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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.

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.

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[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®.

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[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.
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> . . .
>
> 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

[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

From: (215) 790-7300
Stephen A. Sheller, Esquire
SHELLER, P.C.
1528 Walnut Street, 4th Floor

Philadelphia, PA 19102

Origin ID: MUVA

FedEx Express

J1220120718O325

Ship Date: 27AUG12
ActWgt: 1.0 LB
CAD: 3519404/INET3300

Delivery Address Bar Code

Ref # 201991 (Risp)
Invoice #
PO #
Dept #

SHIP TO: (301) 827-6860 BILL SENDER

Food & Drug Administration
Division of Dockets Management
5630 FISHERS LN

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Exhibit B

EXHIBIT B

MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE

Holiday Inn/Gaithersburg, Grand Ballroom
2 Montgomery Village Road, Gaithersburg, Maryland

Tuesday, November 18th, 2008

The meeting was convened at approximately 8:00 a.m.

Members Present (voting) for March 25th, 2008
Marsha Rappley, M.D. *(Chair)*
Amy Celento (*Patient Health Care Representative*)
Avital Cnaan, Ph.D., M.S.
Carl D'Angio, M.D.
Leon Dure, M.D.
Hank Farrar, M.D. (*Pediatric Health Organization Representative*)
Brahm Goldstein (*Industry Representative*)
Melissa Maria Hudson, M.D.
Keith Kocis, M.D., M.S.
Kathleen Motil, M.D.
Daniel Notterman, M.D.
Geoff Rosenthal, M.D.
Alexander Rakowsky, M.D.
Elaine Vining (*Consumer Representative*)

Temporary Voting Consultants
Mark Hudak, M.D.

Executive Secretary
Carlos Peña, Ph.D., M.S.

U.S. Food and Drug Administration (FDA) Participants
Judith Cope, M.D., M.P.H.
Lisa Mathis, M.D.
Ann McMahon, M.D.
Dianne Murphy, M.D.
William Boyd, M.D.
Thomas Laughren, M.D.
Mitchell Mathis, M.D.
Ozlem Belen, M.D.
Norman Hershkowitz, M.D., Ph.D.
Phillip Sheridan, M.D.
Devanand Jillapalli, M.D.
Carole Davis, D.O., M.P.H.

Jill Lindstrom, M.D.
Naomi Lowy, M.D.

Open Public Hearing Speakers
None

Presentations
Welcome and Introductory Remarks
Marsha Rappley, M.D., Chair, Dean, College of Human Medicine, Michigan State University
Carlos Peña, Ph.D., MS, Executive Secretary, Office of Science and Health Coordination, Office of the Commissioner (OC), FDA
Agenda Overview
Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics (OPT), OC, FDA
Zyvox (linezolid) Report Requested at the November 16, 2006 Pediatric Advisory Committee meeting (report in the briefing packet)
Betoptic S (betaxolol) and Timolol (timolol) Abbreviated Process
Risperdal (risperidone) Standard Review of Adverse Events
Felicia Collins, M.D., Medical Officer, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), FDA
Zyprexa (olanzapine) Standard Review of Adverse Events
Felicia Collins, M.D., Medical Officer, OND, CDER, FDA
Levaquin (levofloxacin) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Lamictal (lamotrigine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Ambien (zolpidem) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Lamisil (terbinafine) Standard Review of Adverse Events
Patricia Brown, M.D., Medical Officer, OND, CDER, FDA
Aldara (imiquimod) Standard Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Sandostatin (octreotide) Expanded Review of Adverse Events-Outside Speaker Presentation
Rama Bhat, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
Sandostatin (octreotide) Expanded Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Ethics Discussion
Robert "Skip" Nelson, M.D., Ph.D., Pediatric Ethicist, OPT, OC, FDA

Sponsor Presentations
Sandostatin (octreotide) Expanded Review of Adverse Events-Sponsor Presentation
Todd Gruber, M.D., M.P.H., Head, U.S. Medical Function, Novartis

Summary of FDA Questions, Committee Discussion, Vote and Recommendations

Zyvox (linezolid) Report Requested at the November 16, 2006 Pediatric Advisory Committee meeting (report in the briefing packet)

Question to the Committee

- Follow-up Report contained in the background package. Are there any questions?

Committee Discussion

The Advisory Committee discussed the clinical study on QT prolongation requested by the Review Division and its application to all age groups. The committee requested that they receive the QT Prolongation report that is noted by the review.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed that they had no additional recommendations to the follow-up Report contained in the background package.

Betoptic S (betaxolol) and Timolol (timolol) Abbreviated Process

Question to the Committee

- FDA will continue its standard ongoing safety monitoring for these products. Does the committee concur?

Committee Discussion

The Advisory Committee discussed information in labeling concerning the use of this product in the pediatric population and the availability of data from the trial on the degree of lowering of intraocular pressure in the pediatric population would be useful in labeling.

Committee Vote

- Twelve (12) committee members unanimously agreed to standard ongoing safety monitoring for these products.

Risperdal (risperidone) Standard Review of Adverse Events

Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA

Question to the Committee

- FDA will continue its standard, ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?

Committee Discussion

The Advisory Committee discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously supported more than the standard, ongoing safety monitoring for oral risperidone.
- 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 antipsychotic 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.

- Twelve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee.

Zyprexa (olanzapine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends, in view of the potential metabolic effects with the use of olanzapine, especially in pediatric patients to continue to evaluate the safety of olanzapine and decide if any additional risk-management regulatory action is needed. Does the Advisory Committee concur with this approach?

Committee Discussion
The Advisory Committee discussed the need for additional information, as discussed with risperidone, on use of this product in the pediatric population, obtaining more information from new database resources, and off-label use considerations.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed on the need to continue to evaluate the safety of olanzapine and additional risk-management regulatory actions concerning the monitoring of metabolic changes. Committee agreed with FDA's continued surveillance of metabolic syndrome.
- Please see the recommendations for risperidone.

Levaquin (levofloxacin) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends continuing routine, ongoing post-marketing safety monitoring. Does the Advisory Committee concur?

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to routine, ongoing post-marketing safety monitoring and recommended adding the following text to the warning section (5.8) about prolongation of QT, "and other agents that cause an increase in QT".

Lamictal (lamotrigine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA is working to include suicidality data in the labeling of 11 antiepileptic drugs, including lamotrigine. FDA will continue to monitor medication errors related to name confusion. FDA will continue its standard, ongoing safety monitoring for lamotrigine. Does the Advisory Committee concur with this approach?

Committee Discussion
The Advisory Committee acknowledged that FDA has already worked with other sponsors on labeling products regarding risk of suicidality for antiepileptic drugs.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to standard, ongoing post-marketing safety monitoring.

Ambien (zolpidem) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends returning to routine/standard safety monitoring for all patients. Does the Advisory Committee concur?

Committee Discussion
The Committee noted that the pediatric statement in the prescribing labeling information is inconsistent with the MedGuide and recommended FDA consider harmonizing the pediatric statement about not using these products in children.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to routine/standard safety monitoring for all patients.

Lamisil (terbinafine) Standard Review of Adverse Events
Patricia Brown, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA will continue its ongoing safety monitoring. Does the Advisory Committee have any additional comments?

Committee Discussion: Members recommended that the pediatric section would be clearer if it referred back to the Indication Section as it is unclear that the product was approved for a pediatric indication. Additionally, the Pediatric Use Section 8.4, should have a cross-reference to the pediatric studies described in Section 14 (Clinical Studies).

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to ongoing safety monitoring.

Aldara (imiquimod) Standard Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- In addition to planning to update the labeling related to severe local reactions in females with use in the genital area, FDA will continue its standard, ongoing safety monitoring for imiquimod. Does the Advisory Committee concur?

Committee Discussion:
The Committee recommended that more specific language should be added to the label concerning the adverse event "inability to urinate". The committee suggested FDA utilize Section 1.4, "Important Limitation of Use" to communicate that a product not be used in the pediatric population in a certain way. They also suggested for all product labeling, that Section 1, "Indications" should have a subsection as referenced with this product, "1.5 Unevaluated Populations", which specifically noted when there had been no studies in the pediatric population. Additionally, the Committee recommended that the Patient Information Sheet include a similar statement concerning lack of effectiveness in <12 year old patients as mentioned in the professional component of labeling.
Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to ongoing safety monitoring and the addition of the information concerning inability to urinate.

Sandostatin (octreotide) Expanded Review of Adverse Events-Outside Speaker Presentation
Rama Bhat, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
Committee Discussion

- The Advisory Committee discussed product use in the medical and teaching facilities and duration of use.

Sandostatin (octreotide) Expanded Review of Adverse Events-Sponsor Presentation
Todd Gruber, M.D., M.P.H., Head, U.S. Medical Function, Novartis
Committee Discussion

- The Advisory Committee thanked Dr. Gruber for his presentation.

Sandostatin (octreotide) Expanded Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- One approach FDA is considering is to (1) revise labeling to clarify there are no approved pediatric indications and (2) remove the description of the 49 published case reports from the octreotide Injection labeling. FDA will continue its standard, ongoing safety monitoring for octreotide. Does the Advisory Committee concur with the stated approach?

Committee Discussion

The Advisory Committee discussed approaches on educating the community on product use, need for gathering additional data, and partnerships with other stakeholders on obtaining additional data.

Committee Vote and Recommendations

- Eleven (11) committee members unanimously agreed (1 member not present) to the following recommendations to FDA:
    1. Revise the label to include the statement "Safety and effectiveness have not been demonstrated in children";
    2. Harmonize existing labeling concerning the pediatric population, specifically to remove the forty-nine (49) case reports cited in the octreotide injection labeling;
    3. Include in the label information about serious pediatric adverse events reported to the Agency and acknowledge that no causal association has been established;
    4. Work with NIH and/or other stakeholders to develop a systematic prospective/retrospective review for information on actual use and adverse events of off-label use in the pediatric population.
    5. Once information is collected and reviewed, FDA should provide a follow-up report to the Committee.

Ethics Discussion

Robert "Skip" Nelson, M.D., Pediatric Ethicist, OPT, OC, FDA

Committee Discussion

- The Advisory Committee thanked members of the Pediatric Ethics Subcommittee and accepted the report from the Pediatric Ethics Subcommittee.

The meeting adjourned at approximately 4:15 p.m.

Please see transcript for details

I certify that I attended the November 18th, 2008 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

Carlos Peña, Ph.D., M.S.
Executive Secretary

Marsha Rappley, M.D.
Chair

EXHIBIT C

EXHIBIT C

U.S. FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

TUESDAY,
NOVEMBER 18, 2008

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The meeting was held in the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland, at 8:00 a.m., Marsha D. Rappley, M.D., Chairperson, presiding.

COMMITTEE MEMBERS PRESENT:
MARSHA D. RAPPLEY, M.D., Chairperson
CARL D'ANGIO, M.D., Member
AMY J. CELENTO, Patient-Family Representative
AVITAL CNAAN, Ph.D., M.S., Member
LEON DURE, M.D., Member
HENRY FARRAR, M.D., Pediatric Health Organization Representative
BRAHM GOLDSTEIN, M.D., MCR, FAAP, FCCM, Industry Representative
MARK HUDAK, M.D., Temporary Voting Member Consultant
MELISSA MARIA HUDSON, M.D., Member
KEITH KOCIS, M.D., M.S., Member
KATHLEEN J. MOTIL, M.D., Ph.D., Member
DANIEL NOTTERMAN, M.D., Member
ALEXANDER T. RAKOWSKY, M.D., Member
GEOFFREY L. ROSENTHAL, M.D., Ph.D., Member
ELAINE VINING, Consumer Representative

FDA PARTICIPANTS PRESENT:

CARLOS PEÑA, Ph.D., M.S., Executive Secretary
OZLEM BELEN M.D., Division of Special Pathogens and Transplant Drug Products
VICKY BORDERS-HEMPHILL, Pharm.D., Office of Surveillance and Epidemiology
BILL BOYD, M.D., Division of Anti-Infective and Ophthalmology Products
PATRICIA BROWN, M.D., Medical Officer, Division of Dermatology and Dental Products, Office of New Drugs, CDER
FELICIA COLLINS, M.D., M.P.H., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
JUDITH COPE, MD, MPH, Medical Officer, Office of Pediatric Therapeutics
SUSAN CUMMINS, M.D., M.P.H., Senior Science Advisor, Pediatric and Maternal Health Staff
CAROLE DAVIS, D.O., M.P.H., Division of Neurology Products
IDA-LINA DIAK, Pharm.D., Office of Surveillance and Epidemiology
ELIZABETH L. DURMOWICZ, M.D., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
NORMAN HERSHKOWITZ, M.D., Team Leader, Division of Neurology Products
DEVANAND JILLAPALLI, M.D., Acting Team Leader, Division of Neurology Products
THOMAS LAUGHREN, M.D., Director, Division of Psychiatry Products
NAOMI LOWY, M.D., Medical Officer, Division of Metabolism and Endocrinology Products
LISA MATHIS, MD, Pediatric & Maternal Health Staff, Office of New Drugs, CDER
MITCHELL MATHIS, M.D., Deputy Director, Division of Psychiatry Products
ANN McMAHON, M.D., Office of Surveillance and Epidemiology
DIANNE MURPHY, M.D., Director, Office of Pediatric Therapeutics, OC

FDA PARTICIPANTS PRESENT (Continued):

ROBERT "SKIP" NELSON, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, OC
PHILIP SHERIDAN, M.D., Medical Officer, Division of Neurology Products
AMY TAYLOR, M.D., M.H.S., Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER

ALSO PRESENT:

RAMA BHAT, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
TODD GRUBER, M.D., M.P.H., Head, U.S. Medical Function, Novartis

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P R O C E E D I N G S

(8:03 a.m.)

CHAIRPERSON RAPPLEY: Well, good morning, and thank you to everybody for coming out today.

I think we'll start with introductions. Amy, would you mind if we start on your end?

MS. CELENTO: Amy Celento, patient representative.

DR. CNAAN: Avital Cnaan, statistician, Children's National Medical Center.

DR. D'ANGIO: Carl D'Angio, neonatologist, University of Rochester.

DR. DURE: Leon Dure, child neurologist, University of Alabama at Birmingham.

DR. FARRAR: Hank Farrar. I'm the pediatric health organization representative, and I'm a clinical pharmacologist at Arkansas Children's Hospital.

DR. GOLDSTEIN: Brahm Goldstein. I'm the pharmaceutical industry representative. I'm a pediatric critical care physician, and I work at Nova Nordisk in Princeton, New Jersey.

DR. HUDSON: Melissa Hudson, pediatric oncologist, St. Jude Children's Research Hospital in Memphis.

DR. KOCIS: Good morning. Keith Kocis from the University of North Carolina, and I'm a pediatric cardiologist and intensivist.

DR. MOTIL: Kathleen Motil from Baylor College of Medicine. I'm a pediatric gastroenterologist.

DR. NOTTERMAN: Daniel Notterman from the Department of Molecular Biology at Princeton University, and I'm also a pediatric intensivist.

CHAIRPERSON RAPPLEY: Marsha Rappley. I'm Chair of the Committee, and my area is developmental and behavioral

pediatrics.

DR. PENA: Carlos Pena, senior science policy analyst, FDA, and Exec. Sec. to the Pediatric Advisory Committee.

DR. ROSENTHAL: good morning. My name is Geoff Rosenthal. I'm a pediatric cardiologist and an epidemiologist from the Cleveland Clinic.

DR. RAKOWSKY: Good morning. My name is Alex Rakowsky. I'm the IRB Chair at Nationwide Children's Hospital, Columbus Ohio.

MS. VINING: Good morning. I'm Elaine Vining. I'm the consumer representative of the Committee.

DR. HUDAK: Hi. I'm Mark Hudak. I'm a neonatologist from the University of Florida, Jacksonville.

DR. LISA MATHIS: I'm Lisa Mathis. I'm Associate Director in the Office of New Drugs within CDER at the FDA for the Pediatric and Maternal Health staff, and I'm a general pediatrician.

DR. MURPHY: I'm Dianne Murphy. I'm the Director of the Office of Pediatric Therapeutics in the Office of the Commissioner, and I'm a pediatric infectious disease specialist or I was about ten years ago before I came to the agency.

DR. BOYD: Hi. I'm Bill Boyd. I'm an ophthalmologist in the FDA's Division of Anti-Infective and Ophthalmology Products.

DR. COPE: I'm Judy Cope. I'm a pediatrician, adolescent medicine specialist, epidemiologist in the Office of Pediatric Therapeutics.

CHAIRPERSON RAPPLEY: Dr. Pena has some words for us.

DR. PENA: Good morning to members of the Pediatric Advisory Committee, public attendees, and FDA staff. Welcome to this meeting.

The following announcement addresses the issue of conflict of interest with regard to today's discussion, reports by

the agency as mandated in Section 17 of the Best Pharmaceuticals for Children Act on adverse event reports for Betoptic, Aldara, Lamictal, Levaquin, Sandostatin, Zyprexa, Risperdal, Lamisil, Timolol, and Ambien.

The Committee will be provided a written follow-up report on Zyvox as requested by the Committee at the November 16th, 2006, Pediatric Advisory Committee meeting.

The Committee will also be updated on other activities, including the June 9th and 10th, 2008, Pediatric Ethics Subcommittee meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the Committee participants, it has been determined that Committee participants do not have financial interests that present a potential for conflict of interest at this meeting. In general, the Committee participants are aware of the need to exclude themselves from involvement in discussion of

topics if their interests would be affected, and their exclusion will be noted for the record.

We would like to note that Ms. Amy Celento is participating at the pediatric health care representative. Ms. Elaine Vining is participating as the consumer representative, and Dr. Hudak is participating at a temporary voting member.

We would also like to note that Dr. Brahm Goldstein is participating as a non-voting industry representative acting on behalf of the regulated industry.

Dr. Henry Farrar is participating as the non-voting pediatric health organization representative, acting on behalf of the American Academy of Pediatrics.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

We have one open public comment period scheduled for approximately 1:30 p.m.

I would just remind all to turn on your microphones when you speak so that the transcriber can pick up all that you state and turn them off when you're not speaking.

I also request that all meeting attendees turn their cell phones and BlackBerries to silent mode.

Thank you.

CHAIRPERSON RAPPLEY: Dr. Murphy.

DR. MURPHY: First of all I wanted to again thank everybody -- I'm afraid our IT person is going to have to find my slides on here for me -- for being here this morning and for agreeing to the four set dates that we have for this coming year as far as time commitments on your agenda, in addition to the other meetings that we've also asked this very busy Advisory Committee to participate in.

One of the things we're going to do this morning is to look at the agenda from the

perspective of your new work load, and we're going to do this because we have good news and bad news. The good news is that children are after a decade now of legislation and new legislation that's reinforcing this approach finally getting studied or at least they're getting the products that are being used in the pediatric population, are finally getting studied, and we have a lot of activity going on in the way of pediatric trials.

That brings with it, of course, the responsibilities of making sure that these trials are well designed and implemented ethically, and you are involved in a number of those issues, have been in the past, will be in the future, and this Committee also being specifically mandated to look at the safety, post marketing safety of these products after they have been granted their exclusivity under BPCA and now under FDAAA, which gets to your workload issue, for all of the products that are studied under either BPCA or PREA, and the

products that will be labeled as the new legislation says, because pediatric studies are so limited in number that any study done under these initiatives will have its results commented on in the labeling so that the public will be aware and the practitioners and prescribers that at least some study has been conducted and what the results of that study are.

And I comment on that, again, because it is unlike the adult universe at FDA where if you have a negative study, the information doesn't normally go in the label, but for pediatrics, the outcome of a negative or inconclusive study will now be recorded in the label. And the labeling is what's going to trigger your safety review.

What the Food and Drug Administration's Amendments Act are so fondly called, FDAAA, has done for you, has expanded your responsibilities to include, as I said, pediatric safety reviews for products studied

and labeled under the Pediatric Research Equity Act, and what this slide should say, in addition to your already identified responsibilities to do such under the Best Pharmaceuticals for Children's Act.

The requiring labeling about pediatric studies performed under these, as I've said, will be specifically noted irrespective of the outcome or approval status, marketing status for that product, for those studies for that product.

This has more than doubled your workload, and just to hammer home this, from June of '03 to March of '08, there have been 79 products that have been reviewed at 13 sessions. You have basically reviewed two to 16 products per session, and the only reason we've limited the number of products to two sometimes is because you've had additional issues to deal with, be it an ethics issue or a science issue or a protocol design issue at a meeting, and so we've only had time for a

couple of products.

Otherwise, most of the time we're bringing between eight to 11 products to you at each session. We tried to bring you the infamous 16-wheeler or 16 products one time. There was just so much information because each product comes with basically five different documents -- you can do the math -- that you had to plow through that you asked us to please not do that again.

I told you yesterday that we weren't going to do it again, and then I turned around and said, well, we really are and it's actually going to be 19, but we're going to do it in a different way, and we'll get to that in a minute.

So in five years you had 79 products that you reviewed. We still have 11 products remaining that need to be reviewed from the BPCA. Since FDAAA has been enacted in September of 2007, we have 36 new labels. We have more than that since I prepared this

slide, but actually 36 new labels so that you have 47 products that will need to come for review before the end of 2009.

We're going to actually do some of those today, but the point being there were almost 80 in five years, and you're now going to have approximately 40 in one year. So it doesn't take very much to figure out you're going to be very busy, and that these product reviews will now include biologics and vaccines as far as the safety, and there are additional responsibilities for devices, which we reviewed in your training session yesterday.

We will before the end of 2009 be bringing some biological products to you in vaccines, and yesterday you received some additional information and training on how those safety reviews will be different or the same.

We've had this issue of trying to make this process more efficient and

fundamentally the previous Committees have said don't just give us the top 20 adverse events. Give us the serious and life threatening adverse events and the deaths. We want to see all of those reported to us.

And you have struggled with how to put all of this in context when you don't really have a good numerator or denominator, and we reviewed yesterday for you in your training session the agency's approaches to trying to provide that kind of information for you.

Some of that comes in the form of trying to put these adverse events in context, and so we provide you a very, very succinct and summary review of what the exclusivity studies were, focusing on the safety component. We will be doing that for the PREA studies also, pediatric studies under PREA, again, focusing on the safety issues that may have arisen during those control trials in addition to the adverse events.

We also and by law now look at -- we have always been mandated to look at all of the adverse events for adults and children, but now the law also says since marketing. So we try to put in context for you the adverse events that are pediatrics in the context of what's been happening with the product both for adults and since marketing. That is a big task, and we try to condense it down for you and pick out, again, those areas that we think need to be focused upon, and that's why you will see sometimes in these reviews the safety reviewer who will say we've been asked to focus on the following. It's because we get together with the divisions and the pediatric staff and the safety reviewers and talk about what are the issues that might be already existing with these products.

It doesn't mean that you can't bring up another topic, but that's just the consensus within the agency of where we think the issues might be.

The other thing that we've done in the past is we've tried to classify the reviews, the presentations -- let me correct that -- the presentations into three categories: either an abbreviated presentation, a standard presentation, or an expanded presentation.

The Committee made it very clear to us that they were all right with us having shorter presentations as long as they got all of the materials to review, and that's going to be relevant to the next process that we're trying to implement.

So what we had been doing is we've been giving you very brief presentation for the abbreviated products, not going through all of the exclusivity studies, not going through all the background with them, and all I can tell you is maybe it's just human nature. Maybe it's that we always find it interesting. Our brief presentations we're expanding. We found that we really weren't

getting a real reduction in time and effort, and we were spending time on products that didn't really have any signals and really didn't have any issues.

So what we are now proposing is that if we have identified a product as abbreviated, you will get the full package that you always have, but we are not going to do a presentation. These are products that we've identified as not having any signal at all, not even a question, not a lot of deaths. Sometimes there are hardly any use.

So what we will be doing is you'll see today for the ophthalmologic products that we are going to put up a slide and ask you if you have any questions that have resulted from your reading of the materials that we've sent you for those products which have been identified as abbreviated.

So because the law wants to make sure that we have public input into this, you will have an opportunity to ask questions, but

we aren't going to do a presentation.

The other thing that is happening is that follow-up reports that you have asked us for, if they do not have any signal or we have no, you know -- you asked us to monitor to see if there were any continuing deaths or serious adverse events and we really don't have anything that's remarkable that we can report back to you, we are going to do the same thing for those follow-ups.

Instead of standing up and going through the whole history of what has happened, we're going to provide you that information in the package, but we are not going to do a presentation. We will put up a slide and ask you if you have any questions, and there will be an opportunity for you to ask questions, and you will see that we've done that for Zyvox today.

The standard will be the same. Now, we say standard or expanded. Does that mean we identify the signal? The answer is

no. It means that it's a complicated review because either the underlying disease has a lot of deaths or a lot of complications, people are on a lot of concomitant meds, there are a lot of adverse events, there's a lot of use; it's just something we don't feel comfortable saying we don't think it needs a public presentation.

Often you'll see the majority of the products that we present to you, over 67 percent of them will have a recommendation just to return to routine monitoring, but we feel that because of the complexity of the disease and the adverse event reporting that we need to at least have a public discussion.

This is something for you to be thinking about because you're going to see we're going to ask you for feedback in the future. Is there anything that we should be doing with the standard reviews to somehow reduce that type of time utilization?

The expanded may be a new product

that's come or it may be one like we have today for octreotide where the Committee struggled with the issue of does this product have any relationship to these adverse events that we're seeing in the necrotizing enterocolitis, the hypoxia.

And they said okay. There was a good discussion. The Committee really could not come to any conclusions and said we have some recommendations about labeling at this point, but if we do that, we want to make sure that it's clear that we're not making any causality statement.

And you asked us to continue reviewing and bring it back to you. So in an effort to bring that discussion to some sort of conclusion, we've brought in a neonatologist who is involved with this product to discuss what's going on out there in neonatal medicine and the use of this product, and then we've given you the background information on the discussion

before, and we'll be asking you today for your recommendations.

So that is how we're approaching the future. The abbreviateds are being even more abbreviated. There will be no presentations. You will be receiving packages for reading only from the follow-ups. There will be opportunities for comment, but we are hoping to reduce the time that we are spending and, therefore, the number of days of meetings that we have to have you here because we know there are other ways that we'd like to use your time.

Now, as I said, we've already asked you to hold four dates for this year. We know you have other things to do besides safety review, and the approach that I've just described, however, helps us with some of the time management for scheduling how much time we need you here, but in truth, it does not decrease your work burden. You still have to read all of the background material, you know,

look at the five different documents that comes for every single one, and for some of them that are expanded, you'll be getting literature reviews. You may be getting extra safety reviews. You may be getting extra materials. So it really doesn't reduce your time.

And so we are going to be asking you after our June meeting, which you are going to receive approximately, we think at this time, around nine products with an abbreviated review, plus the others which will be somewhere between the standard and expanded, where we'll be asking you to be providing us feedback as additional ways to make this process more effective or efficient so that we don't undermine the intent of this, which is that there is a focused pediatric review.

Because you saw in your training yesterday that the adverse event reporting for the agency is going up overall, but not for

kids, and it's a very little, teeny part of the adverse event reporting, and if you don't go in and retrieve it and pull it out and look at it separately, you're not going to find signals for children.

So that's the intent of this process. We don't want to undermine that. We want it to be a robust process, but we have to face the reality that you guys can't have additional housing in Washington so that you can be here all the time to do the safety reviews.

So on to today. You're going to get the follow-up report only or you already got it for Zyvox. We'll have an abbreviated presentation for the two ophthalomogic products, Betopic and Timolol, and these, I'm not going to read the list of all the products for a standard review and one expanded update.

You're one of the busiest of FDA's Advisory Committees, and as you know, we appreciate your commitment and expertise, and

we figure that working together we will solve this problem. I know with all of the good minds around this table, we'll figure out a way to make this a robust process that focuses on the things that are really necessary to focus upon.

And, again, we look forward to your discussion today, and thank you very much for your time.

Now, Judith, do we have the first slide? Do you want to come up and put the slides up?

CHAIRPERSON RAPPLEY: While Dr. Cope is getting ready, I just want to make a comment that I will try to keep us on schedule and on time in respect of everybody's time today.

Thank you.

DR. COPE: Okay. In your package, you should have gotten a follow-up report on Zyvox or linezolid. So as Dr. Murphy said, we're starting the abbreviated review. This

was a follow-up from I believe it was November 2006.

There was a question of cardiotoxicity and overall there wasn't any safety signals or concerns. So we're asking you if you had any questions about the report. Yes.

DR. KOCIS: Of course I'm going to extend this from the beginning. So actually I agreed with the conclusions about the review for the peds review and the lack of cardiac toxicity, but then I get to the end and then I see that the FDA is requiring a clinical trial to look at prolonged QT. So there set me back a little bit in examining the cardiac cases that I reviewed and didn't feel there was a signal to now. Is there information that I need to know or will know or other information that could change what I'm going to say?

DR. COPE: Okay. We have somebody sitting here from the division. I think that my interpretation was that was all ages, but

I'm going to let Dr. Boyd. Would you like to come up?

DR. BOYD: Sure. I'm Bill Boyd. I'm an ophthalmologist, but I'm in the same division as the anti-infective folks. They're at a different advisory meeting. Let me try to answer that.

I spoke with the Deputy Division Director, and the reason that they requested that study is the explanation was at the time they did the original studies for the approval of the product, they didn't have the methodology in place to do this type of testing. They want to be complete. They're not convinced that because of the severity of illness in the population that they're studying that they're going to be able to determine if there's absolutely no safety signal. It's part of a mechanism they prefer to go ahead and just have the trial performed, but it is going to be all ages.

DR. KOCIS: And I just bring that

up because any time you're looking at sudden in children and prolonged QT being a rare event, it would be in the same light. So I'm glad they're going to look at that and particularly look at it in children.

DR. MURPHY: I thought you all might ask that because again, it is a confirmatory approach. It's trying to be as thorough and gather as much data as they can, but at this time we really couldn't see any signals.

Somebody was talking about all of the acronyms yesterday. When I was re-reviewing that last night, you know, all of those acronyms in the data mining are explained in the back. So I do hope you got to the back of that review.

Okay. Thank you.

So we, therefore, will return this product to the Committee if anything comes from that review when those studies come in, because I think that's what the recommendation

from the OSE said, and otherwise we will not be bringing it back to you.

Is that acceptable?

CHAIRPERSON RAPPLEY: Anybody opposed to that?

DR. GOLDSTEIN: I have a quick question and follow-up to Dr. Kocis. Given the rarity of these events, is that request feasible?

DR. MURPHY: The study you're talking about?

DR. GOLDSTEIN: Yes.

DR. MURPHY: Do you want to make any comments on that?

DR. BOYD: My understanding with our QT study group is that the request is it is possible it will achieve its objective. I know that the protocol has been submitted and is with that group now for review. I actually don't have more information than that, but my understanding is it has the potential to answer the question they're asking.

CHAIRPERSON RAPPLEY: Thank you.

Next.

DR. COPE: Okay. As Dr. Murphy talked about, this is another abbreviated slide we have in your package, are two ophthalmologic products, the betaxolol HC ophthalmologic suspension, or Betopic, and the timolol gel forming solution.

And with the reviews that you received and all of the work that the team has done, we see that FDA will continue its standard ongoing safety monitoring for these products. That would be the FDA plan, and so I ask you: does the Committee concur?

CHAIRPERSON RAPPLEY: Question?

DR. KOCIS: Again, I just have another process question on both of these drugs, and again, I agree with the safety of them, but I was confused. I remember talking about this the first time we looked at the drugs.

When we talk about safety and

efficacy, you use the phrase that efficacy has been extrapolated from the adult data for both of these drugs, and I'm left in looking at the adult data that's shown in the package insert where the drop in the IOP was much greater than the data that were presented for the drop in the intraocular pressure in children.

I'm not an ophthalmologist, and I don't know what to expect for things like that, and while clearly there's a statistical difference in intraocular pressure, in the pediatric trials that looked at this, it wasn't of the same degree as it was at least in the charts in my reading of the adult data.

And so I'm confused as to why we're splitting efficacy and safety in children or why we don't report the efficacy findings under the pediatric section along with the safety rather than deferring to the adult data to support efficacy.

CHAIRPERSON RAPPLEY: Dr. Boyd.

DR. BOYD: Let me make sure I

understand your question. You are asking about the difference in the IOP lowering effect in children versus adults, and it is difficult to measure IOP in children. It doesn't mean it can't be done and it doesn't mean it's not accurate. There's just a tremendous amount of information on adult IOP lowering versus pediatric patients.

We routinely, when we have studies, do not specifically request that children be excluded. So some of the newer trials have far more children than some of the older.

As far as why is there a difference in the IOP lowering amount, I don't have a good answer for you, other than I think it's a statistical effect. There's no reason for me to suspect that there's a mechanistic reason for the IOP lowering effect to be different.

DR. KOCIS: My only point is that when you look at the adult data, my read -- I'm not an ophthalmologist and I don't want to try to interpret these, and I believe efficacy

was proven both in adults and in children based on the approval process.

What I'm saying though, if you're extrapolating pediatric efficacy based on the adult data, my read on the significance on the drop in IOP and adult data is, you know, a lot different than what numbers we're seeing for the drop in IOP in children, and my only point would be I would say in the pediatric section specifically what the decrease in IOP was from these studies just because we have the data; you know what the numbers are. How you interpret it as an ophthalmologist, I'll leave that to you, but I don't want to mislead pediatric practitioners that you're going to see the same effects in the adult studies in the pediatric studies because at least my read of the data, that's not the case, and again, I think there's lots of reasons to think that increased intraocular pressure in children, neonates, et cetera, can be a very different disease than adults.

DR. MURPHY: Okay. So I just want to clarify because yesterday during training we talked about extrapolation. So you're not really asking about the extrapolation. You're accepting that the division said they can't extrapolate because the disease is similar and they often expect the same response.

Your question is why that response is different.

CHAIRPERSON RAPPLEY: No.

DR. MURPHY: No?

CHAIRPERSON RAPPLEY: I hear Dr. Kocis' question as we have pediatric data. So why don't we comment on that data in the label?

DR. MURPHY: Well, that's what I was getting ready to say. Why don't we say something about the difference? It's not whether you can extrapolate. It's that you did extrapolate, but you had data that showed that the response -- remember if you go through extrapolation, you meet those two

criteria of the disease and the response or you think it is and you do hypothesis testing and you see that it does, which is sort of the situation which you're describing now, and you have differences. So why not put that in the label?

But that's your question. It's not a safety question. It's a labeling question.

DR. KOCIS: It's specifically a labeling question, and the consistency of the safety and efficacy from the peds data being in the peds label rather than splitting it and saying, well, we're going to show efficacy from the adult studies, but then safety from the peds studies. It's incongruent in my thinking.

DR. LISA MATHIS: I think one thing to be really careful about is when the pediatric studies are intended to support extrapolation, they are not powered to demonstrate the same effect as you're seeing in adults. So it may be misleading to put the

information in there in a way that seeks to directly compare the efficacy.

So I hear what you're saying. Maybe next time we'll look at this and consider putting the data into the label, but we'll have to do it in a way that doesn't mislead clinicians and patients to believe that there perhaps is less efficacy in the pediatric population simply because the studies weren't powered to demonstrate that.

DR. KOCIS: I would just go back to we have pediatric data which is rare, and when we have it, we should include it and then clearly we can put all of the caveats that there's power to show this and there was a range of effect and, you know, put it into the clinical context, but we have the data, and it seems less than ideal to not include it in the label.

CHAIRPERSON RAPPLEY: Dr. Mathis, when would be the next time when you referred to next time?

DR. LISA MATHIS: Perhaps the next time a product comes in. I'm not sure if going back and changing this label that was actually done a year ago is going to provide any clinical benefit to patients. So I'm saying the next time that a product comes in or the next time perhaps that this product comes in with another application, that might be a time to address it.

But from a workload standpoint I'm not sure how much bang we'd get for our buck going back and changing this label. I don't think that that's the intent of this Committee either.

CHAIRPERSON RAPPLEY: Dr. Kocis, do you feel you've made your point?

DR. KOCIS: Yes, I've made my point.

CHAIRPERSON RAPPLEY: Thank you.

DR. KOCIS: You know, the pediatric labeling, I know that that's our focus to strengthen that part, and I think we can

strengthen it in these two drugs.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: I guess the message back to the division from the Committee, if I can summarize, is that in light of the intent to get information in the label, even when you are extrapolating, if there's a way when you see differences like that in that part where you're doing, again, I call it hypothesis testing that you can extrapolate and you have the data; if there's a way to put it in the label so that physicians understand because I think Lisa's point is really critical that it's not that it was inferior. It's just that it was limited data, and it had an effect, okay, and this is the range of the effects.

That would be the recommendation of the Committee for future approaches to the labeling of these products.

CHAIRPERSON RAPPLEY: Maybe any time we have pediatric data we would like to be able to refer to it with all of its

limitations clearly described.

DR. BOYD: For whatever reason when people study IOP lowering drugs, it's very common to see one or two millimeters of decrease even in people who receive the placebo all the time. So that's some of what you're seeing with the pediatric data. There just aren't as many patients, but I understand what you've brought up today, and I'll take that back to the division.

CHAIRPERSON RAPPLEY: So the question before us then for these two medications, that is, betaxolol and timolol, the statement is FDA will continue its standard ongoing safety monitoring for these products. Does the Committee concur?

Is anyone opposed?

So there is consensus on the Committee.

DR. COPE: Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Our next is Risperdal and Dr.

Collins.

DR. MURPHY: Just before we go forward, Lisa made a point which I think we brought it out yesterday, but let's put it in the public realm since we did mention it yesterday about the opportunity now. We have with FDAAA for reviewing labeling. Do you want to address that, Lisa?

DR. LISA MATHIS: We do have the Pediatric Review Committee now. So we do look at labeling prior to approval, and so there will be more opportunity to provide feedback to the divisions before approval occurs, and I think that we actually are trying to make sure that data does get into labeling if we have it.

So we'll address that in the future. I just want you to know that we have more opportunity to do that now.

DR. MURPHY: And, Marsha, because actually we failed, meaning FDA failed, to ask to do this one time and it resulted in the

Committee not being aware, the people at the table, I wanted to make sure that when we have the different people come up for the different products that we're introducing the speaker, but I'd also like to have the people at the table from the division who are here to please introduce themselves.

DR. LAUGHREN: I'm Tom Laughren. I'm the Director at the Psychiatry Products Division.

DR. MITCHELL MATHIS: And I'm Mitchell Mathis, the Deputy Director of that same division.

DR. MURPHY: Tom, would you just tell them your background?

DR. LAUGHREN: I'm a psychiatrist by training, and I've been with FDA roughly 25 years.

DR. MITCHELL MATHIS: I'm a psychiatrist and family practitioner by training, and I've been with FDA for about eight years.

DR. MURPHY: Felicia, would you introduce yourself, please?

DR. COLLINS: Sure. Good morning, everyone. My name is Dr. Felicia Collins. I am a general pediatrician within the Pediatric and Maternal Health staff with the clinical practice area exclusively in adolescent medicine.

And this morning I'm pleased to be able to present to you the one-year, post exclusivity adverse event review for risperidone.

Oral Risperdal, or risperidone, is an atypical antipsychotic for which Janssen is the drug sponsor. Original market approval occurred on December 29th, 1993, and pediatric exclusivity was granted on February 28th, 2007.

Prior to the pediatric exclusivity studies, oral Respirdal was indicated for the treatment of schizophrenia in adults, the short-term treatment of acute manic or mixed

episodes associated with Bipolar I Disorder in adults, and the treatment of irritability associated with autistic disorder in children and adolescents.

The next two slides provide information about the use of risperidone in out-patient settings. Seven, point, eight million oral risperidone prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. Ten percent of these prescriptions were for adolescents, 13 to 17 years old, and 15.5 percent were for children zero to 12 years old.

There was a two percent increase in prescriptions for all age groups between the 12-month pre and post exclusivity period and a ten percent increase for the pediatric population. Psychiatry was the top prescribing specialty during the post exclusivity period. All psychiatrists prescribed 53.4 percent of all oral

risperidone prescriptions. Child psychiatrists prescribed 11.4 percent of all prescriptions. Pediatricians prescribed 3.6 percent of all prescriptions and child neurologists prescribed one percent of all prescriptions.

The top diagnosis codes associated with oral risperidone use by children zero to 17 years old were infantile autism and attention deficit disorder.

On November 25th, 2002, the FDA issued a written request for studies of oral risperidone in the acute treatment of schizophrenia in pediatric patients 13 to 17 years old and in the acute treatment of mania and Bipolar I Disorder in pediatric patients ten to 17 years old.

The resulting pediatric exclusivity studies included five studies: one pharmacokinetic study, three efficacy and safety studies, and one safety study.

The results of the submitted

pediatric exclusivity studies indicated that risperidone is effective and reasonably safe for the studied indications in pediatric patients.

The following two slides list all of the labeling sections that were changed based on the results of the pediatric exclusivity studies. Changes were made to the indications and usage section, dosage and administration section, adverse reaction subsection on commonly observed adverse reactions in placebo controlled clinical trials on discontinuations due to adverse reactions and on changes in ECG to the use in the specific population section, pediatric use subsection, and to the clinical study section.

The next five slides will provide details of selected labeling changes. The indication and usage section was changed to extend the schizophrenia indication to adolescents 13 to 17 years old, and to extend the bipolar mania indication to children and

adolescents ten to 17 years old.

The dosage and administration section was changed to note that no additional benefit was seen above three milligrams per day in the schizophrenia studies or above 2.5 milligrams per day in the bipolar mania studies.

In addition, this section notes that for both indications higher doses were associated with more adverse events.

The adverse reaction section, discontinuations due to adverse reaction subsection was changed to note that for the schizophrenia studies approximately seven percent of patients discontinued in the risperidone group versus four percent in the placebo group.

Adverse reactions associated with study discontinuation in the risperidone group included somnolence, dizziness, anorexia, ataxia, hypotension, and palpitation. This subsection also was changed to note that for

the bipolar mania studies 12 percent of patients discontinued in the risperidone group versus seven percent in the placebo group. Adverse reactions associated with study discontinuation in the risperidone group included somnolence, nausea, abdominal pain, and vomiting.

The use and specific population section, pediatric use subsection was changed to note that for the schizophrenia studies 14 percent reported a weight increase and open label studies, and there was a mean weight increase of nine kilograms after eight months of treatment in 103 adolescents.

For the bipolar mania studies, it was noted that increased body weight was higher in the risperidone group than the placebo group, although not dose related.

This subsection also was changed to note that somnolence was the most commonly observed adverse event in pediatric schizophrenia and bipolar disorder trials. In

addition, the subsection notes that in controlled pediatric schizophrenia or bipolar disorder trials, hyperprolactinemia was seen in 82 to 87 percent of children and adolescents in the risperidone group versus three to seven percent in the placebo group.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports since marketing approval. For pediatric patients there were 1,535 adverse event reports which comprise 7.5 percent of the total reports.

Of these reports, there were 48 death reports with 33 being U.S. cases. Of the 48 crude count pediatric death reports identified since marketing approval, 17 of these were duplicates. Of the 31 unique pediatric cases, four involved an indeterminate cause of death, and the 27 remaining cases involved ten nervous system, nine cardiac system, and eight miscellaneous

cases.

After reviewing the 31 unique pediatric death cases, the safety reviewer did not identify any new safety concerns. There are multiple sections of the drug labeling that are relevant to the pediatric death cases. The warnings and precautions section of the drug labeling include subsections on seizures, neuroleptic malignant syndrome, hyperglycemia, and diabetes mellitus with worsening glucose control, orthostatic hypertension, and suicide.

The adverse reaction section of the drug labeling includes arrhythmia, hypotension, pulmonary embolism, and cardiopulmonary arrest.

The next several slides provide more details for the 27 death cases, and you will note that unlabeled events have been underlined. Of the ten nervous system cases, five cases involve adolescents who died after a seizure or related complication while on

risperidone.

Two cases involve patients with a history of epilepsy and one additional case involved concomitant paroxetine use, which has a labeled seizure association.

The sixth case involved a seven year old who experienced encephalitis, hypotension, arrythmia, and cerebral edema, and died two days after risperidone therapy.

There were three cases involving children who died of neuroleptic malignant syndrome, or NMS-like symptoms while on risperidone. Of note, one case involved concomitant medications with a labeled NMS association.

And the last nervous system case involved a nine year old who died due to a cavernous angioma 12 days after initiating risperidone therapy.

For the cardiac cases, two cases involved children who died from cardiac arrest while on risperidone without concomitant

medications, but these case reports lack significant details.

And two additional cases involve children with congenital heart disease who died due to cardiac arrythmia or sudden death while on risperidone.

The fifth cardiac case involved an 11 year old female who died of myocarditis one month after initiating risperidone therapy.

A sixth case involved a seven year old male who experienced QTc prolongation and died due to a heart attack after initiating therapy with risperidone.

The seventh case involved a 16 year old male with a family history of Protein S deficiency who experienced an upper respiratory infection and a presumed pulmonary embolism and died three months after initiating therapy with risperidone.

And the last two cardiac cases involve an 11 year old and a 16 year old on risperidone who died possibly due to left

ventricular hypertrophy.

The last eight death cases are summarized on this slide. Six of the eight cases involved a single report for an adverse event and n o patterns were identified. The cases include a 14 year old who had a viral infection and cardiorespiratory arrest prior to death and while on risperidone; a 14 and a 12 year old who died from suicide which is labeled association; a 13 year old on risperidone who had pneumonia, septicemia, congestive heart failure, and cardiac arrest and died; an eight year old with diabetes who had a hypoglycemic seizure and died while on risperidone; a six year old who died after an accidental ingestion of multiple medications, including risperidone; a five year old who died after a near drowning within three months of initiating risperidone therapy; and a one year old who died of suffocation after receiving her mother's risperidone.

Now, going back to the table

describing adverse events since marketing approval, for pediatric patients, there were 1,207 pediatric serious adverse event reports with 860 of these being U.S. cases. You will note that the definition of a serious adverse event that was used when identifying these cases is provided in the footnote.

Now, looking at the post exclusivity period for pediatric patients there were 131 serious adverse event report with 42 of these being U.S. reports.

Of the crude count, 131 pediatric serious adverse event reports identified during the post exclusivity period, 15 reports were excluded because they were duplicates. Of the 116 remaining unique pediatric cases, no new safety concerns were identified.

The safety reviewer gave particular attention to 35 cases involving labeled metabolic extrapyramidal and gynecomastia and hyperprolactinemia events to see if there was a qualitative or quantitative difference in

the reports for pediatric patients compared to adults.

Again, there are multiple sections in the drug labeling that are relevant to these selected serious adverse events. The warnings and precautions section of the drug labeling include subsections on hyperglycemia and diabetes mellitus, tardive dyskinesia, and hyperprolactinemia.

The adverse reaction section of the drug labeling mentions extrapyramidal symptoms and gynecomastia.

The 15 metabolic effect cases included cases of increased weight, diabetes mellitus, diabetic ketoacidosis and/or glycosuria. The 14 extrapyramidal cases included three tardive dyskinesia and 11 other extrapyramidal effect cases.

Lastly, there are four gynecomastia cases and two cases of hyperprolactinemia. Again, these events are consistent with current labeling.

This chart describes the various combinations of metabolic serious adverse events that were reported in pediatric patients. You will note that there were three groups of reports for diabetes alone or diabetes combined with another metabolic adverse event.

Of the 81 other pediatric serious adverse event cases during the post exclusivity period, the safety reviewer provided case counts according to the categories listed on this slide. There were 29 cases with labeled events and 53 cases with unlabeled events.

The drug labeling sections relevant to these other serious adverse events are the contraindications section, which includes hypersensitivity reactions, including angioedema, the warnings and precaution section, which includes cerebrovascular events, including stroke and transient ischemic attack, neuroleptic malignant

syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus with worsening glucose control, hyperprolactinemia, orthostatic hypotension, seizures, and suicide.

The adverse reaction section controlled clinical trials subsection mentions arrythmia, bradycardia, and tachycardia, leukopenia, anxiety, tremor, increased SGOT and SGPT, edema, and vomiting.

The post marketing experience subsection includes pulmonary embolism, cardiopulmonary arrest, thrombocytopenia, precocious puberty, angioedema, and pancreatitis, and the drug interaction section discusses how risperidone use can result in increased valproate plasma concentrations.

Of the 53 unlabeled events, no new safety concerns were identified. There were 30 non-therapeutic uses, including accidental exposures, intentional misuse or overdose and poisoning of food, 14 events that involved a single case report, and seven other adverse

event types reported in two to four cases.

Of note, the four cases of agitation during the switch from risperidone to methylphenidate are suggestive of off-label use for attention deficit hyperactivity disorder in which agitation can be part of that disorder.

Lastly, some of the remaining serious adverse events are consistent with schizophrenia or Bipolar I disorder, such as hallucinations, aggression, and self-injurious behavior. However, these events also can be seen in children and adolescents without these psychiatric diagnoses.

This completes the one-year post exclusivity adverse event reporting. The safety review did not reveal any new safety concerns for oral risperidone as the identified adverse events were qualitatively similar to those currently found in the product labeling and described in the adult population.

Therefore, FDA will continue its standard ongoing safety monitoring for oral risperidone. And then the question to you is: does the Advisory Committee concur?

And in closing I just would like to acknowledge the assistance I received in preparing for this presentation from numerous FDA staff in the Office of Surveillance and Epidemiology, the Division of Psychiatry Products, the Office of Clinical Pharmacology, the Office of Pediatric Therapeutics, and the Pediatric and Maternal Health staff.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

We're open to questions.

DR. RAKOWSKY: I have a question for Dr. Laughren, please.

We have a very nice report from Dr. Governale looking at the use of Risperdal over the last three years. In looking at the zero to 12 age range there's been basically a stable use in that age range, but the

percentage of change allowed to have the diagnosis or the coding of infantile autism, is that a code that will be used only for children less than two or is that a diagnosis code that you would use for any pediatric age?

In other words, the question is are we seeing more use in off label, in other words, less than five year olds, based on what we're seeing in the use data.

DR. LAUGHREN: Yes, I don't have an answer to that question. You know, in the division we're not the ones who collect the data on use. Maybe, Felicia, you could comment on that code infantile autism. Is that ICD-9?

DR. COLLINS: Actually I would need to defer to someone in the Office of Surveillance and Epidemiology.

CHAIRPERSON RAPPLEY: Please use the mic.

DR. BORDERS-HEMPHILL: I'm sorry. I'm Vicky Borders-Hemphill.

That is an ICD-9 code that we use, and we only looked at age groups zero to 12.

DR. RAKOWSKY: Would the infantile autism ICD-9 code basically be used for any child with autism less than 12, for example, and still be termed infantile autism, or is that just a subset of younger children of autism that this is being used for?

DR. BORDERS-HEMPHILL: Well, we also saw it as an ICD-9 code for 13 to 17 year olds as well.

DR. RAKOWSKY: So probably more of a broad range.

DR. BORDERS-HEMPHILL: Right.

DR. RAKOWSKY: Okay.

CHAIRPERSON RAPPLEY: Dr. Dure.

DR. DURE: Yes. I have a question for the psychiatry products group, too, because I'm a child neurologist, and I have a bias that extrapyramidal syndromes are really under-recognized with the use of these agents, and I would be concerned or my question is:

is enough being done because to try to at least educate people or do you have a concern about that on your panel?

It didn't take long for me to find out about diabetes mellitus and hyperprolactinemia with these agents a few years ago. I heard about that very quickly, but neuroleptic malignant syndromes, serotonin syndromes and akathisia, things like that. There is a lot of concern in the literature about people's ability to recognize this.

Do you feel like, in your Committee, do you feel like enough is being done to keep the public and the practitioners aware?

DR. LAUGHREN: Well, we think this drug is reasonably adequately labeled with regard to extrapyramidal side effect. You know, it's not really probably FDA's primary responsibility to go beyond that to educate the community.

I think it really falls more to the

various practice associations to educate their members, but you know, we're open to suggestions about what you think we might be able to do to further educate.

CHAIRPERSON RAPPLEY: Dr. Farrar.

DR. FARRAR: I would like to follow up on that because I agree. I think one of the things that I have seen is a lot of very hard to define movement disorders in kids who are being treated off label with this, and this is just my experience in the clinical setting, and I don't have any hard numbers to really say what that means.

And so I thought it was interesting that of the movement disorders, 11 of them were described as other extrapyramidal, and so it sounds like there's kind of this general tendency out there for people to have a hard time deciding what it is. These kids are not fitting really typical patterns it doesn't sound like.

Again, I'm not sure what other

studies need to be done.

One of the other things that I was interested in when I looked through this is that although from looking at the prescribing on page 125, yes, bipolar and schizophrenia are the most common diagnoses for which these drugs are prescribed, but all others is 99,000 or almost half of the use of this.

Again, you all can't set policy. You all can't tell doctors how to prescribe drugs, and so I think you're caught a little bit here, but these drugs are being used, and plus that's in the zero to 12 year group, and so just the data looks like there's a tremendous amount of off-label use of these drugs going on out there.

I'm not sure. I agree there's not much you can do with the label right now because qualitatively what you're seen in your reports and the data you have looks like what you talk about in the label, but I don't know. I'm not sure if we can make a recommendation

or what this Committee can do to try to encourage more study of these drugs, especially in children, because I think there's a lot of off label use and I think there are a lot of side effects that are not fitting into the normal categories very well.

CHAIRPERSON RAPPLEY: Dr. Goldstein.

DR. GOLDSTEIN: Again, this is not my area of expertise, but in reading through the data there clearly is a statement that there's a dose response effect regarding safety, and there's also repeatedly in the label that there is no control data to support long-term use either in schizophrenia, bipolar mania, or the irritability associated autistic indications.

So given that there are significant metabolic effects, CNS effects and cardiac effects, and especially the metabolic effects which one would assume would accrue over time, my questions are, not being a practicing

psychiatrist: what's the typical length of treatment? Do we have any data on the long-term use from the adverse event reporting? Is there any way to ferret that out? Is there a cumulative or is there the possibility that there's a cumulative dose effect?

And then my last question is that when you look at the label statements regarding extended periods, the statement under schizophrenia is different than that under bipolar mania and autistic. The statement for schizophrenia just cautions the physician who uses Risperdal for extended periods of time to periodically reevaluate the long-term usefulness, whereas the statements for bipolar mania and irritability associated with autistic disorder caution to reevaluate long-term risk and benefits.

DR. LAUGHREN: Well, in terms of the first question about long-term safety, it's very difficult to get good, systematic, long-term safety data in anyone, but in kids

in particular. The labeling describes the data that we have, and those are, you know, from open label extensions, and we give some descriptive numbers of what happens. You can't really get long-term control data. In other words, you couldn't do a year long placebo controlled trial and systematically look at the cumulative effects. You can only look at a cohort.

And those are suggestive that there are some cumulative effects, and we've reported that in the labeling, but you know, we agree that these drugs, this drug included among the atypicals, have metabolic burden. You know, they increase weight. They alter lipid profiles. They have effects on glucose, and we think that's important for prescribers to know, and we think the labeling, you know, clearly expresses that concern.

CHAIRPERSON RAPPLEY: Dr. Notterman, then Dr. Kosic, and we have two others in the wings.

DR. GOLDSTEIN: I'm sorry. Why is there a difference in the recommendations to the physician for schizophrenia as compared to the other two?

DR. LAUGHREN: Can you again say exactly what you're referring to?

DR. GOLDSTEIN: It's on page 152 of my booklet under schizophrenia, the last statement, the first paragraph at the top of the page. The physician who elects to use Risperdal for extended periods in adolescents with schizophrenia should periodically reevaluate the long-term usefulness of the drug for the individual patient.

DR. LAUGHREN: Okay.

DR. GOLDSTEIN: But then on page 153 and again on 154 under the bipolar and the autistic sections, the last paragraph on page 153 -- I'm sorry -- the second paragraph, the last sentence on page 153, it says, The physician who elects to use Risperdal for extended periods should periodically

reevaluate the long-term risks and benefits of the drug for the individual patient.

And that same sentence is used for the autistic. So my question is that it just looks like efficacy is being recommended for follow-up under schizophrenia, whereas efficacy and safety is being recommended for the other two conditions.

It just seems to be inconsistent.

DR. LAUGHREN: I'm sure that was inadvertent, you know. It certainly wasn't intended that one wouldn't look at both efficacy and safety long term. So it's something we can consider fixing.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: A review of the prescribing indications shows that there's a substantial amount of prescribing for ADD in the under 12 group, 16.8 percent in the latest dates. And I wonder if in light of some of the toxicities and adverse effects that you've

acknowledged are significant, the metabolic burden, we have given substantially enough weight to these adverse events in light of the off label indications for which the drug is being prescribed.

So by that I mean in balancing the benefit and risk of the drug and the burden of the drug, the balance seems clearly in favor when used for a disorder such as schizophrenia or another psychotic illness.

However, it doesn't seem to favor the use of this agent in certain unlabeled indications, in particular for ADD, and so I guess my question is whether some other action, for example, a notice to prescribers regarding the use in ADD is worth considering in the future.

DR. LAUGHREN: You know, it's hard to tease out from the data exactly what the drug is being prescribed for in kids with ADHD. I suspect what it is is being used for co-morbid either oppositional defined disorder

or conduct disorder since that's in child psychiatry probably the most widely used diagnosis. You can't really tease that out from these data.

But to your question about, you know, what can FDA do in terms of off label prescribing, again, you've heard this many times, but we don't regulate the practice of medicine. Once we put a drug out there, we can clearly say in the label what it is indicated for, you know, what the appropriate use is from our standpoint for those approved indications.

Again, we're open to suggestions, but it's not clear what you would want FDA to do to try and influence the way the drug is used in the community.

DR. NOTTERMAN: Well, I do agree that some of the use at least that I'm aware of is for oppositional defined disorder, but I think there's also substantial use for ADD without those characteristics.

And as for what I think FDA should consider, it is the evaluation of the adverse effects in light of the actual use of the drug, and in particular, to consider whether -- and it may be that there isn't and it may be that you're right and this is misleading coding, but to consider whether there is substantial use by practitioners for this indication in the context of a significant metabolic burden.

I also have one other question related to that, and that is whether or not there's data on QTc prolongation for this agent when used in monotherapy.

DR. LAUGHREN: If you look at the labeling under ECG, there were changes made on the basis of the new data that came out of these studies, which basically says that there weren't any important changes noted other than a slight increase in pulse rate.

DR. NOTTERMAN: So do you know if QTc was specifically included in that

surveillance?

DR. LAUGHREN: Well, ECGs were collected, but of course, this is in the context of a typical clinical trial rather than a thorough QT study. So, you know, it's true that you can't take quite as much away from that as you could from a thorough QT study, but this compound risperidone has been looked at a lot for QT, and it doesn't appear to have much of a signal.

DR. NOTTERMAN: Thanks.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: 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 in -- 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 and what they can do.

My sense of reading this, there are some very serious signals and my read on the labeling is that it's inadequate to those signals that you've known about, we've known about, and it doesn't emphasize the life threatening side effects.

So for me when I read through this -- and, again, I don't use these drugs myself. So it's simply naive as I read through these things -- that I think it's inadequate in labeling for seizures in the sense that it doesn't include -- there are seizures and then there is -- epileptic that's leading to seizures and death. There's the metabolic effects where we talk about hypoglycemia and diabetes, but there's also diabetic ketoacidosis that's not emphasized. I'm not sure if that led to death.

And then the cardiac toxicities were reviewed and apparently they brought in a consultant to review that, and it ties somewhat into the QT studies, and I'm curious

about that, if you acquire the EKGs, why QT studies weren't -- or I don't know the results. Maybe they were done. I don't know what that impact was, but I'm curious as to what the consultant found and reviewed to see if there's additional things we need to monitor.

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.

DR. LAUGHREN: Well, I'm a little puzzled about your statement that labeling is inadequate with regard to some of these serious risks. These are all warning statements, very prominent warning statements.

You know, the statement on hyperglycemia talks about the possibility of ketoacidosis, although I must say that what you're dealing with are individual reports, spontaneous reports of children developing what in many of these cases of ketoacidosis is Type 1 diabetes.

The kind of diabetes that we expect to see with a drug like an atypical antipsychotic which induces weight gain and lipid changes and hyperglycemia is Type 2 diabetes. The end stage of that would be hyperosmolar coma. You see ketoacidosis with Type 1 diabetes.

There's no particular reason to believe that this drug induces Type 1 diabetes. More likely what you're seeing are, you know, the natural occurrence in this age group where it's the peak onset of Type 1 diabetes.

So again, I'm puzzled by --

CHAIRPERSON RAPPLEY: Excuse me.

To that point, I believe I've read in the material that you've compiled for us that there have been spontaneous reports of hyperosmolar ketoacidosis, and that, in fact, people do recognize and accept the risk of Type 2 diabetes with the metabolic syndrome, have been part of the metabolic syndrome.

So I wouldn't want to diminish that as a risk factor because children are also developing Type 1.

DR. LAUGHREN: I totally agree, but again, I'm anxious to hear suggestions about, you know, what more we can do in labeling. It's already very prominently labeled. The same with seizures.

CHAIRPERSON RAPPLEY: I'd like to allow Dr. Rosenthal, Dr. Cnaan and Ms. Celento to speak. Dr. Rosenthal.

DR. ROSENTHAL: Thank you.

I actually am just reflecting on the very high incidence of hyperprolactinemia in the pediatric population. I'm sitting here

wondering what is the effect of that over the years in which these medications are going to be used.

I think the label effectively calls out that high occurrence, but I think my question may relate somewhat to Dr. Kocis' question, and that is 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.

DR. LAUGHREN: That's always a good question to ask. The difficulty, of course, is in trying to figure out how you're going to get an answer to that question. How are you going to mount a trial that allows you to follow a cohort for the years and years that you would need to to gather that information, especially if you wanted to have some kind of a control? It's a challenge.

DR. ROSENTHAL: So I guess I'm not asking the agency to design the study, but 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.

You know, the we don't think of the label as being used in this way, but I'm thinking outside the box, 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.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: In the interest of time, my question mostly mimics Dr. Notterman's question. I am very concerned when I look at the second most prescribed indication being ADHD, as was pointed out in Slide No. 5, and the cumulative effect of everything that everybody has said here. It

is not about the labeling, but if there is anything that the agency can do to decrease, at least, off label use for more mild indication, I think I would greatly appreciate it.

CHAIRPERSON RAPPLEY: Ms. Celento.

MS. CELENTO: I second Dr. Cnaan's comments, and really the comments of everyone else. And I will say that, you know, maybe it's the Google generation and people stopped reading at page one. I don't feel that the metabolic indications or the metabolic effects are highlighted in the label, and I realize there's a standard format for the label, but I don't think those concerns are really broadly raised here for the parent of a pediatric patient.

And, again, some of these drugs are being -- this drug is being used maybe for indications that are off label, and there might be other options.

DR. LAUGHREN: Yes, with regard to

the metabolic issue, I can say that there's a review ongoing within the agency right now looking extensively at the metabolic effects for all of the atypicals. We've pretty much completed our review for the other drug that you're going to talk about here this morning, Zyprexa, and the labeling for that drug, I think, better reflects the metabolic risks.

You know, we expect over the next couple of years to improve the highlighting of the metabolic profile for this drug and the other atypicals, but that review is ongoing.

CHAIRPERSON RAPPLEY: I'd like to make an observation that of the 31 deaths that were described here by my reckoning, 11 of those were associated with off label use. Eleven of those had no diagnosis clearly associated with use, at least in the information available, and six were associated with on label use.

It's also an observation, and I know there's not a really rigorous -- there's

no evidence to be gleaned, but just a signal perhaps. Nine of these deaths were associated with SSRI concomitant use, and 12, including that nine, were associated with antidepressants.

So I wonder if there isn't something that we should be looking at there.

I do think we have an avenue perhaps around our shared concern about off label use and the rapid increase in use. You described to us a ten percent increase in use for children zero to 17 within the last year. What was presented to the Best Pharmaceuticals Committee -- am I saying that right? What's the name of that group that we did in June? No, no, the Best Pharmaceuticals Act for Children -- the Best Pharmaceuticals Children's Act. That committee met in June and risperidone was one of their items of concern, was one of their medications that they asked to be reviewed, and I was assigned to review that as a participant in that

committee.

There was information presented there that based on data in seven states in both Medicaid utilization and commercial insurance utilization, that risperidone, in particular, was used by more than 16 or had a prevalence of more than 16 among Medicaid youth and a prevalence of approximately four among those in commercial insurance.

Now, that data comes from 2001 and 2004. So we all have a sense that this increase that you describe over the last year has actually been cumulative since 2000, those of us in practice.

So I think we share a concern about off label use and a very rapid increase in use of this medication. I say this with the caveat that I think it's a very effective medication, and it is a very powerful medication. I use the word powerful because it has brought an improved quality of life to many, many children who could not experience

that previously.

But because of that, it lends itself to off label use, and I think that perhaps we've not in the past viewed the label or the agency as a tool to influence practice, but we do have a request from the Best Pharmaceuticals for Children's Act to recommend --

DR. MURPHY: This is an NIH committee.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: This is the NIH committee, just so everybody is on the same page as Marsha, that looks at the off -- well, actually they're not just looking at --

CHAIRPERSON RAPPLEY: They're asking what should be future research.

DR. MURPHY: Not looking just off patent, right.

CHAIRPERSON RAPPLEY: Where should research for children and pharmaceuticals focus?

DR. MURPHY: Right.

CHAIRPERSON RAPPLEY: And I think we could take the concern of this Committee to them. We could convey to them that we have a concern about off label use; that we have a concern about long-term effects; and that we have a concern about extrapyramidal effects in this very widely used and increasingly used medication.

And that could then be added to the many people who spoke about the importance of studying this particular medication and this particular class of medications in children.

DR. MURPHY: And I think in that situation you might want to articulate at the end here what are the groups that you think, because I've heard a number, you know, of the proactinemia, the endocrine effects, the, you know, long-term effects, maybe the differences in the metabolic effects going through puberty.

I mean, those are some of the

things that I've heard you say, and, Tom, I think what they're saying is they recognize the agency doesn't really have a mechanism to get those things done unless, you know, this probably came in with a supplement for something that would somehow avail itself to that, but otherwise they're trying to search for other ways to get this done.

I think though the one other thing that we need to make sure, and people have been careful about this, is that your concern -- and we've seen this before with other products -- is that the large off label use in a population that has not been documented to receive any benefit from this product is the concern fundamentally I think I'm hearing expressed.

And I don't know if there's a way. Let me just put it this way. We would not go and put in a label, Don't use this for ADHD. I mean, we can't start doing that. It's not what we would do.

If there were some way of enhancing, you know, the do not use any other way -- I can't think of, Tom -- then you already put in here. You've said if you're going to use it long term, you really need to reassess it and they'll fix the difference that was brought up for that, but don't use it.

I guess the question I'm hearing is is there a way to say if you're using it for anything other than the indications, you need to somehow reassess what you're doing. You know, I don't know if --

CHAIRPERSON RAPPLEY: Can I suggest a sentence and then you tell me if it would be reasonable or not? You know, I'm not asking the agency to step outside its bounds.

But would it be reasonable to say caution should be taken and careful consideration of risk of known side effects with perceived benefit in any off label use? Something like that on that first page where

it's --

DR. MURPHY: Well, I'm sure I can tell you right now --

CHAIRPERSON RAPPLEY: That won't work?

DR. MURPHY: -- the lawyers would not let us do that, and they always get upset when we physicians start to practice law. But, I mean, there's no way they would allow us to put something about off label use.

CHAIRPERSON RAPPLEY: Well, I guess we do have other ways that we can bring to light concerns about off label use of any medication and the kind of increasing prevalence that we see with this one.

We do have other people who would like to comment on this. Are these new comments or are they reinforcing?

DR. DURE: Well, I was asked for any suggestions, and that was a while ago, but I mean, under the use in special populations, the only movement disorder you mentioned is

tardive dyskinesia, which almost never gets described, yet 20 percent of children in the pediatric studies have some combination of a movement disorder, distonia, akethisia, et cetera.

I mean, I would echo that that's inadequate because they can be serious side effects, and I would also take issue. I mean, again, I've heard this, that the FDA does not regulate the practice of medicine, and I'm not suggesting a black box warning, but that is what is done.

And so I think this Committee is a little frustrated because we are trying to figure out a way that we can accommodate this concern of ours, and it's a well founded concern that we have.

CHAIRPERSON RAPPLEY: We do need to take a vote on this question. Can you put the question back up on the screen?

DR. MURPHY: And, Marsha, at the end would you summarize the recommendations of

the Committee because that's the thing we're supposed to get from this Committee.

CHAIRPERSON RAPPLEY: Yes, I will try to do so, and you all can monitor that.

Dr. Notterman is very much wanting to make another comment. So one last comment.

DR. NOTTERMAN: I just wanted to ask a process question. It seems to me that part of the concern is that what actually is subsumed under or within the penumbrae of attentional deficit disorder and other emotional diseases of childhood and all others, what's subsumed under that makes many of us uncomfortable. It may be that there's a large nucleus of labeled indications or at least serious illness that's subsumed there, and that would at least make me more comfortable in evaluating the serious nature of these side effects, particularly the extrapyramidal reactions and metabolic burden and perhaps the cardiac toxicity.

So is it possible for the agency to

learn more about the actual prescribing practices over the next year or so and then report back to us and other committees?

CHAIRPERSON RAPPLEY: So you would be considering followup information would be important to the Committee.

DR. NOTTERMAN: On the actual indications with more precision perhaps in a prospective way.

DR. LAUGHREN: We can go back to our colleagues in Office of Surveillance and Epidemiology, the people who collect data on use, and see if they can get more precise about the uses and the numbers and so forth.

DR. MURPHY: I think that's actually a very helpful way to try to move forward, is to better understand that population, and you heard yesterday about the new databases. Some of them they really have not delved into to understand their functionality as well, and so we can give them an opportunity, as they like to say here, to

maybe try out some of these new systems and databases.

CHAIRPERSON RAPPLEY: So the Committee then needs to vote on the question that one year post exclusivity was completed, and the safety review did not reveal any new safety concerns; that the FDA will continue its standard ongoing safety monitoring for oral risperidone.

So we need to vote on that question, and then I will summarize recommendations from the Committee and you can edit my summary.

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.

Yes.

MS. CELENTO: I think the challenge

is that, you know, there are some of us that are thinking, and more, and so how do you answer yes to this question?

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 followup 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 to see 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;

That we would also like to see

encouragement of further investigation and whatever followup information can be gleaned over the next period of time about extrapyramidal side effects.

Additions to that summary?

DR. MURPHY: I just want to make sure that when you said the followup for the actual use, you want more than a -- I think we need a little more specificity on that because I want to make sure that it is addressing the issue that Dr. Notterman is definite the ADHD population, having more information about that population.

CHAIRPERSON RAPPLEY: So we would like more information about how the medication is actually used and for what indications it is prescribed in as great detail or specificity as you're able to glean from your data sets.

DR. FARRAR: I would like to add that, you know, we're going to have this same discussion in just a couple of minutes.

CHAIRPERSON RAPPLEY: Well, that's correct.

DR. FARRAR: And we'll have it probably every time, and there's a bunch of these drugs, and they're starting to come out. Is there a mechanism to do a class of drugs study where you would look at this whole class of drugs with these questions in mind?

Because we're going to be asking this question over and over again. Movement disorders, metabolic diseases have all been identified with, I think, all of these drugs. We're seeing it a lot with risperidone now just because it was the first to market and we have the most data on it, but as time goes on you're going to see it over and over again with a lot of other drugs, and I don't know if there's a mechanism for doing that or if that needs to be considered as part of the recommendation.

CHAIRPERSON RAPPLEY: So correct me if I'm wrong, but I think that would be a

recommendation that could go to the Best Pharmaceuticals for Children's Act Committee at NIH to look at investigating a class of medications as a priority for the nation.

But for us at the FDA, we have to go product by product; is that correct?

DR. MURPHY: Well, you know, I think that's an efficient way to approach it because you do know you're right, Marsha, that we do have to go product by product. But when you do that, you can say we're concerned about the class, and that Lisa and Dr. Rodriguez who works with the Committee also will make sure that we bring back this as an issue to that group, the NIH group, yes.

CHAIRPERSON RAPPLEY: Okay. So then I will ask Dr. Pena to read the summary that I just gave and so that we can think about it again before we vote.

DR. PENA: Okay. So PAC would like followup on extensive off label use. It would like further information on long-term effects

for this medication on metabolic syndrome growth, sexual maturation; would like a followup report on extrapyramidal side effects; would like more information on its use in prescribing information; and recommends potentially a class of medications review at a followup meeting.

CHAIRPERSON RAPPLEY: And I would add specifically hypoprolactinemia under the area where you say sexual maturation and growth.

Yes.

DR. KOCIS: One other thing. Yesterday we learned about some of the new databases that allow for looking not only at single drug use but combination drug use. I don't know if those databases are up and running in such a fashion that we can also glean some look at concomitant multiples. You've heard SSRIs, antidepressives, even some of the hyperglycemic agents and stuff.

But I think that would also be an

interesting question.

CHAIRPERSON RAPPLEY: Dr. Pena just added that. So thank you.

So given that that will be recommendations of this Committee to the agency, we now also need to vote on the question of FDA. So the statement is FDA will continue its standard ongoing safety monitoring for oral risperidone.

I'm sorry?

And the additional items that we described in that summary, yes. Discussion?

DR. NOTTERMAN: I'm not sure. Perhaps you can enlighten me. The continuing of standard ongoing safety and taking under consideration these extensive recommendations are compatible statements

DR. MURPHY: I guess I'm sitting here thinking I think you said no. I think you've said we think there are additional pieces of information that we would like to have, and what we have to --

CHAIRPERSON RAPPLEY: Excuse me. How about in addition to standard ongoing safety monitoring?

DR. GOLDSTEIN: Or you could just say you expand its standard ongoing safety monitoring for oral risperidone and then to include the following.

DR. MURPHY: Well, what this is saying is that there's really nothing more that you want. Okay. That's what this is saying.

CHAIRPERSON RAPPLEY: And we don't agree with that. That's correct.

DR. MURPHY: I know you're not agreeing with that statement.

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: Okay. You're saying that we're not finished with looking at the adverse effects of these products, particularly this product, in the pediatric population. We have additional concerns. We understand the agency can't require some of

these studies. You're expressing to the division at least what your concerns are; that we can look at, the agency can address bringing back to you, because that's what you're telling us -- you want us to come back to you -- with a look at what the co-morbidity populations are in the ADH, which is the large off label use population, and these other things.

And we'll have to sit down with these and figure out. We also know you want a followup report on the extrapyramidal type of effects. You want us to look at that more closely over time. We'll have to figure out how to do that in a way that's meaningful. Okay?

CHAIRPERSON RAPPLEY: Okay. So how about if I divide this then into two questions? We'll take a vote on this statement, and then the next will be our consensus about the recommendations we give to the Committee.

So the FDA will continue its standard ongoing safety monitoring for oral risperidone. All those in support of that, please raise their hand.

And all those who oppose that, please raise their hand.

DR. PENA: So just as a procedural point, just to get it on the record, we'll probably just go around and if you can say, you know, yes or no.

MS. CELENTO: Amy Celento, opposed.

DR. CNAAN: Avital Cnaan opposed.

DR. D'ANGIO: Carl D'Angio opposed.

DR. DURE: Leon Dure opposed.

DR. HUDSON: Melissa Hudson opposed.

DR. KOCIS: Keith Kocis opposed.

DR. MOTIL: Kathleen Motil opposed.

DR. NOTTERMAN: Daniel Notterman opposed.

CHAIRPERSON RAPPLEY: Marsha Rappley opposed.

DR. ROSENTHAL: Geoff Rosenthal opposed.

DR. RAKOWSKY: Alex Rakowsky opposed.

DR. VINING: Elaine Vining opposed.

DR. PENA: And, Mark, you're voting, Mark.

DR. HUDAK: Mark Hudak opposed.

DR. MURPHY: And Lisa wanted me to point out that you're rejecting that this be all that we do.

CHAIRPERSON RAPPLEY: Correct.

DR. MURPHY: But clearly if we think it's --

CHAIRPERSON RAPPLEY: It's a minimum.

DR. MURPHY: -- appropriate to bring other information back to you because you heard yesterday about the agency always has a way of looking at all of these products, they're going to continue that.

CHAIRPERSON RAPPLEY: Yes, we

continue the usual practice.

DR. MURPHY: Right.

CHAIRPERSON RAPPLEY: And now in addition to your usual practice, we recommend to you the statement that Carlos just read.

Yes, Keith.

DR. KOCIS: Can I just throw one other thing on top of that list at least potential for discussion? I'm not sure, at least in my mind, I'm not sure I need to wait another year or two to get additional information before we reconsider the current labeling. So I guess that would be the one question.

And then tied into that would also be what risk mitigation program, information one could consider. I could think of lots of things. Again, I don't use this drug. So I don't really want to say. I simply want to offer that up at this time as to whether strengthening the label, and I don't want to dismiss that it's completely inadequate. I

think it just doesn't emphasize some of the concerns that I and the other people on this Committee apparently have.

And then to address secondarily some of those issues proactively is to consider risk mitigation either with information to the patient and the parent and/or other things that we've discussed yesterday that we could consider.

CHAIRPERSON RAPPLEY: So we could ask the agency to also come back to us with some ways that would be compatible with the agency's mission and meet that concern. Does that make sense, Keith?

Melissa?

DR. MURPHY: I don't think, Keith, as we learned yesterday, that it has to be new, that you're not recommending a risk around, right? That's not what you're recommending, or was it?

Because remember you heard yesterday it has to be a new adverse event and

has to have all of those criteria. So I just want to make sure what you're saying here.

CHAIRPERSON RAPPLEY: You know, I think the Committee needs some guidance from the agency about how are ways that within the mission of the agency that these concerns can be addressed, and if the agency itself cannot address these concerns due to limitations on the agency, then we as a group need to think about other ways to other mechanisms that we could address this.

But we, I think, pretty strongly feel that to whatever extent it is compatible and within the limitations of the agency's ability to make statements we would like to do so in the strongest fashion allowable.

DR. MURPHY: Okay. Because he started talking about labeling. So are you talking about just labeling now? Because remember the ways of communicating are not just in the label. So that's why I'm asking for more clarity here.

DR. KOCIS: I don't want to be specific, but I also want to not say no to any of those things that you just posed to me. In fact, I want to consider all options at our disposal either through the FDA and through the specific avenues we have as an option now or in future when new indications are coming up for approval, and then likewise to consider options that extend beyond this Committee and our own circles.

DR. MURPHY: And the message of these, or the concern about the inappropriate use of this product in areas where it has not been studied.

DR. GOLDSTEIN: Not just inappropriate use, but the cumulative and long-term effects --

DR. MURPHY: Right, right.

DR. GOLDSTEIN: -- on patients who are on maintenance for the approved indications.

DR. MURPHY: Okay.

CHAIRPERSON RAPPLEY: Melissa.

DR. HUDSON: In that regard, I mean, I really think this label is pretty clear. These adverse events are listed in warnings and precautions, and within the sections and special populations and pediatric population it clearly states the long-term effects on growth and development, sexual maturation, bone density, you know, have not been established.

I'm not sure what else they can do at this point. We're asking for something beyond a population that they can really legitimately inform the label.

DR. MURPHY: I'm glad you said that because I actually was going to say this is really an enormous amount of safety information, very specific, large text areas for these in a label.

I mean, I think, I don't know if you guys have any other products that have -- maybe you do -- as much safety information in

them as these products do. So irrespective, it's a lot. You're right. So that's why we're struggling with, you know, exactly how the focus message of what you're concerned about because this is an enormous amount of safety information already.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: I would say that my principal concern, and I think some of my colleagues over the potential adverse effects has been amplified by an uneasiness that we don't understand the complexities or the scope of the unlabeled usage, and so my suggestion would be to defer any potential change or increment or escalation of notification and communication with practitioners until we've received the report that we just requested, with the understanding that it would be forthcoming in a reasonable amount of time.

And at that point the Committee could discuss with FDA whether, based on what

we've just learned, further action is necessary or recommended, I should say.

CHAIRPERSON RAPPLEY: And I would like to close with that statement this discussion. If there are further new comments to be brought forward?

DR. MURPHY: Okay. So at this point, I'm just going to repeat it, because we've got a number of recommendations from you which requires bringing back additional information to the Committee. In the meantime though, the Committee is concerned about a number of adverse effects, and particularly the large off label use in populations that aren't defined as the benefit.

You're willing to not pursue asking the agency to communicate in any other way until we get that additional information back to you, and then you will consider the data and decision about what need to be communicated. Is that fair?

Lisa, do you have any thoughts on

that? Tom?

Okay. Thank you.

CHAIRPERSON RAPPLEY: Thank you.

DR. MURPHY: You can see why standards come to you sometimes.

CHAIRPERSON RAPPLEY: Right. Now, I would like to say that we could repeat, as Dr. Farrar pointed out, much of this discussion when we consider olanzapine. So if we could give the message now that we have these concerns for this class of medication and then not repeat ourselves around this particular medication so that our comments can be focused in on things that are pertinent to olanzapine and not general to the class, is that acceptable to the committee?

(Off-mic comments.)

CHAIRPERSON RAPPLEY: Okay. Thank you.

DR. COLLINS: Okay. Now, I'm pleased to be able to present to you the one-year post exclusivity adverse event review for

olanzapine.

Oral Zyprexa, or olanzapine, is an atypical antipsychotic for which Eli Lilly is the drug sponsor. Original market approval occurred on September 30th, 1996, and pediatric exclusivity was granted on January 10th, 2007.

Prior to the pediatric exclusivity studies, oral Zyprexa was indicated for acute and maintenance treatment of schizophrenia in adults and acute and maintenance treatment of mixed or manic episodes associated with Bipolar I Disorder in adults.

The next two slides provide information about the use of olanzapine in out-patient settings. Four million oral olanzapine prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. 2.5 percent of these prescriptions were for adolescents 13 to 17 years old, and 1.8 percent were for children zero to 12 years old.

There was a five percent decrease in oral olanzapine prescriptions for all age groups between the 12-month pre and post exclusivity periods with an eight percent decrease for the pediatric population.

Psychiatry was the top prescribing specialty during the post exclusivity period. All psychiatrist prescribed 52.6 percent of all oral olanzapine prescriptions, with child psychiatrists prescribing 4.9 percent of all prescriptions. Pediatricians prescribe 0.7 percent of all oral olanzapine prescriptions, and child neurologists prescribe 0.1 percent of all prescriptions.

The top diagnosis codes associated with oral olanzapine use were depressive disorder for patients 13 to 17 years old and anxiety states in early child psychoses for patients zero to 12 years old.

On November 30th, 2001, the FDA issued a written request for studies of oral olanzapine in the acute treatment of

schizophrenia and the acute treatment of mania in Bipolar I Disorder in adolescent patients 13 to 17 years old. The resulting pediatric exclusivity studies included one pharmacokinetic study and two efficacy and safety studies that utilize flexible dosing ranging from 2.5 to 20 milligrams per day.

The pediatric exclusivity studies demonstrated a statistically significant effect of olanzapine for the proposed uses in adolescents. However, the Division of Psychiatry products concluded that additional safety information was needed to adequately describe the relevant risk information for adolescents in the labeling, specifically in the areas of weight gain, hyperglycemia and hyperlipidemia.

To date, olanzapine has not been approved for the studied uses in pediatric patients. However, safety data from the pediatric exclusivity studies have been incorporated into the drug labeling.

Based on the results from the pediatric exclusivity studies, several modifications were made to the warning section of the currently distributed drug labeling. The weight gain section was modified to include a monotherapy in adolescent subsection. This subsection notes that, one, the average adolescent weight gain during a three-week median exposure was 4.6 kilograms for the olanzapine treated group versus negative 0.3 kilograms for the placebo treated group.

And, two, the percentage of adolescent patients gaining at least seven percent of their baseline body weight during a four-week median exposure was 40.6 percent for the olanzapine treated group versus 9.8 percent for the placebo treated group.

The hyperglycemia section also was modified to include a monotherapy in adolescent subsection noting that the mean change in fasting glucose was 2.68 milligrams

per deciliter for the olanzapine treated group versus negative 2.59 milligrams per deciliter for the placebo treated group.

Lastly, the hyperlipidemia section was modified to include a monotherapy in adolescent subsection. This subsection notes that, one, the percentage of patients with fasting triglycerides that increase by greater than or equal to 50 milligrams per deciliter was 37 percent for the olanzapine treated group versus 15.2 percent for the placebo treated group.

Two, the percentage of patients with fasting total cholesterol that increased by greater than or equal to 40 milligrams per deciliter was 14.5 percent for the olanzapine treated group versus 4.5 percent for the placebo treated group.

And, three, the percentage of patients with fasting LDL cholesterol that increased from borderline to high was 48.3 percent for the olanzapine treated group

versus zero percent for the placebo treated group.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports sine marketing approval.

For pediatric patients, there were 949 adverse event reports which comprised 4.4 percent of the total reports. Of these reports, there were 60 death reports with 41 being U.S. cases

Of the 60 crude count pediatric death reports identified since marketing approval, 14 reports were duplicated and two were miscoded adult reports. Of the 44 unique pediatric cases, 12 cases involved drug exposure during pregnancy, and eight cases involved an interdeterminate cause of death. The remaining 24 cases includes six suicide, five metabolic, four cardiac, five unusual use of olanzapine, and four other death cases.

After reviewing the 44 unique

pediatric death cases, the safety reviewer did not identify any new safety concerns.

There are multiple sections of the drug labeling that are relevant to the pediatric death cases. The warning section of the drug labeling includes a subsection on hyperglycemia associated with diabetes mellitus, ketoacidosis and/or coma, and the precaution section includes a subsection on suicide.

The adverse reaction section of the drug labeling includes cardiac adverse events, such as bradycardia, atrial fibrillation, and heart arrest.

The next several slides provide more details for the 24 death cases, and you will note that unlabeled events have been underlines. Three of the six suicide cases involved adolescents who ingested unknown amounts of olanzapine and were not known to have an olanzapine prescription.

The other three cases involved

adolescents with depression, agitation and/or anxiety who committed suicide within two months of initiating olanzapine treatment or increasing the dose.

The five metabolic cases involved adolescents who experienced diabetic ketoacidosis and/or coma with known olanzapine doses ranging from five to 15 milligrams.

Three of the four cardiac cases involved males who experienced cardiac arrythmia or rest while on olanzapine. In two of the cases, death occurred four to eight days after increasing the olanzapine dose to ten or 30 milligrams. The fourth cardiac case involved an 11 year old male who experienced myocardial infarction two and a half years after initiating olanzapine therapy.

For the five unusual use of olanzapine cases, the first case involved a two year old female who, according to the medical examiner, died possibly due to a drug interaction between olanzapine and atomoxetine

used to treat hyperactivity and possible bipolar disorder.

The second case involved a 15 year old male who drowned while on olanzapine and dextroamphetamine. These medications had been prescribed for the treatment of Asperger's Syndrome and Attention Deficit Hyperactivity Disorder.

Cases three, four and five involve children who experience fatal injuries inflicted by their parents when they were asphyxiated after being given olanzapine to sleep and morphine or hydromorphone or killed by other means.

As you will recall, there were four other death cases. The first case involved a 14 year old male with a history of asthma who experienced an acute asthma attack while taking olanzapine.

The second case involved a 16 year old who experienced a possible drug interaction and hepatic steatosis and was

found dead after initiating olanzapine treatment.

The third case involved a 15 year old male who died from necrotizing pancreatitis within three months of initiating olanzapine therapy. Of note, the patient was also on carbamazepine, paroxetine, and valproate, and each of these medications has a labeled association for pancreatitis.

And the last case involved as 12 year old female who died from unknown cases within one month of discontinuing olanzapine and initiating quetiapine therapy. She was diagnosed with diabetes and ketoacidosis three months prior to death and had multiple other diagnoses.

Going back to the table describing adverse event reports since marketing approval for pediatric patients, there were 631 serious adverse event reports with 444 being U.S. reports. You will note again that the definition of a serious adverse event that was

used when identifying these cases is noted in the footnote.

Looking at the post exclusivity period for pediatric patients, there were 69 serious adverse event reports with 42 of these being U.S. cases. Of the 69 crude count pediatric serious adverse event reports identified during the post exclusivity period, three of these reports were duplicates. Of the 66 unique reports, seven were excluded because they were miscoded for age or the adverse event occurred prior to the use of olanzapine.

Of the 59 unique pediatric cases, 11 were excluded because they related to drug exposure during pregnancy. For the 48 remaining cases, the safety reviewer did not identify any new safety concerns.

Once again, there are multiple sections of the drug labeling that are relevant to the serious adverse event cases. The warnings and precautions section of the

drug labeling include subsections on hyperglycemia, weight gain, hyperlipidemia, and Neuroleptic Malignant Syndrome.

The precaution section of the drug labeling includes a subsection on seizures and the adverse reaction section mentioned leukopenia. Of the remaining 48 pediatric serious adverse event cases during the post exclusivity period, there were 27 metabolic effect cases, including cases with increased weight, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, diabetic coma, elevated triglycerides and/or metabolic syndrome.

Four nervous system cases, including three seizure cases and one Neuroleptic Malignant Syndrome case, three blood dyscrasia cases, including two cases of leukopenia and one hemolytic anemia case, and 14 other cases that did not fall into any of these categories.

You will note that out of the cases described on this slide, hemolytic anemia is

the only one that is not included in the drug labeling.

This chart describes the various combinations of metabolic serious adverse events reported in pediatric patients. You will note that there are nine groups of reports for diabetes alone or diabetes combined with another metabolic adverse event.

For the 14 other serious adverse event cases, there were eight cases with labeled events, including three pancreatitis cases and five single case reports. Of note, one of the three pancreatitis cases was confounded by concomitant use of quetiapine and risperidone, both of which are labeled for an association with pancreatitis.

For the six cases with unlabeled events, all of the cases involved a single case report. Once again, the safety reviewer did not identify any new safety concerns.

This completes the one-year post exclusivity adverse event reporting. At

present olanzapine is not approved for use in any patient under 18 years of age, and safety data from the pediatric exclusivity trials have been incorporated into the drug labeling.

In view of the potential metabolic effects with the use of olanzapine, especially in pediatric patients, FDA will continue to evaluate the safety of olanzapine and will decide if any additional risk management regulatory action is needed.

Does the Advisory Committee concur is the question for the group.

And in closing, again, I'd like to acknowledge the assistance of numerous folks throughout the FDA in the Office of Surveillance and Epidemiology, the Division of Psychiatry Products, the Office of Clinical Pharmacology, the Office of Pediatric Therapeutics, and the Pediatric and Maternal Health Staff.

Thank you.

CHAIRPERSON RAPPLEY: Discussion?

Dr. Goldstein.

DR. GOLDSTEIN: Given that this same issue seems to occur in this drug as the other one in terms of metabolic syndrome, and I think your statement before was that there wasn't a differentiation between Type 1 or Type 2 diabetes, but you had thought that most of the cases were Type 1. Is there a mechanism and is it possible to differentiate in these adverse event reports whether or not this is onset of Type 1 or a new onset of Type 2?

I think that information would be helpful, particularly given the epidemic we're seeing of Type 2 in children, in elucidating what the safety effects are of these drugs.

DR. LAUGHREN: Someone from OC would have to comment on that. I mean, I think we are limited by what we have in those reports.

DR. McMAHON: I would like to ask Dr. Diak who did the review to comment.

DR. DIAK: Hi. I'm Ida-Lina Diak.

The reports unfortunately, due to the AERS reports, don't have enough information. So I have specified actually in my review, which I believe you have copies of, not all of the reports did state whether it was Type 1 or Type 2 and whether it was new onset or a preexisting condition.

CHAIRPERSON RAPPLEY: But given the information we received yesterday about the new data sets that are now available and right now you're just learning how to use those and learning what information actually is available there, it might be possible to have more specificity than about diagnoses, not from the spontaneous reporting system, but through some of these surveillance data sets.

DR. McMAHON: Yes, I think if we were to get more specificity about Type 1 versus Type 2 time to onset data when it occurred versus when a person started using the drug, all of that information, it would be

very helpful. I think it's pretty safe to say that the AERS database is not going to reliably give that.

So We will have to turn to other sources for that.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I'm not going to repeat anything I already said. Two comments on this. One, they didn't use the structured label as we had seen previously and the like, and when you look at the label here -- and, again, I find it less than ideal that under pediatric use safety and effectiveness in pediatric patients have not been established, although when you read through and you go through the different subsections integrated into the adult and the specific side effects that we're looking at, there is included that adolescent data.

So I think moving this towards the structured form, it would likely address that concern about it being varied because there is

information and we should use that when we make decisions about using this drug.

The second thing, I didn't get to make this comment to Dianne, and it's similar here in the sense that, you know, throughout the years we are asked to look at these drugs one year after pediatric exclusivity, and when already many of the decisions have been made about risk mitigation and labeling and things, and then we're also told that, well, we can't really do that now or, you know, that opportunity was lost and that was a year ago in the sense that we weren't involved in the initial approval for the indications and stuff.

So it just becomes unsettling to us because I think had we seen this data or at least in some circumstances we might have been able to impact at that time rather than now, a year later, saying now that we review this data, we're looking at this and what can we do about that, and I don't think we should stop

trying to do what we think is in the best interest of the children and the utilization of the drug in the kids.

CHAIRPERSON RAPPLEY: Well, again, I know it's frustrating for you all because you're not involved in the approval process where they are limited to the studies. Okay? And as you know, this one -- you saw the letter -- didn't get the approval. So I don't know if the division wants to make anymore comments about that, but the point as you heard yesterday of why we're doing post marketing follow-up is because, you know, normally after something gets out in the market or you see that there's a new indication for pediatrics, the potential for it being used more and having more problems. That doesn't always work because there's so much off label use, and we understand that.

But the concept that we want to be able to have a post-marketing assessment, so

that's why you end up getting this data that you then have to try and apply. It's not really a retroactive fit. It's just, okay, this is what we knew at the time of approval or in this situation non-approval. Here is what we see in the post-marketing.

Now, is there anything that that post-marketing informs us that we should be doing differently than what was already in the label? That's really what the question is.

DR. KOCIS: And there's two things, and certainly as we talked about, we learned new things in the first year, and that's certainly what we're most interested in, but yet -- and again, I don't want to use a specific to this drug or this morning, but over the meetings of the years I've been here, there has been information in the studies that were done that at least in my mind some of those drugs and some of that information we knew at the time of approval, and we didn't learn anything more during the year. We just

reemphasized -- continued to see what we knew at that time, and again, it's just unsettling at this point to then say, well, we're handcuffed in what we can do because yadda-yadda-yadda.

CHAIRPERSON RAPPLEY: Well, you're not handcuffed. I mean, you can make a recommendation that you think that the information was there, and it still looks like that information is there, and we still need to do additional emphasis or focus on the pediatric part of it.

Now, in this one, I think they really made a point of going in and putting the pediatric safety into the label. So it is there.

Your point about -- and I think what he's saying, Tom -- is that having something more in the pediatric subsection because when it's not approved, the approach now is to try to put that information off, and they refer them back to the clinical trials

part so that it would be helpful to have something there. Okay?

And then, Lisa, I want you to add to your statement. Again, now all of these products before they have an action are coming to an internal review. The pediatric group does have an opportunity to make recommendations before that action is taken. The pediatric group is not always involved in a line-by-line discussion with the labeling. They are frequently, but I think you can speak to that.

But, I mean, it's not always at the same level is what I'm trying to say when it comes to the PeRC as it would be in a lengthy negotiating meeting.

DR. MATHIS: You are right, and I actually think that this labeling change happened prior to the PeRC and prior to a lot of our thoughts about consolidating information in that section of labeling.

But you absolutely are correct, and

I think that that's a really helpful suggestion and something that we'll address in the future PeRCs as well.

CHAIRPERSON RAPPLEY: Dr. Hudak.

DR. MURPHY: So we can fix that.

DR. HUDAK: Yes. I guess I'd just like to ask a general informational question, and from what I understand you had a meeting yesterday that might have spoken to this and you can cut me off at any point if that's the case.

But with respect to all of these reports and so forth, especially when we consider these drugs that are similar classes or similar indications, is there any way you can glean from the database information that would allow you to normalize some of these complications.

In other words, I have no idea looking at these two drugs now whether, you know, these complications which I think are very significant complications from a

metabolic standpoint are more or less frequent in a particular drug. I mean, I don't know if you have information about the number of prescriptions, whether you can break it down by duration of therapy because some of these things, I think the side effects are idiopathic and acute and some may be sort of more likely to occur with a cumulative drug exposure, but I find the numbers fairly unsatisfying in terms of being able to really get my hands around the meat of the risk issue.

If your interest is in getting comparative safety information across drugs in the class, which would be something that we, of course, like to have, I think you'd almost have to have head-to-head comparisons in a controlled setting, for example, to look at metabolic risk.

But, again, it always comes down to who is going to take on a study like that. I mean, it would have to be an agency like NIH.

I don't think you're going to learn that very well from post-marketing reports.

DR. HUDAK: Well, I guess I can't say that I wouldn't learn anything without looking at what the information might be. If you have, you know, a drug that has ten times higher complication of metabolic issues than another drug, I mean, that's pretty powerful.

DR. LAUGHREN: You know, it may be that there are some other databases and maybe some of these newer databases that are becoming available to FDA - Sentinel and so forth - could give us access to large cohorts that might allow you to get at some of those kinds of things.

MS. McMAHON: Ann McMahon, OSE.

I just would agree that it's going to be very difficult using passive surveillance systems to do any kind of comparison that would be very believable as far as rates of adverse events because there are so many different issues that go into

whether someone happens to report a particular adverse event for a particular drug in a particular population. It's going to be very hard to do anything with the passive surround system in that regard, but I would also say that it probably would need to be a head-to-head type comparison. I would agree with that because even in a system, a large database, if it's not a randomized situation, you still could have all kinds of problems with interpreting the data. That would be my guess.

Certainly as far as this passive surround system, it's going to be really hard to make direct comparisons.

CHAIRPERSON RAPPLEY: And that would be something we could include in a recommendation to the BPCA, to let that be part of the thing that they set out as important to look at for NIH funding.

Dr. Rakowsky. Then Dr. Goldstein.

DR. GOLDSTEIN: This is to Dr.

Murphy and Dr. McMahon, and if this was covered yesterday, again, please stop me.

Given that for the approval process, the pediatric age groups between zero and 17 are broken up into four or five different subgroups. I can't remember off the top of my head what they are.

Would it make sense when you're reporting safety data to follow those same age group demarcations?

As this data was being presented, I commented to Dr. Farrar, you know, it's unlikely a newborn is going to be given this particular drug, and of course, the next two slides had a one year old and a two year old.

(Laughter.)

DR. GOLDSTEIN: But that data in and of itself, if you can see to my mind this may be a mechanism to see potentially some age related, at least some safety issues. If there's only an n of one or two in the two year old population with this drug and both of

them had significant safety issues, that may be some relatively low hanging fruit for safety information that could be gleaned from this type of subcategorization.

CHAIRPERSON RAPPLEY: Dr. Dure.

DR. DURE: Yes, I just had a question for Dr. Collins. Those are two nice presentations. The second though is a drug that is not approved in childhood, and so I'm just curious because your bullet here, "decide if any additional risk management regulatory action is needed."

What are you thinking about?

DR. COLLINS: And that I'd have to defer to the division.

DR. LAUGHREN: Well, obviously, we've already included even though the drug is not approved in pediatric use yet, we have included a lot of safety information, in particular the metabolic information in the warning section.

So I guess the question is beyond

that, is there anything that you -- I mean, I just want to point out as context that we obviously do include information and labeling for off label use if we think it's important for prescribers to know about that. That's what we've done here.

So is there anything else that I guess you can recommend that we might do to highlight this?

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: Yes. I wanted to go back to the concept of rates and usage because it struck me, too, when I was looking at these. We cannot calculate rates. We don't have denominators. There's no question about it, and it is passive surveillance.

What has been brought to us typically and at least helped me as I've looked at these over the years are the usage reports because what the usage reports gives us and now yesterday you introduced to us a new database that would also get the mail

order usage reports in which we don't have now. What it gives us is how many were prescribed and at least some context if not of rates at least relative rates between -- they're not absolute rates by any means, but they're relative rates between the various drugs.

And I would suggest that in looking at the few atypical antipsychotics we actually look at those numbers when we come back to this, whenever it is we come back, because it will give us something as long as we remember that we're looking at relative and not absolute.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: You know, I think this drug since it's not approved, we have an opportunity to look at pediatric safety and what we may require upon approval or in the risk mitigation process that follows.

Again, this is not what I do for a living. There's a lot of smarter people

around the table and elsewhere who could give you probably an exhaustive list of things, but certainly the things that pop into my head to require would be things like hemoglobin A1c to look along with weight and glucose to see what is the chronic exposure that we can evaluate, to look at the impact of hyperglycemia over time.

Obviously, I think the sponsor would want to know whether the drugs that are being used will induce or predispose children to developing a chronic, debilitating, life shortening disease. I think that's who would be interested in funding these studies to have that knowledge, and again, at the time of approval, you know, putting in some additional risk management things, the movement disorders, again, from the neurology standpoint to begin to look at that prospectively in that first year, and to be able to gather that data along with the passive surveillance to move this forth since

we have a lot of concern about the class of drugs and as these new drugs are coming out, to begin to refine what we know and learn more as time goes on.

And finally, you know, with the labeling and the negotiation of the labeling, you know, I assume that FDA can say you're saying there's no safety or efficacy data in pediatrics. That section is empty on this label. Well, what can we have?

We have concerns about X, Y and Z. Do you have that data or should you get that data? And, again, incorporating that into what happens after approval. So there's just a few idea.

CHAIRPERSON RAPPLEY: So I'd like to --

DR. LAUGHREN: Just one follow-up on that. This label that you have in front of you is in the old format. This is going to be reformatted into the new format, and a lot of those problems will be fixed.

DR. MURPHY: And just to point to Dr. Kocis that this is your opportunity to tell the division because obviously they're going to be doing some additional labeling what you think needs to go into that because we've obviously heard your concern.

So I think what we're hearing is just what you said, some additional concerns about these areas, and I won't repeat them all that you all have said.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: Just a brief comment to follow up on Dr. Kocis. I think that in terms of the various elements of the metabolic burden and the weight gain, it might be appropriate for the division to specify or suggest some mitigating activities. Monitoring of hemoglobin A1c might be appropriate or have to be studied, attention to diet, nutritional counseling. The average weight gain, I think, was over five kilograms,

which is substantial, and it might be possible to mitigate that through appropriate anticipatory guidance and perhaps those elements could be specified.

CHAIRPERSON RAPPLEY: So the Committee needs to vote. The statement is that the FDA should continue to evaluate the safety of olanzapine and decide if any additional risk management regulatory action is needed.

So those who would support this statement, please raise your hand -- oh, a question. Yes.

DR. CNAAN: How does our statement from the previous summary fit into this?

CHAIRPERSON RAPPLEY: Yes, I think we could then make an additional comment that we'd like those recommendations that we made about risperidone to apply to olanzapine because it is in the same class of medication.

DR. GOLDSTEIN: Well, they may have to be addended because this is not approved,

whereas Risperdal is.

CHAIRPERSON RAPPLEY: Right. Good point.

DR. MURPHY: I think if it's acceptable with the Committee what we will do is we're going to take the class issue that you mentioned before, and I'd like us to focus just on this product because it is in a different stage, as Dr. Goldstein pointed out, and have the Committee make sure you articulate what you're telling the division as they go forward.

CHAIRPERSON RAPPLEY: So you would like us to restate recommendations pertinent to olanzapine, in particular.

DR. MURPHY: Yes, pertinent to olanzapine in particular.

CHAIRPERSON RAPPLEY: Okay. So then this --

DR. MURPHY: Because they're telling you that --

CHAIRPERSON RAPPLEY: I understand

why. So I just haven't formulated it as succinctly as I did with the risperidone.

DR. DURE: Well, in this case they want us to say whether they should continue to evaluate the safety, and then does FDA decide any additional risk management regulatory action.

CHAIRPERSON RAPPLEY: Well, that is their -- they do that. That's what they do and they take recommendations for us about that. So I think what we need to recommend to them now is the specific areas we'd like you to attend to as you do this continuing review.

DR. MURPHY: Right. The question in view of the discussion is, again, a little disconnected, if you will, because what it's saying is do you agree that we're going to go ahead and decide if any additional risk management regulatory action, and what in essence as you have already said is that we agree that there needs to be additional risk management, and here are our thoughts about

it.

CHAIRPERSON RAPPLEY: So we will take a vote on this question, but then we will recommend to the agency that as they continue to evaluate the safety of olanzapine, they consider in particular the metabolic syndrome and mitigation of risk in the pediatric population. Is that acceptable to the Committee?

DR. RAKOWSKY: Can we also add that if it gets approved or if it starts being used more in the pediatric population that they also break it out by age groups and more specificity like we asked for.

CHAIRPERSON RAPPLEY: Does the agency have that recommendation? Did you get that, Carlos?

DR. McMAHON: That's a request to break down the drug use data then or the adverse event data or both?

DR. RAKOWSKY: I think at this time the drug use in pediatrics is so low you get

so few granularities there, but if it would increase, to start breaking it down to more specificity.

CHAIRPERSON RAPPLEY: So we could say break down into the use data and the safety data according to age groups as much as feasible with the database.

DR. GOLDSTEIN: "Stratify" might be a better term.

CHAIRPERSON RAPPLEY: I think that's a good point. We've got lots of really capable epidemiologists on the staff. So as we misstate some of these things, you all substitute the appropriate, I think, terms for that.

DR. MURPHY: Yes. I mean, you all indicated clearly it's a futile act that we won't do it. Okay.

CHAIRPERSON RAPPLEY: So then the Committee, given those recommendations to the agency, continue to evaluate the safety of olanzapine and decide if any additional risk

management regulatory action is needed.

Those who support that, please raise your hand.

Any opposed?

So that is a consensus support of that statement.

Are there any other safety issues or ongoing issues with these last two medications that the agency is working with or sponsors are working with the agency on that we should be aware of?

(No response.)

DR. MURPHY: I think that it's clear that the agency is working on this and we'll take your recommendations into consideration as they move forward with this.

CHAIRPERSON RAPPLEY: Thank you.

I would like for us to take our break now, and then when we return we'll start with Levaquin. Because we have spent a lot of time on this, I'd like us to take a ten-minute break if the Committee is okay with that.

Thank you. So reconvene in ten minutes.

(Whereupon, the above-entitled matter went off the record at 10:34 a.m. and resumed at 10:48 a.m.)

CHAIRPERSON RAPPLEY: Okay. We would like to resume.

DR. COPE: Dr. Durmowicz, would you introduce yourself and background to start?

CHAIRPERSON RAPPLEY: Thank you.

DR. COPE: Thank you.

DR. DURMOWICZ: Good morning. I'm Beth Durmowicz. I'm a general pediatrician with an interest in children and youth with special health care needs, and I'm a member of the Pediatric and Maternal Health staff.

I have the pleasure to present the adverse event review for Levaquin or levofloxacin. My presentation will include background drug information, drug use trends, information from the pediatric exclusivity studies, labeling changes secondary to the

pediatric exclusivity studies, and additional relevant safety information and labeling, adverse events, and I'll conclude with a summary.

Levaquin or levofloxacin is an antibacterial in the fluoroquinolone class. The sponsor is Ortho McNeil. The oral table in injectable formulations were approved originally on December 20th, 1996, and the oral solution was approved on October 21st, 2004.

Pediatric exclusivity was granted on March 14th, 2007, and the labeling changes secondary to the exclusivity studies occurred on September 11th, 2007.

Levaquin is approved in adults for multiple bacterial inflections. No pediatric indication was approved related to the pediatric exclusivity studies.

Of note, in May 2008, Levaquin was approved for inhalational anthrax post exposure in pediatric patients greater or

equal to six months of age.

This slide presents the information on the drug use trends for oral levofloxacin in the out-patient setting during the three-year period April 1st, 2005 to March 31st, 2008. This represents the period two years prior and one year after the granting of pediatric exclusivity in March of 2007.

Overall the pediatric use of levofloxacin is decreasing, approximately 17 percent over this three-year period. Patients zero to 18 years of age represented approximately 1.2 percent of the total projected patients who filled a prescription, and this equates to approximately 112,000 patients in the one-year post exclusivity period. And patients zero to 18 years of age represented approximately one percent of the total dispensed prescriptions. This is approximately 130,000 prescriptions per year over the three-year period. Ninety-three percent of these prescriptions were prescribed

for patients 12 to 18 years of age.

General practice, family medicine, doctors of osteopathy was the top prescribing specialty, and the top diagnosis code in patients zero to five years was urinary tract infection; six to 11 years, cellulitis; and in patients 12 to 18 years, chronic sinusitis.

A written request was issued for studies of levofloxacin in June of 2006. The pharmacokinetic studies showed that systemic exposure at ten milligrams per kilogram per day twice a day in patients less than five years and ten milligrams per kilogram daily in patients greater or equal to five years both orally and intravenously were not equal to adult exposure.

The clinical studies were Phase 3 studies in patients six months to 17 years and four studies were submitted. Two of the studies were active controlled, the first a community acquired pneumonia study in patients six months to 16 years, the second a study of

acute otitis media in patients six months to five years.

The third study was a uncontrolled study of acute otitis media, and the fourth study was a long-term, one-year prospective surveillance study of musculoskeletal disorders in patients six months to 16 years.

Tendinopathy, arthritis, arthralgia, and gait abnormality were the adverse events of interest in this study.

Results of the studies showed that efficacy was comparable and not inferior to the comparators. However, no indication for community acquired pneumonia or acute otitis media was sought or approved secondary to the musculoskeletal events.

I will now briefly discuss the safety data from these four studies. The first study was the controlled study of community acquired pneumonia. Seven hundred twelve subjects were available for safety evaluation.

Two deaths occurred in this study, both within the levofloxacin group, but neither were thought to be treatment related. The first death report or death case of the study was a 13 and a half year old with multiple foci pneumonia, with pneumatocele, fever, and respiratory distress. This patient suffered a cardiorespiratory arrest on day three of the study five minutes after bronchoscopy. The patient had been being treated with levofloxacin 250 milligrams twice a day for three days.

The second death case was a 2.2 year old who died after presentation to the emergency department with a febrile illness associated with virulent laryngitis, leukocytosis, airway trapping, and respiratory distress. The patient had completed a ten-day course for pneumonia and had been considered to be clinically cured.

Serious adverse events occurred in 33 or six percent of the levofloxacin treated

group versus eight or four percent of the comparator treated subjects.

Musculoskeletal disorders occurred in two percent of the levafloxisin treated patients versus one percent in comparator treated subjects.

The second controlled study, the acute otitis media study, had 1,607 subjects available for safety evaluation. This study was actually not requested in the written request but provided for safety data.

No deaths occurred in this study. There were ten serious adverse events in the levofloxacin treated group versus 13 in the comparator treatment group. Most of these serious adverse events were considered doubtfully related or not related to the study drug.

The incidence of musculoskeletal events was higher in the levofloxacin treated subjects, and the difference between the treatment groups was significant with a P

value of 0.02.

The uncontrolled acute otitis media study had 204 subjects available for safety evaluation. This study also is not requested in the written request but submitted for safety data.

No deaths occurred. Seven subjects reported eight serious adverse events: a maculopapular rash with dehydration was reported in two subjects with a possible relationship to the study drug, and one subject developed bloody diarrhea, and the relationship of this was felt to be very likely. Musculoskeletal adverse events occurred in six subjects.

The long-term surveillance study results are presented in this slide. Two thousand three subjects were available for safety evaluation after the one-year period or at the one-year period. Musculoskeletal disorders were reported more frequently in the levofloxacin treated subjects over the one-

year period, and the incidence of the musculoskeletal disorders are presented in this table.

And as you can see, levofloxacin had a statistically higher incidence of musculoskeletal disorders than the comparator group at the 60-day period after first dose and the one-year period after first dose. The most frequently occurring musculoskeletal disorder was arthralgia.

Labeling changes secondary to the pediatric exclusivity studies occurred in September 2007 to reflect that levofloxacin is not indicated for pediatric patients, to describe musculoskeletal adverse events and to provide information on the clinical studies in adverse event profile. Changes to the highlight sections were in the use and specific population, pediatrics, and provided the following information.

Pediatrics, musculoskeletal disorders, arthralgia, arthritis, tendinopathy

and gait abnormality seen in more Levaquin treated patients than in comparator, shown to cause arthropathy and osteochondrosis in juvenile animals.

In subsections from the warnings and precautions, use of specific populations and nonclinical toxicology are referenced. Information included in the full prescribing information under Section 5, warnings and precautions, musculoskeletal disorders in pediatric patients and arthropathic effects in animals. Labeling states that levofloxacin is not indicated in patients less than 18 years due to increased musculoskeletal disorders, and the pediatric use section is referenced, and the animal studies are described.

Under Section 6 of labeling, serious otherwise important adverse reactions, the musculoskeletal disorders in pediatric patients are discussed in greater detail, and warnings and precautions is again referenced.

Within the use in specific

populations, pediatric use subsection, labeling states that levofloxacin is not indicated. The clinical trials are described, including a table with a musculoskeletal disorder incidence which I projected earlier.

There have been additional labeling changes since the changes associated with pediatric exclusivity. Of note, in May 2008 a new indication was approved for inhalational anthrax post exposure in pediatric patients greater or equal to six months of age and the dosage is provided for the patients. And this dosing is based on a model to determine the proper kinetics.

In addition, a boxed warning and medication guide were added to provide information on the risk of tendon rupture in tendinopathy in October of 2008.

This is the boxed warning that was added on October 3rd, 2008, to labeling. Additional relevant safety labeling information is included in the warnings and

precaution section and includes tendinopathy and tendon rupture, hypersensitivity reactions, other serious and sometimes fatal reactions, hematologic and renal toxicities, hepatotoxicity, central nervous system effects, including convulsions anxiety, confusion, depression, and insomnia, Clostridium difficile, associated diarrhea or colitis peripheral neuropathy, prolongation of the QT interval and isolated cases of torsade de pointes, musculoskeletal disorders in pediatric patients and arthropathic effects in animals, light glucose disturbances, photosensitivity and phototoxicity, and the development of drug resistent bacteria.

Levofloxacin is a Category C pregnancy medication, and other important adverse events listed include hypotension after rapid of bolus intravenous infusion, crystalluria or cylindruria, and the other adverse events are all discussed in the warnings and precautions sections.

So moving on from the exclusivity studies to the post marketing reporting of adverse events, this table presents the crude counts of adverse events since marketing approval in December 1996 for patients zero to 16 years of age. As you can see, there are a total of 116 reports, 89 from within the United States, 100 serious adverse events, 77 from the United States, and three reports of death.

This slide presents information about the three deaths since marketing approval. The first report was of a 13 year old male with cerebral palsy, mental retardation, and seizures treated for bronchopneumonia who died of an unknown cause while on levofloxacin. Note this patient was on multiple concomitant medications.

The second patient is a 12 year old male with reactive airways disease and allergies who developed dyspnea and anaphylaxis six to ten minutes after taking

levofloxacin, benzydamine hydrochloride, which is an anti-inflammatory agent, and cromoglicate sodium, which is a mast cell stabilizer for acute pharyngitis. This patient became comatose and died eight days after the event.

The third case is a 12 month old, and we did double check the age on this report. This report is a 12 months old with a complex past medical history, including colectomy, ileostomy, ulcerative colitis, and rheumatoid arthritis, who developed a pelvic collection and sepsis. This patient was treated with levofloxacin and metronidazole while on multiple concomitant meds. The patient developed metabolic acidosis, deteriorated and died of a myocardial infarction.

As mentioned in the table there were 100 serious adverse events reported in pediatrics, and we took a particular focus on musculoskeletal events as well as central

nervous system events. As you can see, 39 percent of the serious adverse events were musculoskeletal in nature. The reports include 21 reports of arthralgia or arthropathy, 13 reports of bone or tendon symptoms, five of those being tendon rupture, five reports of myalgia or myopathy.

The top diagnosis for patients who reported a musculoskeletal event was sinusitis, and the most common age was 12 to 16 years from which 82 percent of the reports were received.

There were 19 central nervous system events, and I reported the events, more than one. So five reports of seizure, four reports of abnormal behavior or confusion, three reports of hallucination, and two reports of panic attack. The diagnosis seized where the patients had a central nervous system event or sinusitis and unknown.

So in summary, no new safety signals were identified after completed

pediatric focused safety review on the use of levofloxacin. A boxed warning and medication guide were added to labeling October 3rd, 2008 to strengthen the existing warnings about the increased risk of developing tendinitis and tendon rupture in patients of all ages.

At this time FDA does not recommend any additional labeling changes. FDA recommends to continue routine ongoing post marketing safety monitoring. Does the Committee concur?

CHAIRPERSON RAPPLEY: Thank you.

Before we go on to discussion, would you like to introduce your new member at the table?

Thank you.

DR. BELEN: Dr. Ozlem Belen from Division of Special Pathogens and Transplant Drug Products. I'm a pediatric infectious disease specialist. I've been in FDA for the past seven years and with the division for the past three years.

CHAIRPERSON RAPPLEY: Thank you.

And just to recognize that we have five standard reviews, including this one, to complete before lunch, so if we can keep our questions as focused and comments as focused as possible.

Dr. Goldstein.

DR. GOLDSTEIN: Just very short, very minor. On page 208 under the musculoskeletal adverse event reports, the second paragraph notes that there were twice as many females reported with musculoskeletal symptoms, but the reviewer was unaware of any biologic reason that would make girls more susceptible to these events.

My understanding is that there actually are biomechanical reasons that adolescent females are more susceptible to these types of events and so it's just a clarification that I wanted to bring up.

DR. NOTTERMAN: I noticed that also. I agree, particularly with ACL

injuries.

The other question I was going to ask pertains to the box warning and to some of the other material where it's indicated that the risk of tendon rupture and tendinitis is particularly great over the age of 60, and I just want to make sure I understand that that is a true biological susceptibility and isn't an ascertainment bias that reflects the fact that the drug is not prescribed to a large extent under the age of, say, 12 or 16, according to the data you provided.

DR. BELEN: Before the approval of the black box warning and the medication guide as well, an extensive review other than the OSE review within our division evaluated the populations at risk.

And so although we identified that overall there is an increase relative risk of tendinitis and tendon rupture in all ages, the elderly population as well as concomitant steroid users, as well as transplant patients

were identified specifically having higher relative risk.

This was basically based on mostly literature search, not based on the OSE review that was provided to us, but maybe they can provide more input if they have more information relating to those patients specifically.

DR. NOTTERMAN: My only concern would be making sure that practitioners don't take this age delimiter as indicating that perhaps it's relatively safer to use it in younger patients, particularly older adolescents.

DR. BELEN: I would like to point out specifically we added in all ages. That concern was discussed within the division, with other divisions, as well as the Pediatric Division as well. So when you look at the black box warning, it says this happens in all ages, but the risk is further increased.

So I want to point out that the

risk is actually beyond whatever is there for this age group. So that was important for us to let the geriatric practitioners to know that this risk is there for when they prescribe it to elderly population because this population is at greater risk when they are debilitated.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. MURPHY: And in our discussions, you know, there is that Section 5.6 which does talk about pediatrics specifically because we were actually concerned when we saw the black box. It did sort of take away. I mean, if you weren't familiar with the field, you could read it, but I think by having that in there and because of the fact that there was an actual increased relative risk in the elderly that the pediatrics is still, I hope, clear that they do have this risk, too, in the labeling.

CHAIRPERSON RAPPLEY: Dr.

Rosenthal.

DR. ROSENTHAL: My comment is actually not necessarily specific to Levaquin, but Levaquin provides a vehicle for making the observation. In the warnings and cautions section of the label under prolongation of the QT interval, there is a sentence which I think is a great sentence, boilerplate sentence. It says Levaquin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class 1A and Class 3 anti-arrhythmic agents.

I would just add to that that some additional phrase or wording that would include in that list other agents known to prolong QT because, you know, as this Committee has discovered and as the work of many in the room have shown, there are agents that aren't included in this list that are important prolongers of the QT interval and increased arrhythmic risk, particularly when

taken with other drugs that also prolong QT.

CHAIRPERSON RAPPLEY: Can you bring up the slide again that has the direct question on it for the Committee?

DR. DURMOWICZ: Yes.

CHAIRPERSON RAPPLEY: So no new safety signals, a boxed warning and medication guide have been added as recently as October. At this time the FDA does not recommend any additional labeling changes. FDA recommends to continue routine, ongoing post marketing safety monitoring.

Does the Committee concur? Do you wish -- go ahead.

DR. NOTTERMAN: Just to follow up on that last point, there are drugs for which FDA has placed a black box warning concerning QT interval change, and those black box warnings refer generally to the concomitant use of other drugs such as Levaquin which prolong or may prolong QT intervals.

So it would be good if there was

some harmonization between this Section 5.8 and the black box warning, for example, on drugs such as ziprasidone, which is a very broad warning about the use of any drug that could produce QTc interval lengthening.

DR. BELEN: Simply when you're making decisions regarding the black box warning, we have to look at the benefit-risk profile of the drug as well. So I have to look into all of the drugs which contain fluoroquinolones, for example, and look at that ratio.

So, therefore, you're right. We have to have harmonization, but we have to also look at certain risk for the certain drug as well.

DR. NOTTERMAN: I'm not suggesting a black box warning for QT interval here. I'm just suggesting that 5.8 mentioned the class of drugs that has a black box warning already for use with drugs like Levaquin. It's the same point that we just heard from Dr.

Rosenthal.

DR. BELEN: Yes. Thank you.

CHAIRPERSON RAPPLEY: So with that recommendation then to the agency, how many affirm that the FDA continue routine, ongoing post marketing safety monitoring? Please raise your hand.

Any opposed?

So we support that by consensus.

DR. MURPHY: Okay. So you're supporting this statement with the addition to the bullet that there is an additional labeling change as stated concerning --

CHAIRPERSON RAPPLEY: That we seek harmonization around the caution of prolongation of QT to include other agents that are known to cause QT prolongation.

DR. MURPHY: Right, in 5.8. So I just want to make clear --

CHAIRPERSON RAPPLEY: Five, point, eight.

DR. MURPHY: -- for Carlos and the

minutes that it's adoption of this concurrence with the recommendation.

CHAIRPERSON RAPPLEY: With that recommendation, yes. Thank you. Very good.

Dr. Collins.

DR. COLLINS: Okay. Good morning again, everyone. I'm now pleased to be able to present to you the one-year, post exclusivity adverse event review for lamotrigine.

Lamictal, or lamotrigine, is an anti-epileptic drug, or AED, for which GlaxoSmithKline is the drug sponsor.

Original market approval occurred on December 27th, 1994, and pediatric exclusivity was granted on February 14th, 2007.

Lamotrigine's current indications include adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastuat Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric

patients two years and older, and conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone or valproate as a single anti-epileptic drug.

In addition, lamotrigine also is indicated for bipolar disorder maintenance treatment to delay the time to occurrence of mood episodes in adults treated for acute mood episodes with standard therapy.

The next two slides provide information about the use of lamotrigine in out-patient settings. Since lamotrigine is not approved for pediatric patients younger than two, I have highlighted the use data for that age group in yellow.

7.2 million lamotrigine prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. Nine percent of these prescriptions were for pediatric patients zero

to 16 years old, and 0.02 percent of these prescriptions were for pediatric patients less than two years old.

There was a 22 percent increase in the lamotrigine prescriptions for all age groups between the 12-month pre and post exclusivity periods and an 11 percent decrease for pediatric patients younger than two years old.

Psychiatry was the top prescribing specialty during the post exclusivity period. Psychiatrists prescribed 50.4 percent of all lamotrigine prescriptions. Neurologists prescribed 18.3 percent, and pediatricians prescribed 1.1 percent.

The top diagnosis codes associated with lamotrigine use in patients zero to 16 years old were diagnoses related to epilepsy at 51 percent and diagnoses related to bipolar disorder at 34 percent.

Of note, prior to the written request for pediatric exclusivity studies,

lamotrigine already had a box warning for serious, life threatening, and fatal rashes in adult and pediatric patients.

In addition, lamotrigine already had an approved pediatric indication for adjunctive therapy for the generalized seizures of Lennox-Gastuat Syndrome in pediatric patients two years and older.

On December 17th, 1998, the FDA issued a written request for studies of lamotrigine as adjunctive therapy for partial seizures in pediatric patients one month to 16 years old. The resulting pediatric exclusivity studies were broken into two groups. For pediatric patients two years and older there was one efficacy, short-term safety, and pharmacokinetic study.

For pediatric patients of one to 24 months, there was one efficacy, short-term safety, and PK study, and one longer term safety and PK study.

For pediatric patients two years

and older, the pediatric exclusivity study demonstrated efficacy for adjunctive treatment of partial seizures. In the safety analysis serious rashes, including one rash related death, were seen in pediatric patients receiving adjunctive therapy.

For pediatric patients one to 24 months old, the Division of Neurology Products was unable to determine that lamotrigine is safe and effective for adjunctive treatment of partial seizures. Protocol specified analyses fail to detect a statistically significant treatment difference between adjunctive lamotrigine versus adjunctive placebo therapy, and adverse event data needed reanalysis using coding scheme more appropriate for a pediatric population unable to communicate symptoms.

Based on the findings of the pediatric exclusivity studies for patients two years and older, lamotrigine was approved for the studied use, and safety data were incorporated into the drug labeling.

For pediatric patients one to 24 months old, lamotrigine was not approved for the studied use. No labeling change was made as labeling of negative pediatric studies was not required when these studies were reviewed. However, the Division of Neurology Products acknowledges that labeling the study data for one to 24 month olds would be consistent with the 2007 reauthorization of the Best Pharmaceuticals for Children Act.

This slide lists all of the labeling sections that were changed based on the results of the pediatric exclusivity studies. Changes were made to the box warning, clinical pharmacology, clinical studies, indications and usage, warnings, precautions, and adverse reactions sections of the drug labeling.

The next several slides provide details of the safety labeling changes. The box warning section was changed to update the pediatric serious rash data. After the

pediatric exclusivity studies, the incidence of serious rash in pediatric patients receiving adjunctive therapy was 0.8 percent, and one rash related death had been reported out of 1,983 pediatric patients on adjunctive therapy.

The clinical pharmacology section, age in pediatric patients subsection, was changed to note that, one, lamotrigine clearance was influenced predominantly by total body weight and concurrent anti-epileptic drug therapy;

Two, oral clearance was higher on a body weight basis in pediatric patients weighing less than 30 kilograms than in adults;

And three, patients weighing less than 30 kilograms may need an increase of as much as 50 percent in maintenance doses based on clinical response.

The warning section, serious rash in pediatric population subsection, updated

the incidence of serious rash associated with lamotrigine in the prospectively followed pediatric cohort, including the occurrence of the one rash related death.

In addition, the revised labeling included data supporting the increased risk of rash with concomitant use of valproate acid.

The acute multi-organ failure subsection noted the updated number of pediatric fatalities associated with multi-organ failure and various degrees of hepatic failure. This subsection also noted the fact that the majority of these deaths occurred in association with other serious medical events.

The adverse reaction section, adjunctive therapy in pediatric patient subsection, was updated to include the most common adverse events seen in pediatric adjunctive therapy trials.

In addition, the subsection was changed to include information on the rate of discontinuations due to adverse events, and

the most commonly reported adverse events leading to discontinuation in pediatric placebo controlled trials, and in the larger group of pediatric placebo controlled and open label trials.

Lastly, the incidence and controlled adjunctive trials in pediatric patient subsection was changed to include updated treatment emergent adverse event data.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports since marketing approval. For pediatric patients, there were 1,787 adverse event reports, which comprised 12.5 percent of the total reports. Of these reports, there were 106 death reports, with 30 being U.S. reports.

Out of the 106 crude count pediatric death reports identified since marketing approval, 23 reports were duplicates, resulting in 83 unique pediatric cases. Of these unique cases, there were 38

cases of expected epilepsy complications, 16 cases of labeled warnings and precautions, 19 cases of adverse events with a high background rate in the general population, but lamotrigine cannot be excluded as a contributing factor, and ten other cases.

After reviewing the 83 unique pediatric death cases, the safety reviewer did not identify any new safety concerns.

There are multiple sections of the current labeling that are relevant to the pediatric death cases. Serious rashes in pediatric patients are discussed in the box warning, and the warning section of the drug labeling.

The precaution section includes sudden unexplained death in epilepsy and status epilepticus, and the adverse reaction section of the drug labeling mentions infection and pancreatitis.

The next several slides provide more details for the 83 unique pediatric death

cases identified since marketing approval, and you will note that unlabeled events have been underlined.

Of these cases, there were 19 cases of seizure, prolonged seizure or status epilepticus, 19 cases of patients found dead, death, or sudden death, and 16 cases of rash, Stevens Johnson Syndrome, or toxic epidermal necrolysis. All of these events are consistent with the current drug labeling.

Again, there were 19 adverse events that have a high background rate in the general population, but lamotrigine cannot be excluded as a contributing factor. Of these cases, nine involved in utero exposures, four involved pulmonary events, such as pneumonia, pulmonary infection, or aspiration pneumonopathy, and there was one case of each of the six events noted at the bottom of this slide.

Of note, pulmonary infection, sepsis and Varicella infection are not

specifically mentioned in the drug labeling, but infection in broad terms is listed as an adverse event.

The ten other death cases are described in greater detail on the next five slides. Overall, an association of these deaths with lamotrigine is unclear, because the cases include concomitant medications, underlying medical conditions and/or insufficient details.

There were four cardiac cases. The first case involved a ten year old male on lamotrigine monotherapy for four and a half years who was found unconscious and could not be revived. Autopsy showed signs of myocarditis.

The second case involved a 13 year old male who experienced increasing seizures over three years of lamotrigine treatment. Topiramate was added. Two months later, he was admitted to the hospital for an unspecified reason, and he died suddenly.

Autopsy found acute myocarditis.

The third case involved a 16 year old who experienced cardiac arrest one month after initiating lamotrigine and oxcarbazepine treatment for unknown indications. He was hospitalized, and died one week later.

And the fourth case involved an eight year old female who was found dead six months after initiating lamotrigine therapy to treat epilepsy. Autopsy found cardiac insufficiency and generalized inflammation of the respiratory tract.

The two pulmonary cases included a three year old male with encephalopathy and on oxygen treatment who developed respiratory and cardiac failure after 18 months of lamotrigine therapy, and a four year old male with global developmental delay, and on lamotrigine for one and a half months to treat seizures, who experienced fever and vomiting, a 30 minute seizure and respiratory arrest, and died.

The first hepatic case involved a

one year old male who developed an unspecified cerebrovascular disorder, hepatic abnormality, and purpura, after one year valproate sodium, and two weeks lamotrigine treatment for epilepsy.

The second hepatic case involved a 15 year old female who experienced rash and discontinued lamotrigine after three weeks of treatment for blackouts. The rash resolved, blackouts continued, occasional vomiting developed, and phenobarbital was started.

Two days later, which was two and a half weeks after lamotrigine was stopped, she was diagnosed with liver failure. A few days later, she had brain edema and death occurred. The occurrence of Reye's Syndrome also was considered.

The last two other cases involved an eight year old female on two years of lamotrigine and two months of topiramate therapy who developed hemorrhagic pancreatitis and died within 20 hours, and a ten year old

male with multiple disabilities on lamotrigine for ten months who developed renal failure and died. Amphotericin and acyclovir, both of which are associated with renal failure, were started two days before the onset of the adverse event.

Going back to the table describing the adverse event reports since marketing approval, for pediatric patients, there were 1,250 pediatric serious adverse event reports, with 635 being U.S. reports. You will note again that the definition of a serious adverse event that was used to identify these reports is provided in the footnote.

Looking at the post exclusivity period for pediatric patients, there were 172 serious adverse event reports, with 105 of these being U.S. reports.

Of the 172 crude count pediatric reports from the post exclusivity period, 398 adverse events were identified in three or more reports. Of these 398 events, 285 were

labeled, 57 were unlabeled, and 56 were events inappropriate for labeling because they can occur with all drugs, for example, the adverse event report of a drug being ineffective.

Once again, the safety reviewer did not identify any new safety concerns during her review of these serious adverse events.

There are multiple sections of the drug labeling that are relevant to the 285 labeled serious adverse events. The box warning section of the drug labeling discusses serious rash, including toxic epidermal necrolysis. The warning section discusses serious rash, including Stevens Johnson Syndrome, angioedema, fever, and lymphadenopathy, hypersensitivity reactions, including generalized hypersensitivity, disseminated intravascular coagulation, and lymphadenopathy, multi-organ failure, including hepatic failure, disseminated intravascular coagulation, and elevated transaminases, and blood dyscrasias, including

thrombocytopenia.

In addition, there are 33 different serious adverse events included in the post marketing reports which are noted in the adverse reaction section of the drug labeling as indicated on this slide.

The 57 unlabeled pediatric serious adverse events identified during the post exclusivity period are characterized on this slide. They included eight abnormal behavior events, six aggression events, four events each for blister, candidiasis, coagulopathy, and septic shock, and three events each for abnormal feces, anuria, blood pressure decrease, coordination abnormal, dysmorphism, hypotension, jaundice, lactose intolerance, and mucosal inflammation.

The safety reviewer did not identify a safety signal in these unlabeled serious adverse events.

Moving from the post marketing adverse event reports to FDA's risk management

activities, on January 31st, 2008, the FDA issued an alert that patients on anti-epileptic drugs should be closely monitored for behavior indicating suicidal thoughts or behavior or depression. This alert was based on FDA analyses of reports of suicidal behavior or ideation from placebo controlled studies of 11 anti-epileptic drugs in which the rate of suicidality was 0.43 percent for patients on anti-epileptic drugs, versus 0.22 percent for patients on placebo. Results were generally consistent among the 11 drugs.

The Division of Neurology Products has given presentations on this topic during prior Pediatric Advisory Committee meetings.

The 11 anti-epileptic drugs included in the analyses are listed on this slide. FDA is working to include information on the risk of suicidality in the labelings of all anti-epileptic drugs used for maintenance therapy.

The FDA's risk management

activities also have included a review of Lamictal medication errors related to name confusion. Lamictal tablets are primarily confused with Lamisil tablets, and this name confusion is well documented, and known to impact both adult and pediatric populations.

However, reported medication errors for Lamictal in pediatric patients have not increased since pediatric exclusivity was granted.

Interventions implemented to minimize medication errors due to name confusion include, one, listing the name pair, Lamictal and Lamisil, on the Institute for Safe Medication Practices Confused Drug Names List;

Two, the current ongoing, extensive educational campaign developed by the Lamictal sponsor to alert patients and health care professionals about the errors involving Lamictal and Lamisil name confusion;

And three, RxSafety Advisor, which

is a software program that alerts pharmacists to potential look alike and sound alike names by displaying a warning message prior to a claim being made, and after the claim is accepted. And overwrite code must be entered to bypass the message, and unlike many pharmacy warning systems, this message cannot be paged through.

The Lamictal sponsor has been working to help pharmacies implement this technology since 2007. In the future, the FDA will continue to monitor medication errors by assessing the communication programs developed by the Lamictal sponsor monitoring the effectiveness of the RxSafety Advisor, and monitoring for name confusion.

This completes the one-year post exclusivity adverse event reporting. At present, lamotrigine is not approved for use in patients under two years of age. Safety data from the pediatric exclusivity trial for two to 16 year olds have been incorporated

into the drug labeling, and the Division of Neurology Products is planning to include inflammation on the one to 24 month old study in labeling.

The safety review did not reveal any new safety concerns for lamotrigine. FDA is working to include suicidality data in the labelings of 11 anti-epileptic drugs, including lamotrigine. FDA also will continue to monitor medication errors related to name confusion, and FDA will continue its standard ongoing safety monitoring for lamotrigine.

And the question to the Committee is does the Committee concur with this approach?

And in closing I just would like to acknowledge the assistance I received from FDA staff in the Office of Surveillance and Epidemiology, the Office of Clinical Pharmacology, the Division of Neurology Products, the Office of Pediatric Therapeutics, and the Pediatric and Maternal

Health staff.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Dr. Murphy, would you like to introduce the new people at the table?

DR. MURPHY: I'll ask each of the individuals from the Division to please introduce themselves, and a little bit about your background.

DR. HERSHKOWITZ: Hi. I'm Dr. Norman Hershkowitz. I'm a team leader in the Division of Neurology Products. I have trained as an adult neurologist. I'm also trained as a pharmacologist. I have a Ph.D. in pharmacology.

DR. SHERIDAN: I'm Dr. Phil Sheridan. I'm a medical officer with the Division of Neurology Products. I'm a pediatrician and pediatric neurologist.

CHAIRPERSON RAPPLEY: Thank you.

So open for discussion. Dr. Cnaan.

DR. CNAAN: Since there don't seem

to be questions in lamotrigine itself, I have a generic question for the division. In this --

DR. HERSHKOWITZ: Could I ask you to speak up?

DR. CNAAN: In the suicidality report, it included 11 drugs because they were the only drugs that had good controlled randomized clinical trials, et cetera. There were several drugs that were not included, because they're mostly too old, and didn't have this quality of studies.

Are there any plans to do anything about the labeling of those older drugs that were not included in this suicidality analysis just to inform that this is an issue in the same vein?

DR. HERSHKOWITZ: I'll refer you to the Advisory Committee, and the Advisory Committee voted that the division should include labeling for these other drugs, and I think legally -- I don't think I can tell you

what we're doing now, but I'll refer you to what the Advisory Committee recommended.

CHAIRPERSON RAPPLEY: Other questions or comments?

I would like to make a comment that it seems to me on hearing this presentation that, in this particular medication, the process worked really well, and what was accomplished here was exactly what was set out to be accomplished with the changes that have brought pediatric issues to people's attention.

One, you identified the very unique communication issues of people who are zero to two years of age, and I think that's important to acknowledge, and to create new mechanisms to determine signs and symptoms in that age group.

Two, we got new clearance data, and looked at new dosing requirements for this medication in children, in particular.

And three, some alerts were

generated in response to signals detected during the post exclusivity analysis that led to generalizations relevant to the entire class.

So it seemed to me that the intent of legislation and special act, and all of your extra workload, and our extra workload, resulted at least in this case in exactly the things we wanted to accomplish. So I commend the division for that.

DR. MURPHY: I think a clarification from the division was that you're basically agreeing or anticipating that they are going to put some information in, but you're reading this as saying that they will get that additional information in the label.

So I can tell you that we had a number of discussions about the wording of this. So because the agency cannot talk about, you know, any activities that are ongoing, so I think basically if you have a recommendation, because that's what you were

saying, and if others on the Committee agree with you, that you think that the division should include the information on the one to 24 month old study in the labeling, which of course, I can predict what your response is, but I just think for the record that if that's what you think should happen, then you need to go on the record to say that.

CHAIRPERSON RAPPLEY: So the Committee would need to concur that that information should be included in the labeling.

DR. HERSHKOWITZ: I didn't catch what you said. If it was a question, I'm a little --

DR. SHERIDAN: The answer is yes.

CHAIRPERSON RAPPLEY: So my own personal comments --

MR. HERSHKOWITZ: I have a little Meniere's disease, and my tinnitus is very high today.

CHAIRPERSON RAPPLEY: I can relate