the FDA, that suggest that J&J's behavior is even worse than that which has been heard by those Courts or the FDA.

[23] Caldwell ex rel. State of Louisiana v. Janssen Pharmaceutical, 04-C-3967, 27th Judicial Court, St. Landry Parish, Louisiana (Opelousas)

[24] State of South Carolina v. Janssen Pharmaceuticals, 2007-CP-4201438, Circuit Court for Spartanburg County, South Carolina (Spartanburg)

[25] State of Arkansas v. Ortho-McNeil-Janssen Pharmaceuticals Inc., CV07-15345, Pulaski County Circuit Court (Little Rock) Arkansas

[26] Texas v. Janssen LP, D-1GV-04-001288, District Court, Travis County, Texas (Austin)

[27] http://www.businessweek.com/news/2012-03-12/j-and-j-said-to-face-u-dot-s-dot-demand-to-raise-risperdal-settlement-offer; http://online.wsj.com/article/SB10001424052702304441404577478803503320464.html

risperidone.[28] Sales of brand-name Risperdal® in the United States sank an astounding **95.8%** as reported in J&J's 2010 annual report.[29]

Most of these sales have migrated to the generic market. The FDA has given approval to at least 10 companies, including Teva Pharmaceuticals, Mylan Pharmaceuticals and Apotex Corporation, for the manufacture and distribution of generic risperidone

As the ability and/or duty of generic manufacturers to alter the Prescribing Information for generic medications is narrowly circumscribed, the Supreme Court, in the case of Pliva Inc., et al v. Mensing, 131 S.Ct. 2567, 564 U.S. ___ (2011) severely restricted the rights of individuals to avail themselves of the civil justice system to seek relief and compensation for injuries caused by their ingestion of generic drugs such as risperidone.

Therefore, as the Civil Justice system has largely been prevented from acting as an instrument to ensure the safety of generic medications, and as J&J has been unmoved by even enormous verdicts and settlements in cases by the Federal and State governments, unless the FDA steps in to either halt sales of Risperdal® and generic risperidone to children and force J&J to demonstrate both its long-term safety and its efforts to prevent or minimize the off-label use that so concerned the Pediatric Advisory Committee, the vast majority of consumers of this medication, many of whom are adolescents, will be left completely vulnerable to the risks of this drug.

Such a regulatory vacuum is unsafe and unacceptable to the public who rely upon the FDA to protect their children's interests and ensure that the prescription drugs that are approved for sale are safe for their intended purposes.

The Prescribing Information for Risperdal® as presently worded is inadequate for a number of reasons:

* It fails to sufficiently highlight and emphasize the fact that children in particular are especially susceptible to significant increases in prolactin levels triggered by Risperdal®;

* It fails to clearly and completely describe hyperprolactinemia and its associated consequences, including gynecomastia, in a way that is understandable and sufficient for physicians and patients to recognize, report and attempt to remedy the adverse events;

* It fails to recommend routine monitoring of patients for gynecomastia and hyperprolactinemia by, among other things, regular blood tests for prolactin levels and

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[28] *See*: J&J Profits Rise As Pharma Puts In Steady Performance; *PharmaTimes (http://www.pharmatimes.com/mobile12-04-18/J_J_profits_rise_as_pharma_puts_in_steady_performance.aspx)*

[29] *See*: *PharmaTimes (http://www.pharmatimes.com/mobile/10-04-21/generics_batter_pharma_sales_at_j_j.aspx)*

physical exams by physicians qualified to assess the conditions, to identify and assess abnormal breast growth.

* It fails to acknowledge that the safety data reported therein was derived primarily from adult instead of pediatric patients and after only short-term exposure;

* It includes pediatric indications which are overly broad and susceptible to abuse and off-label use. Specifically, the indication for "irritability" associated with autism is akin to an approval for autism generally, which the FDA refused to give for Risperdal®. Petitioner doubts any autistic child does not demonstrate "irritability" at some point!

* It understates the propensity of the drug to cause weight gain, which can itself contribute to the development of gynecomastia and/or mask that condition and confound physicians' ability to make an accurate diagnosis

* It fails to acknowledge the conflicts of interest and other factors which demonstrate the bias and lack of objectivity in the published literature used by J&J to promote the drug.

* It significantly understates the propensity of RISPERDAL® to trigger gynecomastia in children by stating an incidence of 2-3% when in fact the true incidence with typical long-term use is 5%.

* It fails to warn that gynecomastia will most likely be permanent if present for one year or more.

* It fails to state that prescribing Risperdal during puberty and/or after weight gain will significantly exacerbate and increase the risk of permanent gynecomastia.

* It fails to state that there are numerous other agents that do not cause as much weight gain and do not increase prolactin.

* It fails to state that almost all children given Risperdal will have raised prolactin and this is dangerous for their health.

* It fails to state that prolactin is raised also within what are described as "normal" ranges but that the drug should be stopped if there is an increase of prolactin within the so-called normal ranges since normal for adults is different for children.

* It fails to recommend that physician who prescribe RISPERDAL® to adolescent patients closely monitor their patients' prolactin levels and routinely examine their patients for abnormal breast growth and impaired sexual maturation and to consider discontinuing RISPERDAL® at the first sign of any of those signs and/or symptoms.

* J&J has never done the long-term study requested by the FDA advisory committee in 2008.[30] For this reason, until such a study is done, the approval of Risperdal and Invega for use in children and adolescents should be prohibited.

Summary of Requested Action

For all of the reasons set forth above, Petitioner respectfully requests that the FDA **immediately revoke approval of Risperdal, Invega, and all generic version of risperidone for use in children unless and until J&J presents evidence supporting: safety of long-term use of the drug; and efforts on their part to prevent the off-label prescription of Risperdal to patients for whom those risks do not outweigh the potential benefits of treatment and otherwise satisfy the concerns of the FDA's Pediatric Advisory Committee; and either voluntarily submit their internal communications and documents as well as litigation documents related to Risperdal or consent to Petitioner's presentation of our own *objective* presentation on these issues to counter-balance J&J's own biased presentation.**

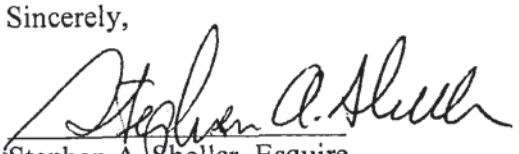
Environmental Impact Statement

Nothing requested in this Petition will have an impact on the environment.

Certification

We certify that, to the best of our knowledge and belief, this Petition includes all information and views on which this Petition relies, and that it includes representative data and information known to the Petitioners which are unfavorable to this Petition.

Sincerely,



Stephen A. Sheller, Esquire
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30 While J&J purported to address the issue in its RIS-NAP-4022 study, issued on 12/28/11, this study was terminated early due to failure to reach enrollment targets and by J&J's own admission, "the low enrollment resulted in an underpowered study." Nevertheless, this study confirmed that Hyperprolactinemia occurs significantly more often with Rispderdal than other atypical anti-psychotics (25.6% vs. 2%).

EXHIBIT

B

Sheller

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2012 AUG 28 A 9:46

August 27, 2012

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg,

Sheller, P.C. represents individuals and groups of individuals who have suffered serious physical and mental injuries caused by prescription pharmaceuticals, biologicals and devices. We presently represent hundreds of individuals who have suffered serious harm, including gynecomastia and prolactin-related injuries as a result of their ingestion of the second-generation atypical anti-psychotic medications Risperdal® (risperidone) marketed by Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Janssen Pharmaceutical, Inc., a subsidiary of Johnson & Johnson (hereinafter "J&J").

This Petition is an Amendment to our Petition previously filed and docketed at **FDA-2012-P-0857**. The purpose of this Amendment is to demonstrate the manner in which the current Prescribing Information for risperidone actively impedes physicians' ability to comply with the standard of care for the monitoring, diagnosis and treatment of hyperprolactinemia (as described by J&J's own prolactin consultant); and how an adequate warning in this regard would result most if not all adolescents being switched from risperidone one of the many other atypical antipsychotics with a safer prolactin profile.

Requested Action

We hereby petition the Food and Drug Administration (hereinafter "FDA"), pursuant to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§352, 321 and 21 C.F.R. §§10.30 and 7.45 **to immediately revoke the pediatric indication for Risperdal®, all generic version of risperidone, and Invega®[1] (an extended release**

[1] Given the pharmacologic similarity between Risperdal® and Invega®, the information set forth in the remainder of this Petition applies equally to both drugs. J&J's conduct with respect to Risperdal® demands that the FDA take the same remedial actions with respect to Invega® in order to protect the public.

FDA-2012-P-0857

2012-1394 AMD

and injectable medication which includes the same primary active metabolite as Risperdal®) unless and until the long-term safety of the drug can be demonstrated, or in the alternative to immediately require that labeling for Risperdal® and all generic versions of risperidone include a black box warning on the lack of sufficient safety data. Additionally, the FDA should **direct J&J to consent to release Petitioner from any and all standing Confidentiality/ Protective Orders so that Petitioner[2] can present to the FDA the internal documents and data, as well as an expert analysis thereof** which we believe support the foregoing requested actions.

Basis for Action

Interest of the Parties

Petitioner represents hundreds of children who have suffered Risperdal®-induced gynecomastia and prolactin-related adverse events as a result of their ingestion of Risperdal®. Our clients constitute a sample of the tens (if not hundreds) of thousands of children who have been prescribed Risperdal® (both on- and off-label) and who are at risk of suffering adverse events if the FDA does not take immediate action.

Nature of the Problem

Our own investigation has revealed that the long-term safety of Risperdal® for children has not been established, and that the current Prescribing Information does not adequately reflect the true risks posed by Risperdal®.

Specifically, and as explained in more detail below:

* The approved Indications for the use of Risperdal® in the pediatric population are unduly vague and lack appropriate guidance of physicians considering the use of the drug.

    * For example, while Risperdal® is approved for use in children diagnosed with Bipolar I, that condition is never defined or described, leaving the potential for the conflation of that condition with the more common Bipolar II Disorder and therefore the inadvertent expansion of off-label use of Risperdal®.

    * The approval for "irritability" associated with autism is so vague and ambiguous as to practically equate with an approval for treatment of Autism generally, which is something the FDA specifically has refused to do.

[2] In the alternative, the FDA should request that J&J themselves submit all internal documents, including e-mails and correspondence, as well as documents and testimony from the Risperdal® litigation. However, given J&J previous submission of data to the FDA, in a manner likely to bury or gloss over significant adverse event information, it is imperative that any documents produced directly by J&J either be available for public review and comment and/or made available to Petitioner for *in camera* review in order to assure the accuracy and completeness of J&J's document submission.

* J&J's conduct prior to pediatric approval by the FDA has created a robust off-label market for Rispderdal for conditions far afield from the limited Pediatric Indication eventually approved by the FDA.

* At the same time, children are particularly susceptible to the significant increases in prolactin-levels which Risperdal® is known to cause. This fact, and its significance, is not adequately conveyed to physicians and patients in the Prescribing Information:

  * The introduction of Risperdal® to pre-pubertal or pubertal adolescents enhances the hormonal and endocrinological processes already at work, resulting in substantially worse and more permanent conditions such as gynecomastia and adverse effects on sexual maturation than would have been experienced in the absence of Risperdal®. This fact is not warned about at all;

  * The propensity of Risperdal® to cause weight gain is understated, leading physicians to inaccurately attribute any abnormal breast growth to weight-gain itself, and therefore fail to consider Risperdal® as a potential cause.

  * Meanwhile, the Prescribing Information lacks clear guidance to physicians in terms of monitoring their pediatric patients' blood prolactin levels and obtaining complete physical exams, by qualified practitioners, to identify and assess abnormal breast growth or effects of hyperprolactinemia. Indeed, if physicians were directed to monitor pediatric patients' prolactin levels, few adolescents would remain on risperidone past their first blood test.

As such, our investigation validates the concerns raised by the FDA's own Advisory Committee regarding the safety of Risperdal® as labeled. As discussed in detail below, the Advisory Committee in 2008 found that the current Prescribing Information for Risperdal® was inadequate and issued a series of recommendations aimed at correcting the situation. To date, however, the Prescribing Information for Risperdal® remains unchanged and we have seen no evidence that J&J has provided the FDA with the information which the Advisory Committee found essential to the creation of an adequate prescribing label.

Background

Risperdal® was approved for adults by the FDA in 1993 as an anti-psychotic therapy for schizophrenia. In 2003 this adult indication was expanded to include use of Risperdal® for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults.

In 2006 Risperdal® received its first approval for children, for treatment of the irritability associated with autistic disorder in children between the ages of 5 and 16. In

2007 the adult indications for schizophrenia and bipolar I disorder were expanded to include adolescents as young as 13 and 10, respectively.

The manufacturer of Risperdal® has augmented these FDA-approved indications through aggressive "off-label" marketing, including the marketing of Risperdal® to children prior to the FDA's approval for use of the drug in that population.

Even after Risperdal® was approved for children in very limited circumstances, J&J has aggressively marketed the drug for off-label conditions such as Autism generally (even absent "irritability"), Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), Oppositional-Defiant Disorder (ODD), Conduct Disorder (CD), Disruptive Behavior Disorder (BDB), Tourette's Syndrome, Post-Traumatic Stress Disorder (PTSD)[3] and Pervasive Developmental Disorder (PDD).

In so doing, J&J largely helped to fuel a veritable explosion of the anti-psychotic pharmaceutical sector. In 2011, sales of anti-psychotic medications in general totaled $18.2 billion, a 12.7% increase over 2010. Atypical anti-psychotics became one of the fastest growing medication classes in the nation.[4]

Risperdal® and Gynecomastia and Prolactin-Related Adverse Events

The current Prescribing Information for Risperdal® **fails** to even mention gynecomastia or hyperprolactinemia in the HIGHLIGHTS OF PRESCRIBING INFORMATION under either the "WARNINGS AND PRECAUTIONS" , "ADVERSE REACTIONS" or "USE IN SPECIFIC POPULATIONS" sections.

In fact, one must search 17 pages into the Prescribing Information to locate data about the rates of gynecomastia in child and adolescent trials. The label reads in relevant part:

> In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.[5]

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[3] Notably, after a study of risperidone for the treatment of PTSD conducted at Veterans' Administration Medical Centers, the United States Army recently gave Risperidone a "D-level Recommendation", meaning that the "harm outweighs benefit"). See: *Memorandum for Commanders, MEDCOM Regional Medical Commnds dated 4/10/12* at p.9. While this Army study involved adults, it demonstrates that the risk/benefit analysis that supported initial FDA approval of risperidone does not support the myriad off-label uses for which J&J has promoted the drug.

[4] . *See: (http://www.imshealth.com/ims/ Global/ Content /Insights/IMS%20Institute %20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf)*

[5] A copy of the Prescribing Information for Risperdal is attached as Exhibit A.

This statement is misleading in that studies have demonstrated that the rate of gynecomastia is actually 5% with long-term use of RISPERDAL®, which clinical experiences shows is the most typical use of the drug.

Further, the statement, combined with the fact that data on the adolescent rates of Risperdal®-induced hyperprolactinemia and its associated disorders of: galactorrhea, amennorhea, infertility in girls; galactorrhea, gynecomastia and diminished libido in boys; and adverse impact on sexual maturation in children of both genders, are buried in the "USE IN SPECIAL POPULATIONS" section of the Prescribing Information, have given physicians and the public a false sense of the safety of Risperdal® for adolescents and concealed the epidemic of prolactin-related adverse events being inflicted upon children by Risperdal®.

The role of Risperdal® in triggering the development of gynecomastia in young boys is particularly invidious, as Risperdal® is responsible for multiple adverse events that, individually or in combination, contribute to the development of abnormal breast growth in that patient population. Specifically, Risperdal® causes hyperprolactinemia particularly aggressively in adolescents, a population particularly susceptible to the adverse sequella of that condition, including gynecomatia and impaired sexual mauration. At the same time, Risperdal® can trigger substantial weight gain which itself increases the risk of the gynecomastia. These two Risperdal®-induced mechanisms combine to wreak havoc on an adolescent's endocrine system. The Risperdal®-induced weight gain is particularly serious because the propensity of Risperdal® to cause weight gain is understated in the Prescribing Information, which leads many prescribing physicians to incorrectly attribute the development of gynecomastia to either "over-nutrition" or puberty.

Indeed, the prescription of Risperdal® to children prior to or during puberty is particularly harmful given that the drug can both exacerbate pubertal gynecomastia and turn pubertal gynecomastia (which is typically a short-lived phenomenon) into a chronic condition often requiring surgical repair.

Nevertheless, the Prescribing Information for Risperdal® is silent on these risks, leaving physicians in the position of throwing gasoline on the hormonal and endocrine fire already simmering in their pre-puberty and puberty aged patients.

By contrast, when the anti-depressant EFFEXOR was found to have an increased risk of adverse events in pediatric patients, the following black-box warning was added to the Prescribing Information, **even though EFFEXOR is not even approved by the FDA for use in children**:

Rx only
Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child,

adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

Likewise, the website for EFFEXOR includes this black-box warning displayed prominently in two different locations on the medication's homepage.[6]

Compared to the responsible and prudent way in which a special pediatric risk is conveyed for EFFEXOR, the risk of hyperprolactinemia with Risperdal® is hidden like a needle in a haystack.

It is Petitioner's experience that misinformation such as exists in the Risperdal® prescribing materials results in the failure of physicians and patients to recognize, report and attempt to remedy adverse events such as Risperdal®-induced gynecomastia and prolactin-related conditions.

For example, RISPERDAL® and other anti-psychotic medications are often prescribed by mental health professionals who are not in the habit of conducting physical examinations of their patients, including assessments of adolescent/teen boys and young men for abnormal breast growth, Tanner staging, evaluation of testicular development and sexual maturation generally.. Young patients who are prescribed RISPERDAL® and risperidone (and their parents) are not instructed to be on the look-out for abnormal breast growth. The adolescent patients themselves who are taking RISPERDAL® may not have the mental and/or psychological wherewithal to recognize abnormal breast growth as a potential drug adverse event, let alone connect it to RISPERDAL®. For that matter, most patients and/or their parents have no idea what the term "gynecomastia" means, or that it is in any way related to abnormal breast growth.

Additionally, all atypical anti-psychotic medications carry the risk of weight gain. We believe the Prescribing Information for Risperdal® understates and inaccurately minimizes the propensity of RISPERDAL® to cause weight gain. Therefore, when gynecomastia *is* recognized by a patient and/or their healthcare provider, it is often misattributed to diet or nutrition-based weight gain and/or puberty and incorrectly assumed to be unrelated to the patient's ingestion of RISPERDAL®.

[6] http://www.effexorxr.com/medication-guide.aspx

On the contrary, between 10-25% of cases of gynecomastia are drug-induced.[7] RISPERDAL® increases prolactin in adolescents more than nearly all other medications. However these facts are not provided to physicians and patients in the Prescribing Information for RISPERDAL®. Were they provided, physicians confronted with adolescent patients on RISPERDAL® who experience abnormal breast growth would reach the unavoidable conclusion that RISPERDAL® had either caused or substantially contributed to the development of that condition. The physician could then take steps, including discontinuing the use of RISPERDAL®, to remedy the gynecomastia.

All of these factors constitute multiple levels at which adverse events can fall through the cracks and fail to be recognized, reported and remedied, permitting the perpetuation of false safety data, and continued and/or increased sales that result in a vicious cycle of yet more unrecognized and unreported adverse events.

Standard of Care for Diagnosis and Treatment of Hyperprolactinemia

While we recognize that the FDA's mission is not to regulate physicians' actual practice of medicine, it is important to emphasize that the current label significantly impedes physicians' ability to conform to the standard of care and recommended best practices for the diagnosis and treatment of hyperprolactinemia.

J&J has consistently refused to provide physicians sufficient guidance in this regard, because if physicians were to monitor their pediatric patients' prolactin levels few if any adolescents would remain on Risperdal®/Invega® past their first blood test.

Specifically, the standard of care and recommended best practices for diagnosis and treatment of potentially medication-induced hyperprolactinemia is described by endocrinologist Mark E. Molitch, M.D. is his article Drugs and Prolactin, *Pituitary (2008) 11:209-218.*[8]

Dr. Molitch, a former member of the FDA's own metabolic/endocrine Advisory Committee, has served as a paid consultant to J&J on the issue of prolactin and testified as a paid expert witness on J&J's behalf in a lawsuit[9] by the State of Arkansas against J&J which resulted in a verdict against J&J in excess of $1.1 Billion.

In his 2008 article, Dr. Molitch noted that "Risperidone . . . can cause [prolactin] elevations even higher than the typical antipsychotics." *Id. at 211.*

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7 Braunstein, G.D., Gynecomastia, *N. Engl. J. Med. 1993:328(7); 490-5.*

8 Dr. Molitch described an identical standard of care in his earlier article Medication-Induced Hyperprolactinemia, *Mayo Clinical Proceedings, August 2005; 80(8):1050-1057*, demonstrating that this standard is well-established.

9 State of Arkansas v. Ortho-McNeil-Janssen Pharmaceuticals Inc., CV07-15345, Pulaski County Circuit Court (Little Rock) Arkansas

Dr. Molitch explains that to diagnose medication-induced hyperprolactinemia, "**the simplest approach is to take the patient off the medication**" and determine whether prolactin levels return to normal. *Id. at 213* (emphasis added).

Should a case of medication-induced hyperprolactinemia be so demonstrated, Dr. Molitch explains the standard of care for a patient whose underlying condition requires continuation of anti-psychotic medication: "**switching to another drug** in the same class that does not cause hyperprolatinemia is the easiest way of correcting the problem and the underlying disorder usually remains controlled." *Id.* (emphasis added). Specifically, Dr. Molitch recommends switching patients to "olanzapine, clozapine, quetiapine, or aripiprazole". *Id.*

The urgency of early monitoring and detection of elevated prolactin levels is demonstrated by Dr. Molitch's admission in the Arkansas litigation that the consequences of long-term elevations in prolactin in children and adolescents include: lack of periods in girls, galactorrhea in girls, impotence and erectile dysfunction in men and potentially delay in puberty.

And on this last point we must emphasize again that J&J has persistently **failed** to conduct adequate long-terms studies on the safety of Risperdal®/Invega® in children and adolescents as specifically requested by the FDA's Pediatric Advisory Committee in 2008.

J&J's Interference with the Standard of Care

FDA must ask why J&J, who has paid for the benefit of Dr. Molitch's opinions that they believe support their dangerous drug, deny physicians the benefit of his guidance on the standard of care for the diagnosis and treatment of hyperprolactinemia induced by that same drug.

We would like to propose an answer to that question.

As noted above, cccording to J&J's own studies of risperidone, **up to 87% of children and adolescents experienced elevated prolactin levels** shortly after starting the medication, compared to as few as **2% receiving a placebo**. As Dr. Molitch notes in his articles, this incidence rate is substantially worse than other atypical antipsychotics.

Thus, assessment of blood-prolactin levels in adolescents taking Risperdal®/Invega® would result in as many as 8 in 10 of those patients being switched to a different atypical antipsychotic in accordance with the standard of care described by Dr. Molitch.

J&J's incentive not to guide physicians to monitor prolactin levels is clear. Appropriate, vigilant monitoring would virtually obliterate their market share. The necessity of such testing for the safety of patients prescribed Risperdal®/Invega® is clear. The impediment to physicians' ability to diagnose and treat this serious adverse

event in accordance with the standard of care identified by Dr. Molitch that is posed by J&J's refusal to provide appropriate guidance is similarly clear.

Therefore the following facts are undisputed:

1) J&J has persistently failed to complete studies that demonstrate the long-term safety of Risperdal®/Invega® for children and adolescents are requested by the FDA's own Pediatric Advisory Committee;

2) J&J has persistently refused to properly guide the physicians who prescribe its medication, to the point of ignoring the recommendation of the endocrinologist whom they retained to consult specifically on the issue of prolactin.

3) As explained by that same J&J consultant, there are numerous alternative widely-available atypical antipsychotics on the market which carry a much lower risk, if not negligible risk of elevating prolactin in adolescents which physicians can use to treat their adolescent patients whom they believe require such therapy.

4) Were J&J to properly guide physicians in regard to monitoring blood prolactin levels in adolescent patients prescribed Risperdal®/Invega®, the standard of care described by J&J's own consultant would warrant switching nearly all of those patients to one of those alternate medications.

In light of these facts, there is absolutely no reasonable basis for FDA to allow children and adolescents to continue to be exposed to the unreasonable risk of hyperprolactinemia and its associated sequella poased by Risperdal®/Invega®

As explained in more detail below, pursuant to recent Supreme Court precedent the generic manufacturers of risperidone are completely immune from civil lawsuits over their failure to warn of these inordinate risks. And as the Supreme Court recognized, generic manufacturers are forbidden by current FDA regulations from altering their Prescribing Information unless and until J&J changes the brand Prescribing Information.

In this context, the only reasonable course for FDA to ensure the safety of children and adolescents is to immediately withdraw the pediatric indication for Risperdal®/Invega® and generic risperidone.

FDA Pediatric Advisory Committee Assessment of the Risperdal® Safety Profile

On November 18, 2008, the FDA's Pediatric Advisory Committee met to consider whether or not to maintain the *status quo* with regard to Risperdal®, or whether a heightened inquiry into the safety of the drug for children was warranted. Specifically, the question posed to the Committee by the FDA was "FDA will continue its standard,

ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?"[10]

The Committee "discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects"[11] and unanimously concluded that the *status quo* for Risperdal® was **inadequate**. Specifically, as part of the Committee Vote and Recommendation, "Twelve (12) committee members **unanimously** supported **more than the standard**, ongoing safety monitoring for oral risperidone."[12] Instead, the Committee made several very specific recommendations:

> Twelve (12) committee members recommended the following:
>
> 1. Additional follow-up regarding on-label and **off-label product use** of this class of drug products with specific attention to age and indication for which the product is being used;
>
> 2. Additional follow-up regarding metabolic syndrome, growth, sexual maturation, and **hyperprolactinemia**;
>
> 3. Studies, which may be collaboratively developed with NIH, on **long-term effects in the pediatric population** of this class of products;
>
> 4. Additional follow-up on extrapyramidal side effects in the pediatric population;
>
> 5. Additional evaluation of this class of anti-psychotic medications and concomitant drug use;
>
> 6. Committee is not recommending any public communication before additional discussion which should occur after receipt of data from above recommendations[13]

Ultimately, the Committee **unanimously** refused to grant its *imprimatur* to Risperdal® as presently labeled, concluding that "Twelve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee."[14]

Three-and-a-half years have passed since the Advisory Committee issued its recommendations. Petitioner is unaware of any evidence that any of the Committee's

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10 *See*: Minutes of The Pediatric Advisory Committee, Tuesday, November 18th, 2008 at page 3 (attached hereto as Exhibit B).

11 *Id.*

12 *Id.* (emphasis added).

13 *Id.* at 3-4 (emphasis added).

14 *Id.*

recommendations have been implemented by the FDA or completed within the intervening 42 months, and the Prescribing Information for Risperdal® therefore remains as it was in November 2008.

The concerns raised by Committee members during their meeting on Risperdal® demonstrate the urgent need for FDA action.

Initially, it should be noted that while the Pediatric Advisory Committee considered a total of nine (9) different "Specific Drug Reviews" during the course of that one-day meeting, their consideration of Risperdal® generated, by far, the most discussion and concern. The Committee's consideration of Risperdal® spans 68 transcript pages and constitutes nearly one-quarter of the transcript pages for "Specific Drug Reviews".

On November 18, 2008, the day of the meeting, the Pediatric Advisory Committee was presented with a "one-year, post-exclusivity adverse event review for risperidone."[15]

Committee Member Dr. Keith Kocis, M.D., M.S. voiced the concern that:

> In looking at this drug compared to many of the drugs that we're going to review or have reviewed over the few years that I've been here, this is somewhat unique in that it's being used – 25 percent of its use has been in pediatrics. It's a drug that has many effects, some that are serious, and I would disagree with your assessment that the FDA is passive in this thing in what they can do.
>
> . . .
>
> And then the final comment is on behalf of the sponsor, in the labeling when they talk about the long-term effects of Risperdal on growth and sexual maturation have not been fully evaluated, **I find that lacking** in the sense that we **know it has profound impact on prolactin** and other endocrine things that I believe should **require them** to study this in children who are undergoing sexual maturation.[16]

Discussing what he characterized as "the very high incidence of hyperprolactinemia in the pediatric population", Committee Member Dr. Geoffrey Rosenthal, M.D., Ph.D. concurred with Dr. Kocis:

> If these medications are used to a significant degree in the pediatric population, and there is information regarding the effects of the medication on the neural endocrine access. Is it reasonable to ask the question of what is the long-term effect on growth and development in these areas?[17]

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15 *See:* Transcript of 11/18/08 Pediatric Advisory Committee Meeting at p.44 (attached hereto as Exhibit C).

16 *Id.* at pp.74-76 (emphasis added).

17 *Id.* at p.79

Dr. Rosenthal specifically noted that this concern should be added to the Prescribing Information:

> I'm wondering whether there aren't some mechanisms even through the labeling process where particular attention can be drawn to this point, which might then stimulate research in this area . . . and **maybe if particular attention is drawn to the very high occurrence of hyperprolactinemia in the label**, that will raise enough eyebrows that the studies will get done.[18]

When it came time for the Committee to vote, not a single member supported continuation of the *status quo* "standard ongoing safety monitoring":

> CHAIRPERSON RAPPLEY: So the vote will be the FDA will continue its standard ongoing safety monitoring for oral risperidone. How many on the Committee support that?
>
> (No response)
>
> CHAIRPERSON RAPPLEY: **So I am not seeing any hands raised.**
>
> . . .
>
> CHAIRPERSON RAPPLEY: So would you like me to summarize our recommendations first before we vote? Okay.
>
> So a summary then of the recommendations that have arisen from our discussion today is that, one, the Committee would like follow-up information regarding **actual use** in light of **concern for extensive and rapidly increasing off-label use of risperidone**.
>
> Number two, that we would **express concern** and like **further information** and further encouragement of **investigation** of **long-term effects** of this medication, including the metabolic syndrome, the other endocrine effects, **in particular, hyperprolactinemia, effects on growth and sexual maturation**.[19]

FDA Participant Dr. Dianne Murphy, M.D., Director of the Office of Pediatric Therapeutics, OC, reiterated the Committee's concern that the safety profile for RISPERDAL® was lacking:

> You're saying that **we're not finished with looking at adverse effects of these products, particularly this product, in the pediatric population. We have additional concerns**.[20]

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[18] *Id.* at p.80 (emphasis added).
[19] *Id.* at pp. 93-94 (emphasis added).
[20] *Id.* at p.100 (emphasis added).

Petitioner echoes the Advisory Committee's concern that the current Prescribing Information for RISPERDAL® fails to draw the attention of physicians, patients or the parents of adolescent patients to the "very high occurrence of hyperprolactinemia" in children and the complete absence of safety-data regarding the long-term effects of RISPERDAL® for pediatric patients.

Petitioner's own investigation has revealed that, historically and notoriously, J&J aggressively marketed RISPERDAL® for off-label uses within the pediatric population and took certain steps to affirmatively mislead the medical community and the public at large about the safety of RISPERDAL® for any duration of use. The repercussions of that conduct continue to be manifest in the extensive off-label use of Risperdal® which the Pediatric Advisory Committee raised concerns about in their November 2008 meeting.

Rather than heed the Advisory Committee's recommendation and attempt to assuage their concerns, J&J, through a spokesperson, **summarily dismissed** the Committee's concerns. Specifically, a New York Times article on the Advisory Committee Meeting, headlined Use of Antipsychotics in Children Criticized,[21] quoted a J&J spokeswoman as saying "Adverse drug reactions associated with Risperdal use in approved indications are accurately reflected in the label."

Three-and-a-half years have now passed since the Pediatric Advisory Committee issued its unanimous recommendations and yet the label for RISPERDAL® and the pervasive off-label prescription of the drug remain unchanged. With each passing month thousands of children are exposed to risperidone. Given the explosive growth of the atypical-antipsychotic pediatric market, and the percentages of children with hyperprolactinemia found in the clinical trials as cited in the Prescribing Information, a large number of children have certainly suffered from this serious problem, and many of *those* children have also experienced severe prolactin-related side effects such as gynecomastia

These children could and should have benefited from either another atypical anti-psychotic medication with a better prolactin safety profile, shorter-term use or cycling of their anti-psychotic medication, and/or some other type of intervention.

J&J Hiding Behind A Wall of Confidentiality Orders

Petitioner, through our representation of hundreds of children and adults who have been injured as a result of their ingestion of Risperdal®, have learned of critical documents related to the risks associated with Risperdal® which contradict, complicate and/or substantially call into question the safety data provided by J&J to the FDA. These documents are in J&J's possession and control, and in many instances were generated by J&J and/or its predecessor companies who were involved in the research and development of Risperdal®. Petitioner believes that some of these internal documents

[21] http://query.nytimes.com/gst/fullpage.html?res=9405E3DA1539F93AA25752C1A96E9C8B63&ref=gardinerharris

have never been reviewed by the FDA, and that others were produced to the FDA buried within "document dumps" of thousands of pages intended to conceal their relevance and significance.

As such, the FDA has been deprived on a more fully-informed, *objective* analysis of this data which is *essential* for the FDA to make a full and fair analysis of the safety profile of Risperdal® and risperidone.

However, J&J has tried to ensure that the evidence in question remain hidden from the FDA by insisting upon confidentiality/protective orders from the Courts overseeing litigation arising from Risperdal®-induced injuries.

In fact, when a specially-appointed panel of "discovery masters", including retired judges, in the New Jersey RISPERDAL® litigation *agreed*, over J&J's vicious *ad hominem* attacks on Petitioner and our clients, that Confidentiality should be lifted so that Petitioner could present the data to the FDA J&J responded by appealing that decision to the trial judge who agreed to allow them to continue to hide the evidence from the FDA.

Nevertheless, J&J remains free to *consent* to Petitioner's presentation of these documents, data, and an expert analysis thereof, to the FDA. FDA must insist that J&J authorize Petitioner to do so in order to counterbalance the biased presentation of the data that J&J has foisted upon the FDA to date. Should the FDA instead request that J&J submit these documents (including internal communications and litigation material such as deposition transcripts) directly to the FDA, Petitioner requests that J&J's document submission be made available for public review and comment, or at the very least be made available to Petitioner for *in camera* review in order to ensure its accuracy and completeness

The Effects of Hyperprolactinemia

While J&J publicly maintains that conditions such as gynecomastia are "mild" and "transient", the experiences of our clients demonstrate that the condition is chronic and devastating.

The development of breasts for even a psychologically healthy adolescent boy or young man can be extremely detrimental. The youngster becomes subject to taunts, derision, and even physical bullying by their peers, as well as questions about their sexual and gender identity at the very time those elements of their psyche are starting to manifest. For boys and young men who are already mentally and/or psychologically impaired enough to have been prescribed anti-psychotic medications, the daily horror that often accompanies the abnormal development of breasts can be the last straw.

Those of our clients who are otherwise quite functional describe having to avoid peers, miss school, forego social opportunities and the development of relationships, all due to the shame and fear associated with their abnormal breast growth. Having to change their clothes for gym class becomes a regularly-scheduled torture session. While

their peers are busy enjoying their summers, playing sports and dating, the victims of RISPERDAL®-induced gynecomastia are hiding at home, under multiple layers of clothing, or bound within home-made compression bands in an attempt to hide the abnormal breasts they have developed.

Indeed, a study presented at the American Academy of Pediatrics Meeting on April 29, 2012 found that being bullied or ostracized increases special-needs children's risk of depression and other internalizing emotional-behavioral conditions.[22] It should be no surprise that the adolescent, teen, and pre-teen boys whom we represent and who have developed breasts as a result of their ingestion of RISPERDAL® uniformly report being bullied (both physically and verbally) and ostracized by their peers. This study now demonstrates the far-reaching consequences of that bullying and ostracism, all caused by an avoidable injury.

Had they known the true risks of RISPERDAL®, these individuals would likely never have agreed to take it, and by and large their physicians would not have prescribed it.

The true devastation of gynecomastia can be recognized by viewing photographs of those suffering this serious condition. Photographs of several young boys who developed gynecomastia as a result of their ingestion of RISPERDAL® are attached to this Petition.[23] Photographs of this type, which demonstrate what gynecomastia is, must be included in the Prescribing Information so that physicians and patients are better informed of the side-effects to look for.

Implications of the Continued Marketing of Risperdal With Inadequate Warnings

J&J has resolutely refused to change its Prescribing Information to more accurately reflect the risk of weight gain, hyperprolactinemia and their associated disorders, which they are authorized to do under the "Changes Being Effected" provision of 21 C.F.R. §314.70(c)(2)(ii).

This is despite the fact that, as judge and jury after jury in civil litigation have heard evidence and reviewed internal J&J documents, the courts have found J&J guilty of inappropriate off-label and otherwise fraudulent marketing of Risperdal®.[24]

Specifically, in 2010 J&J was found liable by a jury in Louisiana and ordered to pay a verdict of **$258 Million**.[25] In South Carolina in 2011 J&J was found liable by a

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[22] http://www.abstracts2view.com/pas/view.php?nu=PAS12L1_3158&terms; http://aapnews.aappublications.org/content/early/2012/04/29/aapnews.20120429-2

[23] see: *Exhibit D.*

[24] Petitioner has personally reviewed additional internal J&J documents, that we believe have not yet been either publicly presented in Court or available to the FDA, that suggest that J&J's behavior is even worse than that which has been heard by those Courts or the FDA.

[25] Caldwell ex rel. State of Louisiana v. Janssen Pharmaceutical, 04-C-3967, 27th Judicial Court, St. Landry Parish, Louisiana (Opelousas)

judge in a bench trial and ordered to pay a verdict of **$327 Million**.[26] Most recently in 2012 a jury in Arkansas found J&J liable and ordered them to pay a verdict **in excess of $1.1 BILLION**.[27] Also in 2012 J&J was forced to settle a case by the State of Texas for **$158 Million**.[28] These are cases that were brought by the States' Attorneys General seeking to protect the safety of the citizens of their States from J&J's inappropriate conduct related to Risperdal®.

In addition, J&J has been in negotiations with the United States Department of Justice to settle federal civil litigation over the same issues. According to news reports, J&J has offered to pay **$1.3 BILLION** to settle that case. The Department of Justice, having reviewed all of the evidence of J&J's improper marketing of Risperdal®, is said to be insisting upon at least **$2 BILLION** to settle the matter.[29] Such a settlement would also allow J&J to avoid **felony** charges over its marketing of Risperdal®.

And yet, despite the fact that J&J has been ordered by pay over **$1.84 BILLION**, and is in negotiations to pay as much as **$2 BILLION** more, for its inappropriate marketing of Risperdal® they have refused to correct their Prescribing Information. Clearly, J&J considers the children harmed by Risperdal® to be merely a cost of doing business. Indeed, these unprecedented verdicts and settlements constitute just a fraction of the money that J&J has made from Risperdal®. For example, Risperdal® had at least $2.5 Billion in sales in 2007 *alone* (the last year that it enjoyed patent-protection).

Nor does J&J have an incentive moving forward to ensure that the Prescribing Information for Risperdal® accurately reflects the risks associated with the drug. In its 2012 annual report, J&J reported a 10.6% drop in the sales of Risperdal Consta®, the long-acting form of Risperdal®. Sales data were not provided for the standard Risperdal®, but are believed to have been essentially "wiped out" by the sale of generic risperidone.[30] Sales of brand-name Risperdal® in the United States sank an astounding **95.8%** as reported in J&J's 2010 annual report.[31]

Most of these sales have migrated to the generic market. The FDA has given approval to at least 10 companies, including Teva Pharmaceuticals, Mylan Pharmaceuticals and Apotex Corporation, for the manufacture and distribution of generic risperidone

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[26] State of South Carolina v. Janssen Pharmaceuticals, 2007-CP-4201438, Circuit Court for Spartanburg County, South Carolina (Spartanburg)
[27] State of Arkansas v. Ortho-McNeil-Janssen Pharmaceuticals Inc., CV07-15345, Pulaski County Circuit Court (Little Rock) Arkansas
[28] Texas v. Janssen LP, D-1GV-04-001288, District Court, Travis County, Texas (Austin)
[29] http://www.businessweek.com/news/2012-03-12/j-and-j-said-to-face-u-dot-s-dot-demand-to-raise-risperdal-settlement-offer; http://online.wsj.com/article/SB10001424052702304441404577478803503320464.html
[30] *See*: J&J Profits Rise As Pharma Puts In Steady Performance; *PharmaTimes (http://www.pharmatimes.com/mobile12-04-18/J_J_profits_rise_as_pharma_puts_in_steady_performance.aspx)*
[31] *See*: *PharmaTimes (http://www.pharmatimes.com/mobile/10-04-21/generics_batter_pharma_sales_at_j_j.aspx)*

As the ability and/or duty of generic manufacturers to alter the Prescribing Information for generic medications is narrowly circumscribed, the Supreme Court, in the case of Pliva Inc., et al v. Mensing, 131 S.Ct. 2567, 564 U.S. ___ (2011) severely restricted the rights of individuals to avail themselves of the civil justice system to seek relief and compensation for injuries caused by their ingestion of generic drugs such as risperidone.

Therefore, as the Civil Justice system has largely been prevented from acting as an instrument to ensure the safety of generic medications, and as J&J has been unmoved by even enormous verdicts and settlements in cases by the Federal and State governments, unless the FDA steps in to either halt sales of Risperdal® and generic risperidone to children and force J&J to demonstrate both its long-term safety and its efforts to prevent or minimize the off-label use that so concerned the Pediatric Advisory Committee, the vast majority of consumers of this medication, many of whom are adolescents, will be left completely vulnerable to the risks of this drug.

Such a regulatory vacuum is unsafe and unacceptable to the public who rely upon the FDA to protect their children's interests and ensure that the prescription drugs that are approved for sale are safe for their intended purposes.

The Prescribing Information for Risperdal® as presently worded is inadequate for a number of reasons:

* It fails to sufficiently highlight and emphasize the fact that children in particular are especially susceptible to significant increases in prolactin levels triggered by Risperdal®;

* It fails to clearly and completely describe hyperprolactinemia and its associated consequences, including gynecomastia, in a way that is understandable and sufficient for physicians and patients to recognize, report and attempt to remedy the adverse events;

* It fails to recommend routine monitoring of patients for gynecomastia and hyperprolactinemia by, among other things, regular blood tests for prolactin levels and physical exams by physicians qualified to assess the conditions, to identify and assess abnormal breast growth.

* It fails to acknowledge that the safety data reported therein was derived primarily from adult instead of pediatric patients and after only short-term exposure;

* It includes pediatric indications which are overly broad and susceptible to abuse and off-label use. Specifically, the indication for "irritability" associated with autism is akin to an approval for autism generally, which the FDA refused to give for Risperdal®. Petitioner doubts any autistic child does not demonstrate "irritability" at some point!

* It understates the propensity of the drug to cause weight gain, which can itself contribute to the development of gynecomastia and/or mask that condition and confound physicians' ability to make an accurate diagnosis

* It fails to acknowledge the conflicts of interest and other factors which demonstrate the bias and lack of objectivity in the published literature used by J&J to promote the drug.

* It significantly understates the propensity of RISPERDAL® to trigger gynecomastia in children by stating an incidence of 2-3% when in fact the true incidence with typical long-term use is 5%.

* It fails to warn that gynecomastia will most likely be permanent if present for one year or more.

* It fails to state that prescribing Risperdal during puberty and/or after weight gain will significantly exacerbate and increase the risk of permanent gynecomastia.

* It fails to state that there are numerous other agents that do not cause as much weight gain and do not increase prolactin.

* It fails to state that almost all children given Risperdal will have raised prolactin and this is dangerous for their health.

* It fails to state that prolactin is raised also within what are described as "normal" ranges but that the drug should be stopped if there is an increase of prolactin within the so-called normal ranges since normal for adults is different for children.

* It fails to recommend that physician who prescribe RISPERDAL® to adolescent patients closely monitor their patients' prolactin levels and routinely examine their patients for abnormal breast growth and impaired sexual maturation and to consider discontinuing RISPERDAL® at the first sign of any of those signs and/or symptoms.

* J&J has never done the long-term study requested by the FDA advisory committee in 2008.[32] For this reason, until such a study is done, the approval of Risperdal and Invega for use in children and adolescents should be prohibited.

Summary of Requested Action

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32 While J&J purported to address the issue in its RIS-NAP-4022 study, issued on 12/28/11, this study was terminated early due to failure to reach enrollment targets and by J&J's own admission, "the low enrollment resulted in an underpowered study." Nevertheless, this study confirmed that Hyperprolactinemia occurs significantly more often with Rispderdal than other atypical anti-psychotics (25.6% vs. 2%).

For all of the reasons set forth above, Petitioner respectfully requests that the FDA **immediately revoke approval of Risperdal, Invega, and all generic version of risperidone for use in children unless and until J&J presents evidence supporting: safety of long-term use of the drug; and efforts on their part to prevent the off-label prescription of Risperdal to patients for whom those risks do not outweigh the potential benefits of treatment and otherwise satisfy the concerns of the FDA's Pediatric Advisory Committee; and either voluntarily submit their internal communications and documents as well as litigation documents related to Risperdal or consent to Petitioner's presentation of our own *objective* presentation on these issues to counter-balance J&J's own biased presentation.**

Environmental Impact Statement

Nothing requested in this Petition will have an impact on the environment.

Certification

We certify that, to the best of our knowledge and belief, this Petition includes all information and views on which this Petition relies, and that it includes representative data and information known to the Petitioners which are unfavorable to this Petition.

Sincerely,

Stephen A. Sheller, Esquire
SHELLER, P.C.
1528 Walnut Street, 4th Floor
Philadelphia, PA 19102
(215) 790-7300
(215) 546-0942

EXHIBIT

C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JAN 29 2013

2013 JAN 30 A 10:36

Stephen A. Sheller, Esq.
Sheller, P.C.
1528 Walnut Street, 4th Floor
Philadelphia, PA 19102

Re: Docket No. FDA-2012-P-0857

Dear Mr. Sheller:

I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your citizen petition received on August 2, 2012. Your petition requests that the Agency revoke the pediatric indication for Risperdal (risperidone), for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated. Alternatively, the Petition requests that FDA require a boxed warning for Risperdal and all generic versions of risperidone. Finally, the Petition also asks that FDA direct Johnson & Johnson, Inc. to consent to release you from any and all standing Confidentiality/Protective Orders.

FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request.

Sincerely,

Denise Esposito

Denise Esposito
Acting Director, Office of Regulatory Policy
Center for Drug Evaluation and Research

EXHIBIT

D

Sheller, P.C.
LAW OFFICES

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CHERRY HILL, NJ 08002

(609) 941-2596

Stephen A. Sheller, Esquire
Email: sasheller@sheller.com

March 26, 2013

VIA FIRST CLASS MAIL
Denise Esposito
Department of Health & Human Services
Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Springs, MD 20993

Re: Docket No. FDA-2012-P-0857

Dear Ms. Esposito:

Thank you for your letter dated January 29, 2013. Due to the complexity of the issues and the unique knowledge/information in our possession we formally request that the Commissioner schedule a hearing in accordance with 21 CFR 10.30 (h)(2).

Very truly yours,

Stephen A. Sheller, Esquire
Christopher A. Gomez, Esquire

EXHIBIT

E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 1 1 2013

2013 JUN 13 P 12:47

Stephen A. Sheller, Esq.
Christopher A. Gomez, Esq.
Sheller, P.C.
1528 Walnut Street 4th Floor
Philadelphia, PA 19102

Re: Docket No. FDA-2012-P-0857

Dear Mr. Sheller and Mr. Gomez:

We are in receipt of your letter dated March 26, 2013, requesting that the Commissioner of Food and Drugs schedule a hearing on the above referenced citizen petition in accordance with 21 CFR 10.30(h)(2). The citizen petition, received on August 2, 2012, requests that the Agency revoke the pediatric indication for Risperdal (risperidone), for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated. Alternatively, the Petition requests that FDA require a boxed warning for Risperdal and all generic versions of risperidone. Finally, the Petition also asks that the Food and Drug Administration (FDA) direct Johnson & Johnson, Inc. to consent to release you from any and all standing Confidentiality/Protective Orders.

Your stated reason for requesting the hearing is the "complexity of the issues and the unique knowledge in [your] possession."

We are aware of two conversations Mr. Sheller has had with FDA staff, most recently in January 2013, when Mr. Sheller mentioned information (specifically citing Dr. David Kessler as the author) that he believed the FDA should have in the course of its review and analysis of the petition. On both occasions, he was invited to submit such information to the docket for full consideration. As of the date of this letter, FDA has not received such a submission to the docket.

Under 21 CFR 10.30(h)(2), the Commissioner is given discretion as to whether to not to employ a hearing in the course of reviewing a citizen petition. The regulation states, in part:

In reviewing a petition the Commissioner may *[emphasis added] use the following procedures: A hearing under parts 12, 13, 14, 15, or 16.*

We believe the submission of relevant information to the docket will be a more effective means than a hearing for FDA to review the information and evaluate the issues and will also be a more efficient use of FDA's limited resources. We therefore decline your request for a hearing under 21 CFR 10.30(h)(2). Once again, we invite you to submit any information or comments to the petition docket. Information on how to do so can be found on the link below.

http://www.fda.gov/RegulatoryInformation/Dockets/Comments/default.htm

Thank you for your interest, and we look forward to receiving the materials you would like the Agency to review in the context of your citizen petition.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

EXHIBIT

F

Sheller

Reply to:
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2339 13 JUL 18 P4:16

July 2, 2013

Janet Woodcock, M.D.
Food and Drug Administration
Director, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51, Rm. 6133
Silver Spring, MD 20993

Re: Docket No. FDA-2012-P-0857; Petition to Revoke the Pediatric Indications for Risperdal®

Dear Dr. Woodcock:

We are writing in response to your letter dated June 11, 2013, in which you denied our request for a hearing regarding issues raised in our Citizen Petition, docket number FDA-2012-P-0857, which urges the Food and Drug Administration ("FDA") either to revoke the pediatric indications for Risperdal®, generic risperidone, and Invega® unless and until their long-term safety in this population can be established, or, in the alternative, require a Black Box Warning on the labels for these products.

You noted that our Citizen Petition also requested the FDA to "consent to release [us] from any and all standing Confidentiality/Protective Orders" in order for us to produce documents and testimony obtained during the discovery process that directly relate to the request in our Citizen Petition. In response, you recommend that, in place of a hearing, we submit the documentation we believe the FDA should have in order to evaluate the petition. It appears you misunderstand both our request and the legal status of those documents.

The full request set forth in the Citizen Petition is

> consent to release [us] from any and all standing Confidentiality/Protective Orders **so that** Petitioner can present **to the FDA** the internal documents and data, as well as an expert analysis thereof which we believe support the foregoing requested actions. [emphasis added].

We would like to submit to the FDA those documents we have uncovered during the discovery phase of various litigations against Janssen and Johnson & Johnson (collectively, "J&J") but we cannot. We are prevented, by court orders issued in the pending litigations,

from providing those documents and testimony to the FDA. They have been designated as "Confidential" under the purview of a Protective Order, so we cannot legally send them to the FDA to be placed on a publicly-viewed docket. We also suggested in our original petition that, in the alternative, **the FDA** could demand the relevant documents from J&J.

The purpose of these requests was not to have the FDA override a court order. It was to have the FDA direct J&J to allow us to turn over these documents to the FDA **or** to have the FDA acquire them directly from J&J. We believe that it is within the power and authority of the Commissioner of the FDA to order J&J to release us from the unjust strictures of a Protective Order in a civil lawsuit. Further, FDA has the authority to demand safety-related documents in order to review them. The J&J information is already available to FDA – all you have to do is ask them for the documents.

If the FDA chooses to request the document directly from J&J, we strongly recommend that oversight by someone in our firm should be permitted to help ensure that all relevant material is provided.

Yet another alternative is for the FDA to acquire a copy of J&J's proprietary safety/adverse event database and perform its own statistical analysis. While we suppose that this is not as cost-effective as acquiring the J&J documents we have examined, we mention it as another example of action that is within the authority of the FDA. We hope that there are no potential conflicts of interest to interfere with any of the FDA's safety-related activities.

Your letter notes that we have previously mentioned a report authored by David Kessler, M.D., former Commissioner of the Food and Drug Administration. Although Dr. Kessler's report is publicly available, the documents to which he refers are still subject to the Protective Order previously discussed so it makes little sense to submit this report to the docket without the substantiating materials.

We are agreeable, however, to submitting it to a designated person at the FDA if the FDA intends to demand the substantiating documents from J&J, as we strongly urge the FDA to do.

Dr. Kessler's report is especially insightful regarding a particular meta-analysis published in November, 2003 entitled, "Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents" by Robert L. Findling, M.D., et al. One of the co-authors of this article, Denis Daneman, M.B.B.Ch., F.R.C.P.C., testified, during his publicly-available deposition earlier this year, that the article's abstract was inaccurate where it stated, "There was no direct correlation between prolactin elevation and SHAP" [Symptoms Hypothetically Attributable to Prolactin, i.e., gynecomastia in boys]. He also agreed that this article failed to report the statistically significant association between elevated prolactin levels and SHAP.

Despite Dr. Kessler's analysis of this article and Dr. Daneman's deposition testimony, J&J and major thought leaders are still citing this article as proof that there is no correlation

or association between elevated prolactin and the incidence of gynecomastia in boys. Dr. Kessler was recently deposed on the subjects of his expert report, including his criticism of the above cited meta-analysis. Although confidential, the FDA has no bar or impediment in its way and can simply ask J&J for a copy of the transcript to review. Regardless of the reason, ignoring the pediatric safety data and information available in these internal J&J documents, as well as the relevant, but confidential, testimony is tantamount to ignoring the safety and interests of the children the FDA is charged with protecting.

The FDA will find value in Dr. Kessler's analysis, **along with a review of the corroborating documents**. We find it difficult to understand, therefore, why the FDA has refused to avail itself of the tools and material it has to require that J&J produce these documents and review the pediatric safety data and information contained therein. It is even more difficult to understand, knowing that you are scheduled to be a keynote speaker at the upcoming Clinical Trials Disclosure and Transparency Summit, whose stated purpose is to examine the "tougher new FDA and EMA disclosure and transparency requirements for clinical trials."

It has been nearly one year since we submitted our Citizen Petition. The only action the FDA has taken in that time is to notify us, in an interim response, that our Petition "raises complex issues requiring extensive review and analysis by Agency officials" and then to deny a hearing request and advise us to submit documents we are legally barred from sharing.

In that time, thousands of children may have been harmed by using one of these drugs, when an alternative medication without these serious, prolactin-related adverse effects could have been administered instead.

If, indeed, the safety actions requested in our Citizen Petition are "complex issues" which require "extensive review and analysis," we urge the FDA to begin that process immediately and we reiterate our request for a hearing as the first step.

We ask that you contact us to arrange a meeting where we can discuss the issues raised in our Citizen Petition.

Sincerely,

Stephen A. Sheller, Esq.

Christopher A. Gomez, Esq.

SAS/

EXHIBIT

G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

AUG 16 2013

2013 AUG 20 A 11:46

Stephen A. Sheller, Esq.
Christopher A. Gomez, Esq.
Sheller, P.C.
1528 Walnut Street 4th Floor
Philadelphia, PA 19102

Re: Docket No. FDA-2012-P-0857

Dear Mr. Sheller and Mr. Gomez:

We received your letter dated July 2, 2013, requesting that the Food and Drug Administration (Agency) take certain actions related to your pending citizen petition regarding Risperdal (risperidone) and Invega (paliperidone).

Your letter addresses issues related to your citizen petition and is being considered as part of that deliberative process. We will issue a response once our review has been completed and a decision has been made. You also requested to meet with the Agency. We do not believe that such a meeting would be beneficial at this time. Therefore, your request is denied.

Finally, I note that you sent your letter directly to me in my capacity as Director of the Center for Drug Evaluation and Research. For reasons of transparency, and in compliance with Agency policy, we ask that you submit your letter to the petition docket (Docket No. FDA-2012-P-0857), as you have done with prior submissions. Information on how to do so can be found on the link below.

http://www.fda.gov/RegulatoryInformation/Dockets/Comments/default.htm

We appreciate and understand your interest in this matter and can assure you that it is receiving active Agency attention.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

EXHIBIT

H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

NOV 25 2014

Stephen A. Sheller, Esq.
Christopher A. Gomez, Esq.
Sheller, P.C.
1528 Walnut Street, 4th Floor
Philadelphia, PA 19102

Re: Docket No. FDA-2012-P-0857

Dear Mr. Sheller and Mr. Gomez:

This responds to your citizen petition received on July 27, 2012, and amended on August 27, 2012.[1] Your petition, as amended,[2] requests that the Food and Drug Administration (FDA or Agency) revoke the pediatric indication for Risperdal (risperidone), for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated. Alternatively, you request that FDA require a new boxed warning for Risperdal and all generic versions of risperidone that would warn of what you characterize as a lack of sufficient safety data. Finally, you also ask that FDA direct Johnson & Johnson, Inc. (J&J) to consent to release you from any and all standing Confidentiality/Protective Orders so that you can present to the Agency "internal documents and data, as well as an expert analysis thereof," which you believe support your requests (Petition at 2).

We have carefully considered your petition and the comments submitted to the docket. For the reasons described below, your requests are granted in part and denied in part.

I. BACKGROUND

A. Risperdal and Invega

Risperidone and its active metabolite, paliperidone, are antipsychotic drugs marketed in

[1] We also acknowledge your March 26, 2013, letter to FDA requesting that the Commissioner of Food and Drugs schedule a hearing to discuss your petition. In addition, we acknowledge your July 2, 2013, letter reiterating certain requests contained in your petition. We responded to these letters and posted both the letters and our responses to the docket associated with your petition.

[2] Your August 27, 2012, submission, which you characterize as an "amendment" to your August 2, 2012, petition, appears to be a replacement of your original petition. It contains some additional discussion in support of your requests but is otherwise identical to the original. Accordingly, we refer to your August 27, 2012, submission as the "Petition" or "your petition" throughout this response, and do not further refer to your original August 2, 2012, submission.

the United States as Risperdal and Invega, respectively. Risperdal (risperidone) is the subject of new drug application NDA 20-272 and was approved on December 29, 1993. It was indicated for the management of the manifestations of psychotic disorders. An additional indication for treatment of irritability associated with autistic disorder in children and adolescents was added in 2006. In 2007, the indications for schizophrenia and bipolar I disorder were expanded to include adolescents aged 13-17 and children and adolescents aged 10-17, respectively.

Invega (paliperidone) Extended-Release Tablets was approved on December 19, 2006. It is the subject of NDA 21-999. It was indicated for the treatment of schizophrenia. It is designed to deliver paliperidone — the active ingredient derived from risperidone.

Both drugs are known to elevate blood levels of prolactin, a naturally occurring hormone produced by the pituitary gland in the brain. Elevated levels of prolactin (hyperprolactinemia) from any cause can be associated with a number of clinical effects, including breast enlargement (also called gynecomastia).

Both Risperdal and Invega have been studied in adequate and well-controlled clinical trials in pediatric patients. As noted above, supplemental new drug applications (sNDAs) for the use of Risperdal in the treatment of irritability associated with autistic disorder in children and adolescents (ages 5-16 years), treatment of schizophrenia in adolescents (ages 13-17 years), and treatment of bipolar disorder in children and adolescents (ages 10-17 years) were approved on October 6, 2006; August 22, 2007; and August 22, 2007, respectively. An sNDA for the use of Invega in the treatment of schizophrenia in adolescents (ages 12-17 years) was approved on April 6, 2011.

B. Regulatory Framework

FDA's regulation of drug safety is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et. seq.) and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations). The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved NDA or abbreviated new drug application (ANDA).[3] Before approving an NDA, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[4]

After an approved drug enters the marketplace, FDA may have cause to reassess its safety and take regulatory action if warranted and appropriate. One possible action is withdrawal of a drug product's approval. Section 505(e)(1)-(2) of the FD&C Act provides that FDA shall withdraw approval of a drug product if the agency finds, after notice and opportunity for a hearing, that "clinical or other experience, tests, or other

[3] See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).

[4] Section 505(b)(1) of the FD&C Act; section 505(d) of the FD&C Act.

scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved," or that:

> . . . new evidence of clinical experience, not contained in [the] application or not available to the Secretary until after [the] application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when [the] application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.

Another possible regulatory action would be to require the inclusion of new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, in product labeling (see section 505(o)(4) of the FD&C Act).

II. DISCUSSION

A. Request to Revoke Pediatric Indication or Require a Black Box Warning[5]

You request that the FDA revoke the pediatric indication for Risperdal (including all generic versions of risperidone) and Invega unless and until the long-term safety of these drug products can be demonstrated. Alternatively, you request that FDA require a boxed warning for Risperdal and all generic versions of risperidone (Petition at 1, 2).

You base your requests on the incidence of adverse events associated with Risperdal and Invega, including hyperprolactinemia and gynecomastia. You assert that the current labeling of these products fails to adequately inform and guide prescribers and contend that, as a result, patients who might otherwise be provided with alternative treatments are led to suffer adverse effects associated with Risperdal. As grounds for your request to revoke the pediatric indication or require a black box warning, you cite a lack of long-term safety data for these drug products.

For the reasons discussed below, we disagree with your assertion that what you characterize as a lack of long-term safety data is a basis for either revoking the pediatric indications for Risperdal or Invega or adding a new boxed warning to the labeling of these drug products.

1. Safety Information Supported Approval of Pediatric Indications; Subsequent Review Does Not Alter Our Conclusion

Before the approval of each pediatric indication for Risperdal and Invega, the Agency

[5] You note that your requests and the grounds for your requests apply to Risperdal (including generic versions of Risperdal) and Invega, though you do not specifically request a boxed warning for Invega (Petition at 1).

determined that sufficient short-term and long-term safety information to support approval had been presented by the drug sponsor.

Since the pediatric approvals were granted, we have: (1) examined required Annual Report submissions for any new safety signals related to Risperdal and Invega; (2) routinely monitored Agency data, including our adverse event reporting systems, for new safety signals; (3) asked for and received from the drug sponsor any data in their possession relevant to the use of Risperdal or Invega in children or adolescents that had not previously been submitted; and (4) conducted a thorough review of published literature[6] to identify any new safety concerns, including any concerns related to the long-term use of these drug products.

In sum, based on reviews of clinical data submitted by the sponsor, published literature, and postmarketing surveillance, there is no evidence that the drug is unsafe, and no evidence that the drug is not shown to be safe, for use under the conditions of use upon the basis of which the applications were approved that would warrant revocation of the pediatric indication of these drugs.

2. *The Absence of Additional Long-Term Safety Data Does Not Support Revoking the Pediatric Indications for Risperdal and Invega*

We acknowledge that we lack quality, long-term, comparative safety data on the use of antipsychotic agents in the pediatric population. Indeed, the lack of such data is a common theme emphasized throughout the relevant published literature.

Unfortunately, long-term, randomized, placebo-controlled drug safety trials are often not feasible, and that is the case here. Among other considerations, it is unethical to require acutely ill patients to be randomized to placebo and be observed for several months or more without effective treatment. Trials that use another active drug as the comparator instead of placebo might be conducted, but the results of such trials would be difficult to interpret because the absolute risk attributable to the other active drug may not be known or evaluable. Likewise, simply following patients receiving these drugs for a long time with no control group would produce data that would be highly challenging to interpret because it would be unknown whether any observed differences should be attributed to the drug, passage of time, or intercurrent factors. Finally, retention of patients in long-term studies can be difficult, and if a large number of patients drop out over the course of a study, its conclusions may be substantially weakened. For these reasons, assessment of the effects of long-term drug exposure primarily relies on animal data,[7] together with any

[6] Our literature search set out to identify any published adequate (placebo or active-controlled) trials in children or adolescents that provided data with respect to preselected adverse events associated with the use of the new generation antipsychotic drugs (i.e., risperidone, paliperidone, aripiprazole, olanzapine, and quetiapine). These drugs were selected because they have approved pediatric indications. Our search focused on long-term safety data referencing those adverse events we believed to be most important in the pediatric population: hyperprolactinemia, weight gain, hyperlipidemia, extrapyramidal symptoms, and tardive dyskinesia. The PubMed, Embase, and EBSCO Host were among the databases we used.

[7] In fact, before conducting studies in children, juvenile toxicity studies are conducted in young rats,

other relevant long-term safety information available to the Agency.

Thus, we acknowledge that not all adverse reactions associated with the long-term use of these drugs in pediatric patients are detected by clinical investigations or postmarketing surveillance. These include effects on measures such as growth and sexual maturation. We have no comparative data for known adverse events such as gynecomastia.

However, the lack of quality, long-term clinical safety information of the type discussed above is not an appropriate reason to revoke the pediatric indications of Risperdal and Invega when weighed against the potential therapeutic benefit derived from the use of these drugs.

Clinical efficacy of Risperdal and Invega in their approved pediatric indications was demonstrated prior to approval, and numerous pediatric patients have benefited from these drugs despite their known risks. Granting your request that the pediatric indications for Risperdal and Invega be withdrawn unless and until long-term safety is demonstrated would be tantamount to a long-term or permanent withdrawal, thereby removing an important and beneficial therapeutic option for many children and adolescents with these disorders. Withdrawal of these indications would constitute a disservice to the public health.

Accordingly, we do not believe that the standards for withdrawal of approval enumerated in section 505(e) have been met here. Based on reviews of clinical data submitted by the sponsor, published literature, and postmarketing surveillance, there is no evidence that the drug is unsafe, and no evidence that the drug is not shown to be safe, for use under the conditions of use upon the basis of which the applications were approved that would warrant revocation of the pediatric indication of these drugs.

3. *There Is No Basis for Requiring a Boxed Warning Regarding Lack of Long-Term Safety Data Associated With Pediatric Use of Risperdal and Invega*

FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" on a drug product's labeling (21 CFR 201.57(c)(1)).

As described in the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) (the Boxed Warnings Guidance),[8] a

followed for a period corresponding to human childhood, to detect signals of potential adverse effects with long-term use in developing children. The following areas are assessed in these animal studies: (1) learning, memory, and general behavior (e.g., hyperactivity); (2) histopathology, which entails an examination of various body organs to detect drug-related injury, and (3) reproductive functioning upon reaching young adulthood (including evaluation of mating behavior, fertility, and offspring). See Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products (February 2006), pp.11-12.

[8] Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

boxed warning is ordinarily used to highlight for prescribers one of the following situations:

> There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug;
>
> *OR*
>
> There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation);
>
> *OR*
>
> FDA approved the drug with restrictions to ensure safe use because the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under [21 U.S.C. 355-1(f)(3)] "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).[9]

The Boxed Warnings Guidance also states that, infrequently, a boxed warning can be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it warrants inclusion in a boxed warning (Boxed Warnings Guidance at 11).

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate. For example, a contraindication for use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which an adverse reaction has not been observed. A boxed warning can also be considered for a drug that poses risk-benefit considerations that are unique among drugs in a drug class (Boxed Warnings Guidance at 12).

None of these situations is applicable here, and the concerns you have raised do not otherwise justify a boxed warning. The risks of treatment with these drug products, including the risks with which your petition is principally concerned, are well known.[10]

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[9] Boxed Warnings Guidance at 11.

[10] BJ Sadock, VA Sadock, and P Ruiz (eds.), Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 9th Edition (2009). Williams and Wilkins, pages 3215, 3217-3219.

Gynecomastia is a common clinical manifestation of hyperprolactinemia, regardless of cause,[11] and does not represent a serious adverse event as defined in 21 CFR 312.32(a). We would expect prescribers and patients to discuss these potential risks (together with the potential benefits) before and during treatment, consistent with the applicable standard of care.

Furthermore, we do not think it is appropriate to use a boxed warning to convey, as you request (Petition at 2), a mere *lack* of certain safety data (the long-term comparative safety data discussed in section II.A.2 of this response), particularly where, as we have previously discussed, the risks in question are already well known by prescribers and do not represent serious adverse events.

Finally, other antipsychotic drugs (such as haloperidol, fluphenazine, and perphenazine) have been known for decades to produce hyperprolactinemia as a side effect of their therapeutic action, and this fact is well known within the psychiatric community. The risk of hyperprolactinemia associated with certain antipsychotics has been basic textbook knowledge in psychiatry for many years. For example, there is considerable discussion of the tendency of antipsychotic drugs to elevate prolactin in *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, (4th edition, published by Cambridge University Press (2013)).[12] This is one of the standard textbooks in the field of psychiatric drug therapy.

Accordingly, your petition does not present any data, nor does the Agency possess any data, that would lead us to conclude that a boxed warning regarding the risk of gynecomastia or, more generally, hyperprolactinemia, is appropriate for the labeling of Risperdal or Invega. For these reasons, we deny your requests to require a boxed warning for Risperdal and all generic versions of risperidone.

B. Labeling Adequacy

Although your petition includes an extensive discussion of the current labeling of Risperdal and Invega, you do not make specific labeling requests other than the request, addressed above, that FDA require a new boxed warning for Risperdal and all generic versions of risperidone. We therefore do not respond to your specific contentions regarding the current labeling of these products. As is the case with all drugs regulated by the Agency, labeling is assessed as appropriate to ensure that it reflects all relevant safety information and labeling updates are sought and implemented as necessary.

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[11] Id. at page 3218.

[12] See Page 336.

C. The 2008 Advisory Committee Meeting

Your petition (Petition at 9-13) references the FDA Pediatric Advisory Committee Meeting that was held on November 18, 2008,[13] and asserts that several follow-up actions/recommendations have not been undertaken, including:

1. additional follow-up regarding on-label and off-label product use of this class of drug products, with specific attention to age and indication for which the product is being used;

2. additional follow-up regarding metabolic syndrome, growth, sexual maturation, and hyperprolactinemia;

3. further studies on long-term effects in the pediatric population of this class of products;

4. additional follow-up on extrapyramidal side effects in the pediatric population; and

5. additional evaluation of this class of antipsychotic medications and concomitant drug use.

You do not explain how the 2008 Advisory Committee Meeting supports the specific requests made in your petition – in particular, that FDA revoke the pediatric indication for Risperdal, for all generic versions of risperidone, and for Invega (paliperidone), unless and until the long-term safety of these drug products can be demonstrated; or, in the alternative, that FDA require a new boxed warning for Risperdal and all generic versions of risperidone that would warn of what you characterize as a lack of sufficient safety data. Moreover, we disagree with your contentions regarding asserted Agency inaction following the Advisory Committee meeting. The Agency has been actively engaged in the issues addressed at the 2008 Advisory Committee meeting and has followed up on the Advisory Committee's recommendations as appropriate and necessary.

D. Request for FDA to Direct J&J to Consent to Release Confidentiality/Protective Orders

You request that FDA direct J&J to release your firm from "any and all standing Confidentiality/Protective Orders" so that you can present to the FDA the "internal documents and data," as well as an expert analysis thereof, which you believe support your requested actions (Petition at 2). In the alternative, you ask that FDA request that J&J submit "all internal documents, including e-mails and correspondence, as well as documents and testimony from the Risperdal litigation" (Petition at 1, footnote 2). You further ask that should FDA make such a request to J&J, any documents produced by J&J

[13] Transcript available at http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4399m1.pdf.

should either be made available for public review and comment or made available to you for "in camera review" (Petition at 2, footnote 2). We refer collectively to these alternative requests as the "Additional Information Request."

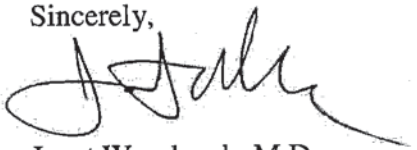
In response to the Additional Information Request, we asked J&J to provide any data in its possession relevant to the use of risperidone or paliperidone in children and adolescents that J&J had not previously provided to the Agency. We referenced your petition and your amended petition in our letter and included those documents as attachments to our letter. J&J provided certain information in response to our request, which we considered along with all other relevant information available to us in addressing your Petition. We decline to take any of the other specific actions you requested in connection with the Additional Information Request.[14]

Accordingly, the Additional Information Request is granted in part and denied in part.

III. CONCLUSION

For the reasons stated above, your requests are denied, except for the Additional Information Request, which is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[14] Given our disposition of the Additional Information Request, we need not reach, and make no comment on, our legal authority to take any of the specific actions you request in connection with the Additional Information Request.

EXHIBIT

I

JOSEPH GLENMULLEN, MD
1770 Massachusetts Avenue, No. 263
Cambridge, MA 02140

August 14, 2013

Margaret Hamburg, M.D., Commissioner
Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research
Russell Katz, M.D., Director, Division of Neurology Products
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Doctors:

As a practicing psychiatrist and Clinical Instructor in Psychiatry at Harvard Medical School, I am writing to bring to your urgent attention a critical safety risk for children prescribed Risperdal. According to Risperdal's official prescribing guidelines, the antipsychotic causes elevation of the sex hormone prolactin (hyperprolactinemia) and is worse than other antipsychotics in this regard. Nevertheless, Risperdal has been the antipsychotic most frequently prescribed to children. In 2003, Risperdal's manufacturer, Janssen Pharmaceutical published a meta-analysis of five of its pediatric studies allegedly demonstrating that elevated prolactin levels in children and adolescents are not associated with an increased risk of prolactin-related sexual and reproductive side effects, including loss of menstruation in adolescent girls, impotence in adolescent boys, and abnormal breast development and milk secretion in boys.[1]

However, according to previously (but no longer) confidential Janssen documents, the company's analysis demonstrated the opposite: pediatric patients on Risperdal with elevated prolactin have a statistically significant more than doubling of the risk of sexual and reproductive side effects.[2] Moreover, Janssen's study identified a critical time period—eight to twelve weeks—when elevated prolactin predicts this significantly increased risk, making blood monitoring imperative for children on Risperdal. According to Janssen e-mails, senior executives advised removing the critical safety findings—including the need for blood monitoring—from the final, published version of the study, apparently due to concerns over the potential negative impact on sales of the drug. The misleading published version of the study has been very influential, influencing guidelines for treating children with antipsychotic drugs, peer-reviewed medical literature, and therefore practicing physicians. Moreover, according to company documents, the misleading version of the study with the critical findings omitted was submitted to the FDA, allayed the agency's concerns about the long-term

risks of sexual and reproductive side effects in children, and influenced the FDA to approve Risperdal for pediatric conditions. Janssen's studies showed Risperdal can cause a rapid elevation of children's prolactin levels within six weeks. Over the course of a year, 70% of children develop elevated prolactin and 5% develop sexual and reproductive side effects, making them a frequent, serious public health concern.

I have attached for your review the critical documents referenced in this letter. These documents have come to light in litigation. I have been a lead witness in Risperdal litigation brought by the Department of Justice, the Texas State Attorney General's Office, and private law firms. The attached documents were recently made public by a Corpus Christi, Texas judge presiding over litigation involving some 1,400 boys and men with Risperdal-related abnormal breast development, including some who have already suffered double mastectomies.

No doubt you will want to:

1. Re-evaluate Risperdal's appropriateness for children and adolescents

2. Consider immediately revising Risperdal's official prescribing information to reflect the risk

3. Investigate potential corporate misconduct on Janssen's part

If I can be of any further assistance in protecting children and adolescents from these serious sexual and reproductive side effects, please do not hesitate to contact me.

Sincerely,

Joseph Glenmullen, M.D.

[1] Findling R, Kusumakar V, Daneman D, Moshang T, De Smedt C, and Binder C, Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents." *Journal of Clinical Psychiatry*, November 2009; 64:1362-1369

[2] JJRE 01555628-642; JJRIS 00272595-609; JJRE 02399406-451; JJRE 05002596-2701; JJRE 05011838-1960; JJRE 08415273-3433; JJRE 0840029-119; JJRE 08088e9-8971; JJRE 09012407; JJRE 14079718-747; JJRIS 01882898; JJRE 00115168-198; JJRE 04407881-8817; JJRE 03900007-113; JJRE 03892154; JJRE 14088063-8093; JJRE 03895496-97; JJRE 03895394; JJRE 02439875-77; JJRIS 00533590-93; JJRE 0e32707-712; JJRIS 025623360-447; JJRE 0e7e94e8-505; JJRE 04982271-365; JJRE 02297143-155; JJRP 00371640-1982; JJRE 04995e98-9e133; JJRE 12781105-115; JJRE 11069206-89; JJRE 14076751-770; JJRE 03888722-729; JJRIS 01880329-421; JJRE 03893192-268; JJRE 11082065-2100

CERTIFICATE OF SERVICE

I certify that the I served the foregoing First Amended Complaint upon the following counsel today by hand delivery and email:

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Counsel for Defendants

Dated: May 1, 2015

Robert M. Palumbos
(Signature Validation Code: RMP8881)