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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