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CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

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Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

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P R O C E E D I N G S

(1:00 p.m.)

DR. VENITZ: Welcome back for the afternoon session of the Pharmacy Compounding Advisory Committee. We will have a conflict of interest statement read on the record before we start with the official proceedings.

Conflict of Interest Statement

DR. HONG: Before we begin this afternoon's session, we would like to disclose for the record that Mr. William Mixon, the committee's standing industry representative member for the Pharmacy Compounding Advisory Committee, will not be participating in the discussion for domperidone due to a conflict of interest. Thank you.

DR. VENITZ: Thank you, Dr. Hong.

With that in mind, we are going to start with the topic of the afternoon session. That's domperidone, whether it should be placed on the 503A bulk drug substances list or not.

We will have presentations from the FDA first, followed by our nominator presentations. So

I would ask now our first presenter, Dr. Sewell, to review the FDA'S summary and recommendation.

FDA Presentation - Catherine Sewell

DR. SEWELL: Good afternoon. I'm Dr. Catherine Sewell. I'm a clinical reviewer in the Division of Bone, Reproductive and Urologic Products, and I, along with my colleagues Dr. Leslie McKinney, who's a pharmacology/toxicology reviewer in DBRUP, and Dr. Anil Rajpal, who's a medical team leader in the Division of Gastroenterology and Inborn Errors Products, will discuss domperidone.

FDA'S review of domperidone was extensive and included experts from many different disciplines, and I'd like to gratefully acknowledge our collaborators in this presentation.

Domperidone blocks dopamine receptors in the gut and increases gut motility. It also blocks the dopamine receptors in the pituitary gland, which increases prolactin secretion and can affect milk production. Its primary uses in compounding are in gastrointestinal conditions like gastroparesis and

nausea and vomiting, and in lactation disorders.

Today, we'll discuss the physical and chemical characterization of domperidone and its historical use in compounding. We'll review the evidence for efficacy in gastrointestinal and lactation disorders. We'll cover the safety concerns.

First, in that, I'll just review the basics of the QT interval and the risk for arrhythmia, and then discuss the regulatory history of domperidone in the context of that risk; review the nonclinical and clinical evidence for the safety concern; provide you with our conclusions, and a final recommendation.

Domperidone is well-characterized. It's a synthetic small molecule and is stable under ordinary storage conditions. Domperidone is not approved for any indication in the United States. It has been approved outside of the U.S. since 1978 to treat certain gastrointestinal conditions.

Prior to 2014, the maximum recommended daily dose was 80 milligrams, and as of 2014, this was

reduced to 30 milligrams per day, and the maximum duration of treatment was reduced to 7 days. Domperidone is not approved for lactation in any country in the world, but it is used in doses between 30 milligrams and 120 milligrams daily for lactation disorders.

To ascertain domperidone utilization in the United States, FDA conducted a drug utilization review encompassing the time frame from June 2009 through May of 2015, and found that between 7,500 prescriptions and 11,600 prescriptions are dispensed annually in the United States.

Most of the prescriptions are dispensed to women, 77 percent, and of these, 20 percent are to women between the ages of 20 and 39, and 26 percent to women between the ages of 40 and 59. Obviously, these age ranges encompass women who could become pregnant or breastfeed.

Sixty percent of the prescriptions are written by gastroenterologists and 6 percent by obstetrician/ gynecologists. An office-based physician survey showed that the most commonly

reported indication was gastroparesis.

Next, Dr. Anil Rajpal will review the efficacy of domperidone in gastrointestinal conditions.

FDA Presentation - Anil Rajpal

DR. RAJPAL: The first GI condition that will be discussed is gastroparesis. There are efficacy data to support the use of domperidone for gastroparesis. There are three trials.

The first was a randomized, withdrawal, placebo-controlled 4-week trial in diabetic gastroparesis; 208 patients were enrolled. There was a 54 percent lower total symptom score with domperidone, 20 milligrams orally 4 times a day, versus placebo.

The difference was statistically significant. The total symptom score was defined as the sum of five investigator-assessed scores, ranging from 0 to 3, for nausea, vomiting, early satiety, abdominal distention, bloating, and abdominal pain.

The second was a randomized, active-

controlled 4-week trial in diabetic gastroparesis; 95 patients were enrolled. There were two treatment arms, domperidone, 20 milligrams orally 4 times a day, and metoclopramide, 10 milligrams orally 4 times a day.

There was a similar reduction in total symptom score between domperidone and metoclopramide, 41 percent versus 39 percent. Total symptom score was defined as the sum of four investigator-assessed scores ranging from 0 to 3 for nausea, vomiting, early satiety, and bloating/distension.

The third was a randomized, active-controlled 8-week trial in pediatric diabetic gastroparesis in patients over 5 years of age; 28 patients were enrolled. The treatment arms were domperidone, 0.9 milligrams per kilogram daily, and cisapride, 0.8 milligrams per kilogram daily.

There was a lower median total symptom score with domperidone than cisapride, 3.1 versus 7.4. Total symptom score was defined as the sum of four investigator-assessed scores ranging from 0 to 6

for regurgitation or vomiting or heartburn, feeling of abdominal fullness or bloating, early satiety or anorexia, and abdominal epigastric and mesogastric pain.

All three trials have the limitation that the primary endpoint was assessed by the investigator. Currently, patient-reported outcome measures are recommended.

The second trial had an additional limitation. Although reductions in total symptom score appeared similar, not statistically significantly different, the trial was not designed as a noninferiority trial. A noninferiority trial aims to show a novel treatment is not clinically worse than an active treatment based on a specific noninferiority margin.

The second GI condition that will be discussed is nausea and vomiting. Domperidone is currently approved outside of the U.S. for treatment of nausea and vomiting at a dose of 10 milligrams orally up to 3 times a day.

However, it should be noted that the

population studied to support approval of this indication had nausea and vomiting in the context of chronic postprandial dyspepsia, not gastroenteritis, chemotherapy, or motion sickness. This population may have had underlying gastroparesis as the cause of their symptoms.

Efficacy data are mainly from three trials, each 4-week duration, in chronic postprandial dyspepsia that together enrolled 251 patients receiving domperidone and 249 patients receiving placebo.

These data support the use of domperidone, 10 milligrams 3 times a day, in the suppression of nausea and vomiting at week 2 and/or week 4 of treatment, and clinically relevant improvement in nausea and/or vomiting scores were reported in these studies following domperidone treatment compared to placebo. Nausea and vomiting were each assessed on a four-point scale in these trials.

For gastroparesis, there is one FDA-approved therapy, Reglan, or metoclopramide. It has been shown to be effective in treating gastroparesis.

It has a boxed warning for tardive dyskinesia, a serious movement disorder that's often irreversible.

For nausea and vomiting there are multiple FDA-approved therapies. These, or some of these, have been shown to be effective in preventing or treating nausea and vomiting in the post-op, chemotherapy, motion sickness, and gastroenteritis settings. None were specifically approved for nausea and vomiting associated with gastroparesis.

In conclusion, there are data from randomized, controlled trials to suggest efficacy for both gastroparesis and nausea and vomiting. For gastroparesis, trials were either small or suffered from significant design limitations. For nausea and vomiting, trials were in the chronic postprandial dyspepsia population.

There is one FDA-approved therapy for gastroparesis and numerous FDA-approved therapies for nausea and vomiting in various settings, although none specifically for nausea and vomiting associated with gastroparesis.

FDA Presentation - Catherine Sewell

DR. SEWELL: Going back to lactation, there is minimal quality data on the efficacy of domperidone for lactation disorders. A Cochrane review from 2012 included only two randomized, placebo-controlled trials, with a total of 59 mothers of preterm infants.

Domperidone, 10 milligrams 3 times daily, taken for 7 to 14 days, resulted in a modest placebo-corrected increase in expressed breast milk of 99 milliliters per day, or about 3 and a half ounces. The studies did not detect significant improvements in longer-term outcomes of breastfeeding.

There have been several uncontrolled studies of domperidone, from 30 to 60 milligrams daily. Domperidone did result in increases of prolactin levels from 150 percent to 600 percent of baseline within 15 to 45 minutes of ingestion in both nonpregnant and in lactating women.

Domperidone also increased milk production one and a half to two times from baseline in

lactating women. Sixty milligrams was not found to be more effective than 30 milligrams. It is important to note that these studies were mostly observational and uncontrolled, and had a short duration of follow-up.

So in terms of efficacy, there's scant reliable clinical data to support the drug's effectiveness or to support dosing recommendations for lactation disorders. It's important to note this, however, in the context that there are no approved pharmacologic therapies for lactation disorders.

Next, we'll discuss the major safety concerns of domperidone, specifically QT interval prolongation, Torsades de Pointes, ventricular arrhythmias, and sudden death. I just want to set the stage first by discussing the basics of the QT interval and how a QT interval prolongation risk of a drug is assessed.

The mechanism by which a drug can cause QT prolongation is as follows. A drug blocks the potassium ion channel and reduces the potassium

current. This then will delay the repolarization or the recovery phase of the heart. This is seen as a prolonged QT interval on an EKG, right here. If another beat starts before the recovery phase is complete, this can trigger an arrhythmia like Torsades de Pointes.

There are many factors that can increase a person's risk for drug-induced Torsades de Pointes. I've listed a few here. Notable ones are female sex, electrolyte abnormalities like hypokalemia or low potassium and hypomagnesemia or low magnesium.

If a person is taking another drug that also prolongs the QT interval, this can compound the effect; or if they are taking a medication that increases the level of the drug in question, this can increase the QT prolonging effect. Additionally, if the patient already has an arrhythmia like a bradycardia, that increases their risk.

To address how we determine that a drug carries a risk for QT prolongation, we'll discuss the research studies that are recommended.

In 2005, the International Committee on Harmonization, or ICH, issued a guideline called the ICH-E14 Guideline. The ICH, as you know, is a collaboration between the regulatory bodies of the European Union, Japan, and the United States.

They provided recommendations for the design, conduct, analysis, and interpretation of studies to determine whether a drug has an effect on cardiac repolarization, as measured by QT prolongation. These studies are called thorough QT studies. They are typically conducted in healthy volunteers.

If a drug's safety and tolerability allow, multiple exposure levels of the dose, or supratherapeutic dose exposures, are studied so that the drug concentration response relationship with the QT interval can be adequately characterized.

According to the ICH Guideline, if the QT interval is prolonged by 5 milliseconds and the upper bound of the 95 percent confidence interval is 10 milliseconds, this reaches the regulatory

threshold for concern and is considered a positive thorough QT study. A negative QT study is one where the upper bound of the 95 percent confidence interval is less than 10 milliseconds.

Now, if a study is positive, additional information is needed -- for example, from nonclinical data or from postmarketing safety reports -- in order to fully assess a drug's QT prolongation risk.

Also, for some background, many drugs have been withdrawn from the U.S. market due to QT prolongation and Torsades de Pointes. You're probably familiar with terfenadine, which was marketed as Seldane, and cisapride, which was marketed as Propulsid. The risks were detected only after these drugs were taken by hundreds of thousands or millions of people.

Further, using terfenadine as an example, terfenadine alone blocks the potassium ion channel and causes QT prolongation, which you can see here. When terfenadine is ingested, it is metabolized by the liver.

Now, if a person is taking another drug that's metabolized by the same enzymes in the liver, this can result in increased levels of terfenadine. So, for example, if a person is taking terfenadine and then takes ketoconazole as well, this can increase the levels of the terfenadine by 20 times. And then these increased levels can further significantly prolong the QT interval.

In the case of terfenadine, the FDA received several reports of people developing arrhythmias and people who died. FDA determined that this risk of a life-threatening arrhythmia, even when the risk was rare, outweighed the drug benefit of symptomatic relief, and revoked the drug's marketing approval.

So to summarize the information on QT so far, drug-induced QT interval prolongation can lead to Torsades de Pointes, a potentially life-threatening arrhythmia. A thorough QT study is one of the ways that we determine whether a drug has a pharmacologic effect on cardiac repolarization at

the doses and exposures evaluated in the study.

It's important to note here that supratherapeutic exposures would ideally be studied. I'll get back to that point as it relates to domperidone later. The risk of Torsades de Pointes is also influenced by an individual patient's risk factors.

Now, Dr. Leslie McKinney will review the proarrhythmic risks of domperidone.

FDA Presentation – Leslie McKinney

DR. MCKINNEY: The proarrhythmic risk of domperidone has been characterized in detail in several different nonclinical preparations. Domperidone has a significant off-target effect. It blocks a cardiac potassium channel called Kv11.1, or hERG, that conducts a repolarizing potassium current called IKr.

The assay demonstrating this is shown on the left, this left panel. The upper trace shows the stimulus paradigm that activates the current, which is shown in the lower set of tracings. That's the current tracings right there.

Domperidone blocks this current completely at 1 micromolar and shows half maximal block at 57 nanomolar. This assay was conducted in vitro in cells expressing human potassium channels, so it is relevant to humans.

The result of domperidone block of potassium current is shown in the panel on the right. The depolarizing phase of the cardiac action potential is prolonged, which leads to overall prolongation of the action potential. That would be the rightmost action potential.

In this example, which was recorded from a guinea pig heart, 100 nanomolar domperidone increased action potential duration by 24 milliseconds, which is considered to be a large increase.

In this slide -- this expands on the results from the previous slide -- prolongation of the action potential by domperidone can disrupt the normal propagation of the electrical signal through the whole heart, which can lead to arrhythmia. This has been demonstrated in the rabbit heart

using the TRIaD test, which is shown on the left panel.

The TRIaD test measures different aspects of the stability of the heart rhythm, and I will not go into detail about all the different parameters that are measured in this test. What I'd like to emphasize is that as domperidone concentration is increased, the heart rhythm shows an increasing number of irregularities, which can ultimately lead to arrhythmia.

So in conclusion, nonclinical studies have established a mechanism of action for the proarrhythmic risk of domperidone, and have demonstrated that this risk occurs at extremely low nanomolar concentrations.

FDA Presentation - Catherine Sewell

DR. SEWELL: So going back to the patient side, you remember just a few slides ago we discussed the utility of a thorough QT study in determining a drug's risk for QT prolongation. So the makers of domperidone actually conducted a thorough QT study, which was just published this

year.

This was a randomized, double-blind, four-way, crossover, placebo and positive controlled, single and multiple-dose study in 44 healthy adults, 12 of whom were women. They assessed the effects of domperidone on the QT interval at the then-European approved doses of 10 milligrams orally four times a day and 20 milligrams four times a day. You will note that supratherapeutic doses and exposures were not studied.

The study showed no clinically relevant effect of domperidone on the QT interval at the doses and exposures evaluated. This sounds positive. However, the study had the major limitation in that it did not evaluate the effect of supratherapeutic doses and exposures, which could reflect the real-world worst-case scenarios.

The European Medicines Agency, or the EMA, explained that supratherapeutic doses were not studied because the potential for QT prolongation was foreseen based on nonclinical data and based on

reports in humans. The governing body basically thought that it was unethical to expose healthy volunteers to such an unpredictable, serious risk, even in a monitored study setting.

So now I'd like to review with you the reports of domperidone's cardiac risk in humans. In the early 1980s, there were reports of seven cancer patients with serious cardiac adverse reactions, including QT prolongation, Torsades de Pointes, cardiac arrest, and sudden death, with a rapid infusion of intravenous domperidone for anti-nausea treatment during chemotherapy.

An increasing number of such cases worldwide led to withdrawal of the IV formulation in 1985. These serious cardiac reactions were subsequently noted with other forms of domperidone, specifically the oral and rectal formulations.

Cases with these other oral and rectal formulations were delineated in the 2013 EMA report. The EMA evaluated data from the drug maker's safety database through 2012. There were 342 cases of serious cardiac adverse events

reported, including cardiac arrest, myocardial infarction, EKG QT prolongation, and tachycardia.

Eighty-seven of the cases were fatal, 64 percent of these were in females, 41 percent were in people who were at least 65 years of age, and it occurred most commonly in people taking more than 30 milligrams daily.

There were 156 cases of cardiac conduction events, and for 60 of these, information on time to onset was included. Twenty occurred on the same day as the first dose of domperidone. In another 24 cases, the cardiac event occurred within the first week of domperidone dosing.

The EMA also examined its pharmacovigilance database up to 2013 and found 219 cardiac adverse events, including ventricular arrhythmias, cardiac arrest, and rate and rhythm disorders. The median time to onset was two days from domperidone exposure.

The risks again were increased in patients who were over 60 years of age and in those who were taking more than 30 milligrams of domperidone

daily. The risks were also increased in patients who were taking other QT prolonging drugs or taking products that increased domperidone's exposure.

This highlights then that serious or fatal cardiac arrhythmias can occur at doses that are approved for use in jurisdictions outside of the United States. The time to onset suggests that there is a causal relationship with domperidone.

The risk is increased with increasing doses of domperidone, and the risk is increased in the population wherein people are taking other drugs that can prolong the QT interval or that can increase domperidone's exposure.

The FDA also conducted its own review of the FDA Adverse Event Reporting System, or FAERS. And as you all know, FAERS is a computerized database of spontaneous adverse event reports for human, drug, and therapeutic biologic products. Data has been collected since 1969, and there are over 9 million reports currently stored. About 1.2 million reports were received in 2014 alone.

The system has multiple strengths, including

that it receives adverse events on all uses of drugs, whether they are approved or unapproved, within and outside of the United States. FAERS is ideal for detecting rare events like Torsades de Pointes or acute liver failure. It's also useful when the report is received shortly after exposure because we can make that time connection.

FAERS has some limitations. As you know, it's a passive surveillance system, so we receive isolated volunteer reports. We don't have a denominator and therefore can't calculate an incidence for a particular event.

Because reporting is voluntary, there is likely underreporting, and this is especially true for unapproved drugs. People may not be aware of the side effect profile of a drug, may not connect a specific adverse event to a particular drug, and may not report it. The quality of information in the reports is also variable.

Here, I'll present some cases from our evaluation of the FAERS database. I would like to point out that these do not represent the sum total

of the cases in the database. They are merely illustrative to our points today.

We conducted a FAERS search in females less than or equal to 50 years old who were taking oral domperidone, and we searched between January of 1965 and April of 2015.

In 2013, we received a report of a 46-year-old female with longstanding gastric esophageal reflux disease. She was taking domperidone, 20 milligrams daily for 4 days, and when she went for a scheduled stress test, she experienced Torsades de Pointes, cardioversion was unsuccessful, and she died.

In 2012, we received a report of a 34-year-old woman who was taking 120 milligrams of domperidone daily for lactation. After 4 days, she had palpitations, shortness of breath, and difficulty getting out of bed. Her EKG showed QT prolongation. She stopped the domperidone and the QT prolongation resolved.

The FAERS also yielded cases of women who had other risk factors for QT prolongation that

could increase their risk with domperidone. And again, these cases do not represent the sum total from the database; they are merely illustrative to our point.

In 2013, we received a report of a 34-year-old woman in Great Britain who was treated with oral domperidone, 30 milligrams daily. She collapsed and was found to have complete heart block. Her risk factor is that she was also taking the medications sumatriptan, sertraline, and ondansetron.

In 2012, a 19-year-old female in Canada was taking oral domperidone of an unknown dose, ciprofloxacin, and metronidazole. She was also found to have hypokalemia and borderline hypomagnesemia, and she was diagnosed with QT prolongation.

Her symptoms resolved when she discontinued the drug and had her electrolytes repleted. Her risk factor was that she was also taking the medication ciprofloxacin, and she also had electrolyte abnormalities.

In 2006, a 35-year-old healthy woman was treated with oral domperidone of an unknown dose for lactation enhancement. She developed QT prolongation and syncope 2 days after adding azithromycin to her medication regimen. There are no further outcomes reported on this patient. Her risk factor is that she was also taking azithromycin.

So far we've reviewed case reports from the literature and then cases from the pharmacovigilance databases in the European Union and the United States. We would also like to present some data from pharmacoepidemiologic studies.

The FDA conducted a systemic literature search that yielded 15 articles from six interpretable, non-experimental studies of domperidone and QT interval prolongation, Torsades de Pointes, serious ventricular arrhythmia, or sudden cardiac death. The review found evidence for a 1.5 to twofold risk of sudden cardiac death from current use of domperidone in the general

population.

The EMA conducted a pharmacoepidemiologic review as well, including many of the same studies, and reached similar conclusions. This review did not provide any data that could inform whether there are differences in risk to breastfeeding women.

I will highlight here two of the bigger studies in the FDA review. In 2010, Johannes et al. published a population-based nested case control study using the electronic databases of Saskatchewan Health. She found 1,559 cases of sudden cardiac death, and 49 cases of serious ventricular arrhythmia. These were matched with 6,428 controls.

The mean age of cases in controls was 79 years, and over 50 percent of the cases were female. The adjusted odds ratio for the composite endpoint of sudden cardiac death and serious ventricular arrhythmia associated with current domperidone use was 1.59.

These findings suggest then that current

domperidone use was associated with a 1.6-fold increase in the risk for the composite endpoint of sudden cardiac death and serious ventricular arrhythmia in the general population.

In 2010, Van Noord et al. published a population-based case control study using the Netherlands Integrated Primary Care Information database. She found 1,304 cases of sudden cardiac death and 62 cases of serious ventricular arrhythmia. These were matched with over 14,000 controls.

The mean age of the sudden cardiac death cases was 72 and a half years; 42 percent of the cases were in women. The adjusted odds ratio for the composite endpoint of sudden cardiac death and serious ventricular arrhythmia was 1.92, and for sudden cardiac death alone, 1.99.

These findings suggest that domperidone was associated with an approximate twofold increase in the risk of sudden cardiac death and serious ventricular arrhythmia in the general population.

The drug maker also conducted drug-drug

interaction studies to evaluate QT prolongation. When domperidone, 10 milligrams 4 times daily, was taken in combination with another drug like ketoconazole or erythromycin -- these drugs are strong or moderate CYP3A4 liver enzyme inhibitors that also prolong the QT interval -- they found the following: a two- to threefold increase in domperidone blood concentrations, and a statistically significant increase in the QT interval compared with placebo at most time points during the 24-hour observation period.

The maximum mean increase of the QT interval was 13.6 to 15.3 milliseconds. And as you may remember, this exceeds the ICH-E14 Guideline regulatory threshold of concern, which is a maximum mean increase in the QT interval of 5 milliseconds, with the upper bound of the 95 percent confidence interval being 10 milliseconds.

The next several slides show the many classes of drugs that interact with domperidone and should be avoided. And you'll note that they include many commonly-used drugs -- for example,

antihypertensives, antidepressants, diuretics, antidiarrheal agents, and antihistamines. The full list is in the briefing document, so these slides are not complete.

As it pertains to lactation, we must consider other safety implications of domperidone, mainly in the pediatric population. Several studies were published between 2005 and 2013 that reported QT prolongation in infants treated with domperidone for various gastrointestinal conditions.

Three of the studies reported doses, and those range from 1.0 to 2.1 milligrams per kilogram per day in divided doses. One study could not find a relationship between QT prolongation and the dose of the drug. Another study reported QT prolongation with an accidental overdose at home.

We do know that domperidone is transferred into human breast milk. Maternal doses of 10 milligrams TID or 20 milligrams TID do result in breast milk levels of domperidone. And if we assume a daily milk intake of 150 milliliters per

kilogram for an infant, this does result in doses we can calculate that infants might be exposed to.

Therefore, breastfed babies may be exposed to levels of domperidone, perhaps over weeks or months, depending on how long their mothers take the drug. This potential risk is of real concern.

So our safety conclusions are as follows. Domperidone is associated with serious risk of QT prolongation, ventricular arrhythmias, and sudden cardiac death. Cases of cardiac toxicity have been reported with domperidone in intravenous, rectal, and oral formulations.

Patients with cardiac toxicity do often have cardiovascular risk factors, or are taking concomitant medications, or have other risks for QT prolongation. But serious adverse cardiac arrhythmias have also occurred in otherwise healthy young women with no apparent risk factors.

We know that domperidone prolongs the QT interval, but the dose and exposure-response is not well characterized. We've seen QT prolongation, cardiac arrhythmias, and sudden death

with doses of domperidone approved in jurisdictions outside of the United States.

The thorough QT study did not evaluate supratherapeutic exposures, and therefore it does not inform the risk threshold of QT prolongation with real world use of the drug. To this point, domperidone is susceptible to drug interactions with other medications that can increase domperidone exposure and that also prolong the QT interval. Also, domperidone is secreted in human breast milk, and this poses as yet an unknown risk to the exposed infant.

Given the safety concerns, there is potential for significant harm to the public if domperidone is prescribed and used without important safeguards to ensure adequate patient protection. Examples of these safeguards include, but are not limited to, assessment of the patient's risk factors and medications that could increase their risk of QT prolongation; proper patient selection; appropriate dosing and dosing regimen; and proper patient monitoring.

There are some safeguards in place outside of the United States. In 1985, as we said, the IV formulation was withdrawn worldwide due to reports of QT prolongation, ventricular arrhythmia, and sudden death.

In 2014, the EMA recommended restricting the indication of domperidone to only nausea and vomiting. The maximum daily dose was reduced to 30 milligrams, and the maximum duration to 7 days. They also withdrew higher dose oral and rectal formulations from the market, and provided new contraindications in labeling.

In 2014, the nonprescription status for domperidone was revoked in Belgium, the Netherlands, and the United Kingdom so that access now is only by prescription. In 2014 and 2015, Health Canada issued a healthcare professional warning, a public communication warning, and a recalls and alert advisory about the cardiac risks of domperidone, and provided the same recommendations as the EMA.

In the United States, in 2004, the FDA

issued an import alert and a safety alert because of the potential cardiac toxicity of domperidone, including QT interval prolongation. These alerts were based on the postmarketing adverse events reports from non-U.S. markets.

The warning also highlighted the secretion of the drug in breast milk. The absorption and infant exposure is unknown, so not only is there a safety risk to the lactating mother, but also to the breastfeeding infant. This is just a screenshot of that warning from 2004.

In the U.S., no pharmacies are allowed to compound domperidone. Since 2004, the FDA has issued multiple warning letters to pharmacies that compound products containing domperidone and to the firms that supply domperidone for use in compounding.

Domperidone is available in the United States through the IND expanded access program to patients who need it. Dougherty's Pharmacy in Dallas, Texas is currently the only pharmacy authorized to dispense manufactured domperidone.

There are two authorized manufacturers.

The IND expanded access protocol allows for the treatment of refractory GERD with upper GI symptoms, gastroparesis, and chronic constipation in patients at least 12 years of age. It provides for exclusion criteria, specifically focusing on a patient's cardiac risks.

It provides a specific dose regimen, 10 to 30 milligrams 4 times a day. Most importantly, it has patient protections, including informed consent, scheduled cardiovascular monitoring, and the list of drugs that interact with domperidone that should be avoided.

So in conclusion, the efficacy and appropriate dosing regimen for domperidone in lactation are uncertain. Given the serious proarrhythmic risks reported, the use of domperidone in the compounding setting for lactation is unacceptable.

The evidence of efficacy of domperidone for nausea, vomiting, and gastroparesis is not robust. Given the serious proarrhythmic risks reported and

the availability of FDA-approved products to treat these conditions, use of domperidone for GI conditions in the compounding setting is also unacceptable.

I will note that patients do have access to domperidone through the expanded access IND program, which ensures a specified dose range, appropriate patient selection, exclusion of patients who have risks for QT prolongation, and it provides for informed consent and adequate safety monitoring.

Finally, we do not recommend that domperidone at any dose be placed on the list of bulk substances that can be used to compound under Section 503A of the FD&C Act. Thank you.

Clarifying Questions

DR. VENITZ: Thank you, Dr. Sewell, Dr. McKinney, and Dr. Rajpal.

We now have time for some clarifying questions by the committee. Dr. DiGiovanna?

DR. DIGIOVANNA: John DiGiovanna. Could you tell us a little bit more about the expanded access

IND? How does that actually happen? How does a physician request it? Who pays for it? Is it difficult to do? Is it available across the U.S.? Are people who would want to prescribe it aware of it?

DR. RAJPAL: There's a standard protocol that's available on the FDA website where it gives instructions on how to apply for an IND, for an expanded access IND. And it's pretty much standardized. So it's available for any physician based on the diseases we have listed, the refractory GI conditions now on patients 12 years of age and older.

DR. DIGIOVANNA: So it's something that an individual physician needs to look at the FDA website to determine that it's available, and then actually put together an IND form, and IND package? It's not something that's there and they can just sign onto and they're told, you do A, B, C, and D, and you get it; they have to actually submit paperwork as an IND?

DR. RAJPAL: It's a standardized form. So

there's just portions to complete, that the physician has to complete.

DR. VENITZ: The information that's required is about the patient and the physician. The physician doesn't actually file for the IND; they are just working under the purview of an IND? I think that's the question that Dr. DiGiovanna had.

DR. DIGIOVANNA: Yes. How difficult is it for someone to do it, and what do they actually have to do to do it? How much? Is it one page? Is it a hundred pages?

DR. RAJPAL: It's a two-page IND. It would be a new IND.

DR. VENITZ: Can I ask a follow-up? Do you know how many patients are actually enrolled in that program?

MS. AXELRAD: I don't think we're allowed to disclose that. We were told there's disclosure issues associated with INDs and expanded access protocols, and I don't believe that we're allowed to talk about how many.

DR. VENITZ: You're not allowed to disclose?

MS. AXELRAD: Yes. It's confidential information. We're not allowed to talk about INDs and numbers associated with it. I know.

DR. BRAUNSTEIN: I Googled this. Right? So it comes right up. And the FDA's program says what you need to do. But unfortunately, there's no forms online. You have to send an email to the Division of Drug Information to request the packet.

So we don't really know and we're not able to evaluate at this committee what actually is involved. So that's what's available that I could find online, just doing a quick search.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: There was also a public comment from a physician who was aware of this IND program and was very willing to use it, was offered that option by FDA. But he raised the difficulties of finding access to an internal review board in his particular private practice setting.

I believe that came up in our first meeting in February as well, is the lack of availability of IRBs outside of hospital systems and universities.

And that still concerns me, that that might be a roadblock to patients getting this through the IND program.

DR. VENITZ: Go ahead.

DR. KORVICK: I'm Dr. Korvick. I'm the deputy for safety for the Division of Gastroenterology and Inborn Errors Products. And you're correct. The individual physician can apply for an IND, and they would contact the FDA the way anyone who would want to initiate an IND would do.

We have paperwork that we have made for practicing clinicians who can -- it can expedite the process so that they don't have to develop a whole protocol and certain various other things. So we don't put that on the website, but we do freely give it out to any physician who would call to have that particular protocol given to them.

Then we do have to do our due diligence in exchanging information between our clinicians and the doctor who wants to prescribe this for a set indication. So we do the usual things that we do for INDs, but we try to facilitate that.

MS. AXELRAD: Dr. Korvick, can you address the IRB question?

DR. KORVICK: I think that these issues are brought up for every IND that some physician wants to do out there. So these are not uncommon to other areas of practice. I don't know what to say beyond that. We don't have an IRB. We do? We don't?

MS. AXELRAD: If they don't live in a place where there is an IRB that they can go to, what do we tell them to do?

DR. KORVICK: Anil?

DR. RAJPAL: Yes. I just pulled up our forms, and it does say on there that if IRB review -- it gives instructions on how to get IRB review. And it says if IRB review cannot be accomplished, it directs them to contact the FDA Human Subject Protection Branch.

DR. KORVICK: So again, we can try to help facilitate that issue if they're working with us. We also have individual patient INDs under this program, or there are physicians who apply to

enroll multiple patients if they have a clinic that has more than one patient.

DR. VENITZ: Dr. DiGiovanna?

DR. DIGIOVANNA: So this then would be considered a research activity, I would gather, if an IRB is required, which means that if I were to want to use it, which I wouldn't because it's outside of my purview, but then my institution, I would have to write a protocol for my institution to go to the IRB to use it and then, in addition, to have that paperwork.

So it sounds like it is not just a matter of filling out one page. I'm just trying to get a sense as to understand the simplicity or lack thereof of what's involved with it.

DR. RAJPAL: The protocol's just a few pages, and I think it has all the inclusion and exclusion criteria standardized. And the most important thing about the assessment and monitoring, in terms of EKGs, it goes into detail. We did include that as an attachment.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Other than, of course, the safety reports, 15 days and things of that nature, what are the other reporting requirements that a physician would have? I'm in industry, so we do this stuff all the time. But I don't know about what kind of burdens we have on an individual physician. So I'm just asking this, trying to find out for the committee.

DR. RAJPAL: Well, I believe there's annual reports are required. And in addition to that, I would have to ask what's required.

DR. BRAUNSTEIN: But for something like one or two patients, would they simply tell you what's going on with the patients, what's been the experience? Have you made this easy enough so that a practicing physician -- I'm trying to find out how easy you're making this for a practicing physician. I'm hoping it's easy. That would be --

DR. RAJPAL: Well, I think it's standard for any IND. But mainly, the protocol is standardized. And in terms of the reporting requirements, I

believe they're the same as for any IND in terms of reporting serious adverse events and giving email reports.

DR. KORVICK: This is Dr. Korvick again. I would just say your question about how easy it is for a practicing physician is a very difficult question to ask, depending on the type of practice that they run, et cetera and so forth.

The steps that we've taken under this IND are to help to provide them with basic components of what they would need to submit to us so that they are not de novo looking for an IRB. They're not de novo creating a protocol under which that they would use to treat the patient.

So is it more work than they would do if they were writing a script? It is more work. However, we try to work with the physicians to do this. And this is an IND, and what that implies is that this is a drug that's not approved in the United States and it's being used under "experimental" conditions, which is why we have a protocol.

DR. SEWELL: Dr. Carome?

DR. CAROME: A comment and question. I don't think it should be easy to get an experimental drug like this with the toxicity it has. So I think it's appropriate that there are certain thresholds that someone has to get over in order to prescribe this dangerous drug.

Could FDA explain, how do the preclinical and clinical data set for the QT prolongation toxicity seen with this drug compare to the drugs that have been withdrawn from the market for the same reason?

DR. NGUYEN: As you can see from the nonclinical evidence, it's pretty clear that there is an established mechanism that explains the drug's pharmacologic effect. So while I can't really compare it to another drug, I think, on its own, certainly it's convincing evidence.

As for the clinical evidence, again, we didn't undertake a comparative review. But I'd like to point out, for a drug that's unapproved, any case of Torsades is impressive. So I hope that

answers your question.

DR. VENITZ: Dr. Wall?

DR. WALL: Two questions. One, there was a mention about a drug interaction list. Can you tell me, does that go just to the physician? Does it go to the patient? Is it to go for the patient to give to all their pharmacies? How in the real world is this list being implemented to make it safe for this patient?

DR. RAJPAL: Again, it's part of the domperidone packet that's sent to the physicians when they are applying for the IND. So they're made aware of all the drug interactions as they submit the protocol.

DR. WALL: But is there any guidance to say you need to make sure that the patients give it to their pharmacies? Because --

DR. RAJPAL: Yes.

DR. WALL: -- doing enough med histories, I know that these folks don't necessarily get an accurate history. It needs to be out there in a live document.

DR. RAJPAL: Okay. Yes. I'm sorry. I forgot to mention that there's also an informed consent where all this information will be given to patients.

DR. WALL: Then the patient signs off on the informed consent?

DR. RAJPAL: Yes.

DR. WALL: And secondarily, as I was reading some of the letters, some of the patients had commented that I believe -- is this a tablet that comes from this facility? It's like there's one product, I think, that comes. Isn't there one pharmacy that's allowed to dispense it within the U.S.?

MS. AXELRAD: I think she's asking about the nature of the manufactured product that comes from the two facilities, one in Canada and one in the U.K. She's asking what it is.

DR. WALL: Right.

DR. NGUYEN: It is an R [ph] tablet.

DR. WALL: And it comes from a pharmacy in Texas. Correct? I believe?

DR. NGUYEN: Correct. As a manufactured product, as a, you know --

DR. WALL: Is there any flexibility within this protocol for that tablet to be made into suspensions or into something else that may make it more palatable or appropriate for patients? Or is it you have to use this tablet or nothing?

DR. NGUYEN: I'll let Dr. Rajpal speak to the protocol. But just to allude to your point, do we say, go ahead and crush a tablet and put it in a liquid? We certainly wouldn't do that just for the very reason that we don't know the QT behavior of this drug if you changed its formulation somehow such that the exposures could be changed.

So for a drug with this sort of safety risk, one has to be very careful in terms of you break it up, you chew it, or change it in its form.

DR. RAJPAL: As far as I know, it's available as a tablet, and the dosing is allowed in the protocols between 10 and 30, 4 times a day, 10 to 30 milligrams 4 times a day.

DR. WALL: With the new information about

decreasing the dose, is there a look at that protocol to decrease that 30 milligrams 4 times a day?

DR. RAJPAL: I'm sorry?

DR. WALL: Didn't we receive information that there's new dosing guidelines, that maybe the 30 4 times a day was too high? Is there any discussion to decrease that dosing down in that protocol? Just curious.

DR. KORVICK: This is Dr. Korvick again. I think that we try to work with the individual physicians to address the patient's needs. And you said that you got letters, and I guess they're complaining about the size of the tablet or --

DR. WALL: These were the letters FDA had sent to us.

DR. KORVICK: Oh, all right.

DR. WALL: Patient letters about having -- that dosage form wasn't necessarily compatible with them.

DR. KORVICK: We try to work with our individual patients to see what we can do for them.

Again, these are pre-manufactured, similar to things that are dispensed in Canada and Europe. And that's what's available on the market.

Certainly under an IND we might be able to work with a patient to see if it was appropriate to cut the pill in half or whatever we would have to do. So under the auspices of an IND on an individual case-by-case basis, we might look into that, depending on the patient need.

DR. VENITZ: Let me just point out to the committee, on page 426 of the document that we got, the briefing document, it is pretty specifically outlining the activities that are involved in enrolling a patient, screening for drug interactions, EKGs, and so on. So you might want to look at it.

But Dr. Vaida, you had a question?

DR. VAIDA: Yes. In the few written comments that we had, and I don't know what the public hearing -- it seems like the use that's really being requested is for gastroparesis. But yet it seems like the EMA restricted it to nausea

and vomiting.

Is Canada also -- now, again, once a drug's available, you could use it for anything. But the availability in Canada or the other countries, is that restricted for a certain indication or recommended for a certain indication only?

I'm just a little -- it seems like the use here in the comments are for -- like the only drug available is metoclopramide for that condition, whereas for nausea and vomiting, we have many drugs available. So that's where I'm just a little questioning. In the other countries, is it restricted for use?

DR. KORVICK: I think it's interesting, and my colleagues have talked about the European review of the product, and they had previously approved it in various countries for various indications. The drug is not approved in this country, and we would need an NDA to be submitted to show proof of safety and effectiveness.

One could look at the spectrum of GI diseases around this, which would include

dysmotility, functional gastromotility issues. And so then when we look at this, we see it in that light. And there are other drugs that we have to treat simple nausea and vomiting. I don't know if that answers your question.

DR. VENITZ: Any other questions?

(No response.)

DR. VENITZ: Then I just wanted to confirm that on one of your slides, you pointed out there's only one alternative treatment available in the United States that's approved for gastroparesis, and that is metoclopramide. Is that correct?

DR. RAJPAL: That's correct.

DR. VENITZ: Okay. Any other questions by the committee?

(No response.)

DR. VENITZ: Any questions from our committee members on the phone?

DR. CHANG: Yes. This is Lin Chang. I just wanted to make a comment. I'm a gastroenterologist, and I take care of patients with chronic GI conditions. And I just wanted to

make a clarification on one of the questions.

Gastroparesis is a chronic condition, as everybody knows. For nausea and vomiting, we really have options, like ondansetron, for example. Domperidone has been -- the efficacy has been assessed in chronic upper gastrointestinal disorders. So the patients with chronic nausea or chronic nausea and vomiting would be more likely gastroparesis or functional dyspepsia, which is an overlap with gastroparesis.

So even though there may be alternatives to just strictly nausea and vomiting, they're not necessarily efficacious treatments for patients with gastroparesis and functional dyspepsia, which are probably the more common causes of chronic nausea and vomiting in the patient population.

DR. VENITZ: Thank you, Dr. Chang.

Any final questions?

(No response.)

DR. VENITZ: Okay. Then let's move to the nominator presentations. We have two presentations on domperidone. The first presentation is by

Dr. A.J. Day from PCCA. Dr. Day?

Nominator Presentation – A.J. Day

DR. DAY: Good afternoon. My name is A.J. Day. I'm with PCCA out of Houston, Texas. We don't actually have a financial disclosure on this. We provide domperidone for use in animal medicine at this point.

So the FDA's presentation on domperidone was quite lengthy. It provided a lot of detail. So I won't spend a lot of time getting into as much detail so that we can focus on what the concerns are that have already been coming from the discussion.

A little bit of background. We know that it's a dopamine-2 receptor antagonist. We know that it is inhibiting dopamine, mostly peripherally, but also in the chemoreceptor trigger zone. It does not cross the blood/brain barrier as readily as metoclopramide, and due to that, you do see a reduced incidence of extrapyramidal side effects compared to metoclopramide.

It is commercially available in 112

countries around the world. The common trade name that is found is Motilium. There are many other commercial names, and it's been marketed worldwide since 1978.

Now, we've got about 37 years of history on this substance, and there's some good and bad with it. Right? So we know a lot about its physical, chemical, and clinical characterizations. As a result of that, we've had a lot of time to analyze some of these warts that we see with it.

The FDA has done a really good job at honing in on the biggest wart and the one that we need to be concerned about. So let's take a little bit of a look into domperidone and its clinical use and how we see it used in the United States, as well as some of the clinical studies.

First, the American College of Gastroenterology does recommend the use of domperidone as second-line therapy. First line is metoclopramide, as it should be, and when patients are refractory to metoclopramide or when the side effect profile of metoclopramide is intolerable,

then they move to domperidone. This is in the current recommendations from the American College of Gastroenterology.

Now, let's look at some of the nonclinical cardiac studies that were presented by FDA from the FDA briefing document. We see that in the study that looked at the effective dose causing the cardiac parameter effects. We see that the dosing is on the scale of 30 to 100 nanomolar.

This is important because in that same study, they do also acknowledge the -- and what they find in the clinical evidence is that the systemic human studies show that doses are between -- or, excuse me, concentrations are in the range of 3 to 19 nanomolar, significantly lower than what is reported in the animal study, in the nonclinical cardiac studies.

The commentary on Sugiyama -- this article is from the British Journal of Pharmacology in 2008 -- talked about predictive animal models, and of course acknowledging that however close they look, those extrapolations from the drug's effects

and those predictive animal models and in vitro models is difficult even when the concentrations are similar between patients' plasma and perfusion solutions. So these predictive models that we looked at in the previous slide are not always perfect or even all that accurate.

So let's jump forward to what is the actual risk of ventricular arrhythmias and sudden cardiac death. This is the most publicized concern. This is where we've spent most of our discussion, and the FDA did spend a lot of time.

We know that there have been some recent studies that were epidemiologic studies, case control studies, nested case control studies. And as a result of some of these publications, the guidelines within Europe, U.K., and recently in Canada have been amended.

So let's put that safety in perspective. What is the real risk of the QT prolongation and Torsades? This is again from Clinical Pharmacology. These are the medications that have gone through our approval process that have both

the risk of QT prolongation as well as Torsades. These are all of the medications that we have on the market right now with that risk.

If we remove the "and" comment, these are the medications that have just the risk of QT prolongation. When we saw the list potential interactions or likely interactions that the FDA put up with regards to domperidone, it's because you don't want to give it with medications that will increase your risk of QT prolongation.

This is not a full list. I couldn't fit it all onto the slides. So here we have a few screenshots where it's already smushed together of the medications we use today. And erythromycin as being one of the medications that's suggested for use in gastroparesis, is on this list for causing QT prolongation. Amoxicillin. Amitriptyline. Quinine. The list goes on. It is quite extensive.

It brings into perspective why there are so many potential interactions because we're already dealing with these medications on a regular basis. Sulfamethoxazole/trimethoprim. How many doses of

that do we see in the clinical and in a community setting?

So there are a number of data points that have been published and that have been referenced in the FDA's briefing information. Here we have the article by Vieira about effects of domperidone on QTc interval in infants. So the range of these patients were 0 to 1 year; 45 infants were enrolled. And here we have another study that looked at effect of domperidone on QTc interval in premature infants.

In this first study, we see that of the 45 infants, there were no significant changes in QTc interval noted. There were two infants, both boys -- and as FDA pointed out, the incidence is more likely in females -- and they had QTc prolongation without symptoms.

In the premature infants, they noted that -- cautiously and modest. So our experience suggests that domperidone administered cautiously and modest doses does not result in arrhythmias or conduction defects in premature infants

statistically.

So let's look at the domperidone with regards to ventricular arrhythmias and sudden cardiac death. Now, these are the two primary studies that were on a larger scale that led to the reclassification in Europe, U.K., and Canada.

Highlights of the Van Noord study, there were 1,366 patients in the database that were identified, 14,114 controls; 95 percent had sudden cardiac death, and the 5 percent had sudden ventricular arrhythmias.

None of the users of domperidone had the SVA. Ninety-two percent of patients with sudden cardiac death did not use domperidone, 7 percent were past users, and 0.8 percent were current users. The researchers determined no statistically significant risk with past users, but there was increased risk with current users on doses greater than 30 milligrams. However, the number of patients that were part of that group was too small to make broad-based conclusions.

Now, here we have the chart from that

article, so we're talking about the dose where patients were on greater than 30 milligrams. What the conclusion was from that study had 4 cases out of 1,304. That's pretty significant to note, that there were only 4 cases where they were on that dose where they experienced sudden cardiac death.

The risk of sudden cardiac death and nonfatal ventricular arrhythmia, again, out of 1,366 patients, there were 4. And that is the only group where the data reached statistical significance.

So some of the limitations of this study, there were significant differences in baseline characteristics for the patients. This does limit the external validity as well as our ability to extrapolate to broader populations.

The mean age was 72.5 years, and the patients all had high frequency of cardiovascular comorbidities at baseline. So we know that we're starting with a very high-risk patient population for cardiac issues. It is not surprising that this data can then not be extrapolated to all age groups

and all users.

The study participants were significantly older at baseline. Again, the study acknowledges 65 and older, with multiple cardiovascular-associated comorbidities. No associations can be made between domperidone use and the risk of nonfatal VA based on the results of this study.

Then we have the second study with Johannes, the combined risk of SVA/SCD in the cohort of users of domperidone. Evaluated combined risk of SVA and SCD in past and current users of domperidone. So they looked at current, past, and non-users who died, and did they have an SVA or from combined SVA/SCD as a combined outcome.

They excluded the patients with cancer, deaths of hospital inpatients, deaths from noncardiac causes. They did have confounding variables that were identified by the authors, and they did do adjustments, and there's statistical analysis.

There were no significant increases in SVA/SCD in past users, and in current users,

10 percent had SVA/SCD. However, a significant limitation here is they did not mention any doses. No doses of domperidone were revealed for any of these patients.

So we cannot make any conclusions as to the specific risk imparted by the domperidone apart from there is a risk. We know the mechanism. There is a risk. We're not denying that, but the scope of that risk, what is the scale of that risk, is what we have to keep in mind. As we know, the QT prolongation mechanism, so many of our other medications utilize that.

So here we have the chart from the study that specifically looked at what were those confounding variables? What are those medical conditions? 3.3 percent had cardiomyopathy, but 35 percent of those patients had heart failure; 37.4 percent had ischemic heart disease; 25 percent had hypertension.

So in their results, when we look at no exposure to the drug, we had 740 patients; past exposure, 168 patients; current exposure, 169

patients. And looking at the current exposure to domperidone, greater than 60 years, that is the group where you read statistical significance.

So our mean age in this study was greater than in the Van Noord study. We have 79.4 years. The use of SVA/SCD is a composite endpoint, and no doses were mentioned.

Now, nested studies is another issue about the study design. These do tend to decrease the power of the study, and it increases the chance of type 2 errors.

Another point is the wide range for the 95 percent confidence intervals, which means you have wide variation from one patient. So as I go back to this slide, your distance from one standard deviation from the norm is quite broad, indicating not consistent results from your patient outcomes.

So the alternatives to domperidone, the FDA does point out that the recommended alternative is metoclopramide. However, in their briefing information, they talk about the boxed warning for tardive dyskinesia and that it is often permanent.

Metoclopramide. We talked a lot about the EMA recommendations and how they've changed their guidelines on domperidone. Well, they've also changed their guidelines on metoclopramide, and they're even more restrictive than you would find for domperidone.

So they looked at safety concerns over the side effects and concerns over efficacy for nausea and vomiting, and what the EUMA analysis confirmed were the well-known risks of the neurological effects that increase with long-term therapy.

So this analysis also uncovered very rare cases of serious effects on the heart or circulation. The EUMA recommendations now have changed metoclopramide to be prescribed for short-term use only up to 5 days, not to be used in children below 1 year of age at all, and in children from age 1 to 18 years of age, only second-line therapy. And metoclopramide-recommended maximum doses in adults should be restricted as well.

Now, to analyze the FAERS data, we didn't

have time. The turnaround time to get the information is greater than a month, and we had about two and a half, three weeks between receiving the briefing information and here today.

Fortunately for us, we had access readily to Health Canada's data, and we know that there is a manufactured product that is commercially available in Canada. So we checked out the data in Canada. We looked specifically at serious events, and there were 133 reported serious events with domperidone between 1985 and 2014. The date range is broader than that; however, the actual dates of the events were between 1985 and 2014, which is, on average, 4.6 serious events per year.

Of those, only one was a death, which has a percentage of 0.75 percent. Twelve were life-threatening. And of those 12, patients were on several medications that contribute to QTc issues. As we saw, the list of the medications we use commonly is extensive.

One patient had 29 concomitant medications and a pacemaker. Eleven of those 12 patients were

on a minimum of six medications. Only one of those 12 had two medications, lorazepam and phenobarbital.

Now, we compare that to the same search within the Health Canada database for metoclopramide. Between 1994 and 2014, we had 122 events, which gives us an average of 5.8 events per year. Fifteen of those were deaths. That's a 12.3 percent incidence rate. Seven were life-threatening.

When we look at the side effect profile specific to metoclopramide, as we discussed earlier, there is a black box warning for tardive dyskinesia. It is often permanent. It is irreversible in many patients. It does include a number of other cardiac and CNS side effects in addition to that.

Now, when we looked at the FDA's presentation and they talked about the trial that examined metoclopramide versus domperidone and the TSS, they talked about that the reductions appeared to be similar; however, it did not meet the current

recommendations for evaluation by FDA.

Well, the evaluation by FDA that they're looking at here, which is the noninferiority basis, is in draft form, published 2015. This is a copy and paste from the FDA's briefing information. That study was conducted in 1999, so I did not expect it to meet today's standard.

Domperidone risk to infants. As we said in the FDA's presentation, we have to be aware of what are we risking if the mother is nursing the infant and exposure to the infant, where are we leaving that safety profile?

So this is a randomized, controlled trial, placebo-controlled. Domperidone was given as 20 milligrams as a single dose. They noted that in the analysis of the milk, 2 hours post-dose, 0.24 nanograms per milliliter, and in 4 hours post-dose, there was 1.1 nanograms per milliliter found in the breast milk.

The authors of that study then compared those results to another study that used metoclopramide, 10 milligrams as a single dose.

That study resulted in 125.7 nanograms per milliliter 2 hours post-dose. They did not do another 4-hour analysis.

The authors of this first study also compared it to a third study that looked at domperidone, 8 milligrams 3 times a day, and they found 2.6 nanograms per milliliter in the breast milk.

So the metoclopramide level that was found in the breast milk, when you compare those two studies, was 500 times greater than domperidone. Now, this was comparing one study to another, so that is a weakness of this comparison.

However, we do know that metoclopramide carries a larger risk due to the irreversible side effects and its ability to cross the blood/brain barrier much more readily than domperidone.

So when we look at that Q 8-hour dosing, we notice that there was a higher concentration of domperidone found in the breast milk, 2.6 nanograms per milliliter. That equates to 6.1 nanomolar.

Now, the package insert from the approved

products found worldwide give us that there is 13 to 17 percent oral bioavailability. So if we estimate at the highest end of that range at 17 percent oral bioavailability, that's 0.442 nanograms per milliliter, or 1.037 nanomolar, potential serum levels in the infants.

So what is the amount of domperidone that we're really exposing that infant to? Well, it's calculated that there's 1.037 nanomolar. And if we go back to the study, the nonclinical study, animal data, we're looking at doses around 30 to, more commonly, 100 nanomolars to create those cardiac side effects.

Again, I'm not denying that there is a risk. The mechanism is clearly outlined. But what is the scope of that risk? And what can we do to protect our patients and appropriately screen our patients to ensure that we're minimizing that risk?

Now, the FDA does also talk about the effect on prolactin. They mention the study by Brouwers, where they found 150 to 600 percent increases from baseline on prolactin. What they did not mention

is from that same article, metoclopramide raised prolactin levels even more than domperidone. And that's what you're seeing on that screenshot on the bottom. Metoclopramide raised it from a lower baseline to a higher final number, 7.4 to 124.1 nanograms per milliliter.

This is data from the Australian government showing the propensity or the utilization of domperidone. The most recent data that we could get was from 2010 and 2011. You can see that the number of prescriptions is fairly consistent with population increase. So in 2011, there are about 365,000 prescriptions for domperidone written. That's not doses, but that's prescriptions written.

Here we have the package insert for the product, Motilium in Australia. They do indicate short-term treatment of adults, specific for idiopathic or diabetic gastroparesis. And they talk about the attempt to discontinue the Motilium. They talk about contraindications, including the hypersensitivity, the prolactin issues, as well as the number of potential drug interactions and QTc

concerns.

They go on to specifically address in more detail the cardiac effects and the information from those recent studies that led to some of the reclassifications in Europe. They explain, what are the incidence? Approximately 4 per 1,000 per year, compared with no use of medication.

The risk is increased in patients aged over 60 or who have cardiac disease or diabetes. And this risk is also increased with Motilium doses greater than 30 milligrams, and when taken in combination with medications that prolong the QT interval. So their recommendation is use this in caution in older patients or those with current or a history of cardiac disease.

So the conclusion that I have here is that domperidone is a widely utilized medication. Vast global availability, 37 years of clinical use in 112 countries. We know that the experts in gastroenterology have determined a need for this medication. It's part of their guidelines.

It has been compounded extensively. We

know that there are fewer CNS side effects versus metoclopramide, and that there have actually been millions of doses prepared prior to the passage of DQSA, H.R. 3204.

There are some safety concerns at higher doses, particularly with other medications affecting cardiac rhythm. So clinical studies that have been presented to elicit what that risk is have multiple methodology flaws, and so those conclusions cannot be extrapolated to larger patient populations. However, the overwhelming body of evidence does point towards safety. The number of adverse effects from those clinical studies does not reach significance.

Now, on May 11, 2015, five months ago, in this room, the FDA held a public meeting on functional GI disorders. I happened to be in town for another meeting, so I joined in at that time.

The FDA was interested in the impact of functional GI disorders on daily life and patients' views on currently available therapies to treat those disorders. This is something that was

patient-centric.

Several patients spoke to the importance of access to domperidone. The age of those patients was well below 50 years old, i.e., it does not apply to the studies that were presented. And they did talk a lot about the snowball effect of gastroparesis on other aspects of overall health.

Now, as part of that meeting to assess the currently available therapy, the FDA did ask several survey questions. One of the questions that they asked of those patients was, of the medications that currently you have experience with, where are you finding relief?

Eighty percent of the respondents indicated proton pump inhibitors. Seventy percent indicated other. Obviously, they answered for all that they have experience with. Sixty-five percent indicated domperidone. Fifty percent indicated metoclopramide.

One patient spoke about her specific story, saying that, "I cannot get a doctor to prescribe domperidone even when I was hospitalized in Johns

Hopkins Clinic. My treating physician told me to just get it from Canada because it's easier than dealing with the FDA's IND process. I couldn't go to Canada. I was laying in a hospital bed. My mother had to go and find a compounding pharmacist and a physician who would write for it because I was refractory to Reglan." This was a high school student.

The FDA has been requested to submit some information by two congressmen, Congressmen Scott and Carter, on the number of IND applications that have been submitted, the number that have been denied versus the number that have been approved, the number of adverse events that have been reported from those. The request had a deadline requested date of September 15th. And to date, as of this morning, those congressmen have not received a response from FDA.

I'd like to remind the group of two other quick points. There is a BP monograph, British Pharmacopoeia, a European Pharmacopoeia monograph for this substance, as well as back when FDAMA was

first passed in 1997, PCCA did nominate domperidone for inclusion on the positive list. And again, we have received no response until this meeting about the consideration of domperidone.

The American Academy of Pediatricians since 2001 has classified domperidone as compatible with breastfeeding. They have made no changes to that recommendation despite FDA's warnings in 2004 and 2012.

And as FDA pointed out, there is a study published this year, 2015, that was a randomized clinical trial using real-world dosing of what is approved in the labeled products showing no impact on QTc effects when used appropriately. Thank you.

DR. VENITZ: Thank you, Dr. Day.

Our next presenter is Dr. Moon from NCPA.

Nominator Presentation - Richard Moon

DR. MOON: Hello again. For those of you who weren't here yesterday, I'm Richard Moon. A.J. did a great job on the science and the studies, so obviously I'm going to address what happens for us on the front lines again.

Every month, my team fields requests from physicians to consider dispensing domperidone for a GI patient. Every month, we have to say no. The FDA will not allow us to dispense domperidone even though there is an animal approval for the medication, and every month prescribers and patients look for an alternate source for the medication.

Prescribers are aware of the side effects of domperidone and the other agents that affect the heart's sinus rhythm. If prescribers had none of those agents available to them, they would not be able to care for any people.

If we did not accept a level of side effects, we would have no chemo agents available to us. We would have no pain agents. We would have nothing. And the reality is, every drug is a poison at a certain dose. Even water can be fatal.

Domperidone is a superior medication for GI motility and an important tool for the GI prescribers. We understand that there are plenty of FDA-approved nausea and vomiting medications

available to the public. There are, however, very few medications that have the prokinetic effects on gastric emptying that domperidone does.

Gastroparesis is a disorder that we've talked about here, affecting people with both type 1 and type 2 diabetes, in which the stomach takes too long to empty. It affects approximately 40 percent of the patients with type 1 and about 30 percent of the patients with type 2.

Gastroparesis has a significant effect on the quality of life for these people. Other FDA-approved medications with prokinetic effects are metoclopramide and erythromycin, as we talked about; they do not serve this population well, especially giving an antibiotic for gastric emptying.

The most feared, chronic metoclopramide, is tardive dyskinesia, as we have addressed, involuntary movements of the face, tongue, or extremities. Domperidone has a better safety profile, as we've outlined with this; no reported cases of tardive dyskinesia.

When a patient fails FDA-approved metoclopramide therapy due to side effects, physicians go to domperidone. Often it's a life-changing medication. This is significant. Physicians need this tool in their arsenal to improve the patients' quality of life, and that's what we are here for, is for the patient. They shouldn't have to go outside of this country to do that.

As we all know, patients today are much more sophisticated than they've ever been. The internet has allowed a proliferation of information across the globe to happen instantly. We just did a Google search here today while we were in the meeting for somebody, and when a Google search turns up 300,000 hits in under a second, there's no way to contain information.

Patients know that the medication is available in other countries. Prescribers suggest and patients seek domperidone. Because we have a free flow of people and items into this country, patients go to Canada to get the medication, or

they have friends in other countries smuggle it in to them here.

This behavior cannot be controlled, and it shouldn't be. If a patient and prescriber choose a therapy that is a worldwide option, they should have that choice. We would be better off if we could dispense domperidone legally here so that information can be on the medication profile of the patient so that that is available for decision-making processes when it's needed.

We are not protecting the public by not allowing domperidone to be on the positive list. We're just poking our heads in the sand and letting the world go on around us.

We understand that there is some manufactured controversy with domperidone and its effectiveness. Tens of millions of doses of the medication have been administered worldwide. We also know that the IND process is available to dispense this agent. The vast majority of clinicians simply will not follow the IND process when they can get the medicine elsewhere without

the extra headache, as was outlined by A.J.'s story.

We are not asking for domperidone to be available for nausea and vomiting properties or its lactation properties. We feel strongly that it can increase the quality of life of a large segment of our population.

We would ask that the committee examine domperidone from both the clinical view, a worldwide view, and from the patient who suffers and has to smuggle the medication into the country. And we would ask that all the pharmacies that compound be allowed to dispense domperidone, have that option for the prescribers and the patients. Thank you. Any questions?

Clarifying Questions

DR. VENITZ: Thank you.

Any clarifying questions for any of the two speakers? Go ahead, Dr. Davidson.

MS. DAVIDSON: I have a question for A.J. I'm finding the lack of denominators in all of these figures and statistics very disturbing.

A.J., you've got the Health Canada data. Do we have a denominator for how many scrips of domperidone they have dispensed? I know 133 or whatever the number was seems like a large number. But we need to know what the denominator is.

Or, conversely, were you able to get the adverse event rate in Australia? Because we do have a denominator for that.

DR. DAY: Interestingly, the health systems within those governments make different information available at different rates. So in Australia, the prescribing information is readily available. The adverse effect information is not. In Canada, it's vice versa, where the adverse effect information is more widely available.

If we want specific prescribing information, I was told that we could get something within a more limited time frame, say one year, which does not really give us the scope that we're looking for. And still within that request, it would take several months to get the information back as well as at a significant fee. If that's something that

would be helpful to the committee, I can make that request.

MS. DAVIDSON: Just generally, since we can't know the number of how many patients are using the legitimate IND process now -- that's proprietary -- and we don't really know how many patients are actually receiving domperidone through compounding pharmacies outside of the IND process -- and even if they are, where are they getting it because of the import ban -- I'm just really troubled by knowing how large the incidence of need is for this drug in this country. If there are gastroenterologists on the phone that can comment, I'm really having trouble grasping what the need is.

One last question to throw out there. Would domperidone qualify for an emergency IND?

DR. VENITZ: Can you stick with the presenters? We have time for general discussion.

So any more questions for Dr. Day or Dr. Moon?

(No response.)

DR. VENITZ: What about our colleagues on the phone? Any questions on your end?

DR. CHANG: No.

Open Public Hearing

DR. VENITZ: Okay, then. Thank you again for your presentations.

We are now going to move to the open public hearing, and I'll just read the statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a product, and if known, its direct competitors. For example, this financial

information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

I will ask our first open public hearing speaker to step to the microphone, identify yourself, make any disclosure statements, and give your presentation.

DR. BIRNS: I'm Mark Birns. I'm a gastroenterologist, and I have no disclosures or financial conflicts.

Thank you for granting me the time to speak before this distinguished panel at the FDA. My purpose in presenting my experience and data with the drug domperidone is that it serves to fulfill a need in a category of treatment for multiple difficult problems related to gastrointestinal motility.

At the present time, there is really only one drug available to use in that category, and that is Reglan or metoclopramide, which has its own set of issues, which have been brought to our attention upon prescribing by FDA, the most significant of which is tardive dyskinesia.

Propulsid or cisapride, a drug that had similar promotility properties to domperidone, was pulled from the American market in July of 2000 after being available for seven years.

There were 270 reported cases of cardiac arrhythmias, including V-tach, of which 70 deaths, although unequivocally, were felt to be attributable to the drug, followed by class action lawsuits and bashing from consumer-related advocacy groups. Interestingly, very little about the drug's side effects appeared in the medical literature prior to its withdrawal.

My credentials to speak on behalf of domperidone are as an experienced physician first starting in academic medicine in the late 1970s as assistant chief of gastroenterology at the Walter Reed Army Medical Center and assistant professor of medicine at USU, the Uniformed Services University, and later in the 1980s at Georgetown University Hospital.

I entered practice in the 1980s in Rockville, and I remain the senior partner of the

Birns, Gloger, Witten & Bhinder division of Capital Digestive Care. As our patients can attest, we are busy, high-quality, aggressive, well-respected gastroenterology practice.

Currently in my practice alone, speaking about my patients, we have 46 patients that are receiving ongoing refills for domperidone, ages 17 to 89, that are listed in the electronic medical record.

However, since institution of the electronic medical record by our practice in 2011, domperidone is not a recognized drug in the e-prescribing system, and thus cannot be prescribed by or recorded in a document or a prescription drug list from which this data was gleaned, except if entered manually.

In fact, domperidone prescriptions in most cases were handwritten, sometimes called in to local compounding pharmacies, or sent to the international prescription services, the correct number of which cannot be accurately obtained through the EMR but somehow numbers in the

hundreds, according to the medical assistants. Local pharmacy data shows 434 prescriptions of domperidone were filled, or approximately 87,000 doses, in 2014.

As I previously related, the history of domperidone dates back to 1979, when it was released as Motilin in Germany. And being at Walter Reed, we were able to get the drug or have soldiers returning from overseas who were on the medication. It was a natural transition to using it in private practice.

The drug was available in several forms over the years, manufactured overseas by reputable companies like McNeil, Johnson & Johnson, GlaxoSmithKline, and Janssen, until 2014 when it came under the scrutiny of the FDA. That is why I'm appealing to let this medication be compounded or dispensed since it has an unblemished track record in our experience.

What is my take on domperidone? It is efficacious on a variety of motility disorders that are difficult to treat with conventional therapies.

These include gastroparesis, scleroderma back, colonic inertia, intestinal pseudo-obstruction, cyclical vomiting syndrome, hyperemesis gravidarum, refractory reflux, presbyesophagus and esophageal motility disorders, Parkinson's disease-induced dysmotility, medication-induced alterations of motility. I have had success in treating all of the disorders above with domperidone.

But it is most rewarding for diabetic gastroparesis, where it improves gastric emptying and helps stabilize the wide fluctuation in glucose, particularly in children and young adults.

What side effects have I seen? Galactorrhea in a few patients, reversible by lowering the dose or discontinuation of the drug; hyperprolactinemia in three. There have been no cardiac side effects, for which the drug has been withdrawn, and periodic EKGs done in older patients reveal no problematic prolongation of the QT interval, as reported.

Why do I think domperidone is superior to existing therapies? Currently, Reglan or metoclopramide has a black box warning and is

recommended initially for short-term use in gastroparesis; the antibiotic erythromycin, limited by its tachyphylaxis after initiation of therapy; antiemetics like Zofran, Compazine, Tigan, and Marinol are not able to be utilized for long-term management and are prescribed mostly for acute vomiting illnesses or control of nausea from chemotherapy.

Domperidone does not cross the blood/brain barrier. It enhances gastrointestinal coordination while facilitating gastric emptying and decreasing small bowel transit time, making it ideal for prolonged therapy of upper and lower motility disorders.

It is not covered by insurance, remains an out-of-pocket expense, and may require a compounding pharmacy, internet pharmacy, or overseas source to obtain the drug. It is not in any retail pharmacy or health plan's covered pharmaceutical list.

Yet at every GI meeting, national or international, domperidone is mentioned as a

medication available for the treatment of motility disorders. However, the presentation slide will usually have it appear in grey with the words next to it, "Not available in the U.S., in parentheses, while other medications that are available appear in dark print."

It is time to have domperidone appear on this slide in bold. Thank you.

DR. VENITZ: Thank you.

Our next presenter, if you'd please step to the microphone. Identify yourself.

MR. PHILLIPS: Thank you, colleagues. My name is Baxter Phillips. I'm president and CEO of NeuroGastrx. NeuroGastrx -- excuse me. I do have a financial interest in the success of NeuroGastrx.

NeuroGastrx is a company founded by a practicing gastroenterologist with decades of experience in treating gastroparesis and a leader in the field of neurogastroenterology, with a focus of bringing safe, efficacious treatments to patients that suffer for disorders of gastrointestinal motility.

Our first target indication is a major topic today of gastroparesis. For this reason, we are thankful to have the opportunity to speak with you all in today's discussion regarding the evaluation of domperidone, a known D2 antagonist that has historically been used to treat gastroparesis.

We applaud our colleagues, both the compounding industry and the patient community, for their passionate and well-placed interest in bringing easier access to domperidone. We agree that we must do a better job to improve the treatment paradigm for the millions of patients that suffer from gastroparesis.

Currently the only FDA-authorized treatment for gastroparesis is, as discussed, metoclopramide, also a potent D2 antagonist. While efficacious, metoclopramide has a high propensity to cross the blood/brain barrier and cause a myriad of central side effects, the most severe of which is tardive dyskinesia.

As noted by the agency, gastroparesis and its associated symptoms of nausea and vomiting and

considered serious or life-threatening conditions, and we as a community need to work collectively to bring better, safer alternatives forward.

Despite the significant need of treatments for patients with gastroparesis, at NeuroGastrx, we agree with the agency's recommendation that domperidone at any dose should not be included in the 503A compounding list for any indication, including gastroparesis.

We commend our colleagues again for recognizing the potential of this potent D2 receptor antagonist. However, as noted by the FDA, due to the significant risk of QT prolongation, cardiac arrhythmias, and sudden death, risks, which have been well highlighted by the agency, we do not believe open access to this drug is warranted.

As we have not noted today, there are even calls for its withdrawal from certain European countries. It should be noted that hundreds of thousands, up to millions, of patients suffering from gastroparesis and chronic nausea and vomiting in the U.S. can still access domperidone, as we

discussed, through a restrictive patient-based IND. We believe this is appropriate, given the safety risk, yet we acknowledge that it is quite burdensome on both the healthcare system and the sponsoring physicians.

Despite these significant side effects, both metoclopramide and domperidone have been shown to be effective for the treatment of gastroparesis, and as such, we believe validate D2 antagonism as an effective mechanism of action for the treatment of this condition.

It is apparent by the discussion today neither drug is satisfactory for our patients, who continue to suffer. Although these drugs have a mechanism of action of proven benefit on gastroparesis, again we must do a better job as a collective community in finding better, safer alternatives to current D2 receptor antagonism.

As such, I am pleased to inform the community that NeuroGastrx is currently developing a formulation of a separate, potent D2 antagonist that we call NG101 that we believe, at therapeutic

doses, may not elicit the side effects of either domperidone or metoclopramide.

Our belief in this drug candidate's safety is supported by decades of use currently in Europe for the symptomatic treatment of acute nausea and vomiting and from principally used as an antiemetic, anti-nausea for seasonal gastroenteritis.

Over 100 million patient days of experience with this compound, the product appears to have an attractive safety and tolerability profile. In fact, due to the overall safety profile, the product is both sold over the counter, as prescription, and is also approved for children.

We recognize significant development work is required by this community and NeuroGastrx to bring this candidate to patients in the United States. In support of this, NeuroGastrx is currently working on the appropriate studies to file an IND here in the U.S. in the near future.

Our purpose of speaking today is not to promote NeuroGastrx or our drug candidate. Rather,

we would like to highlight to both the patient and physician communities that we recognize there is a significant need for better, safer alternatives to treat gastroparesis; and that easier access to domperidone, we believe, is not the solution; and that with our resources and commitment, we are seeking solutions.

Indeed, the burden of illness and the lack of good treatment options was the sole factor that led our physician founder to establish NeuroGastrx. We invite the community at large to reach out to us to continue this dialogue in finding better, safer alternatives for the treatment of gastroparesis. Thank you.

DR. VENITZ: Thank you.

Now I'm asking our third and final speaker to step forward, identify yourself, and present.

DR. DIAMOND: My name is Dr. Alan Diamond. Thank you for the opportunity to speak with you today. I have no financial relationship with domperidone whatsoever.

I am a gastroenterologist. I practice in

Montgomery County. I'm part of a large group; Birns is actually one of my associates in Capital Digestive Care, a large group of gastroenterologists in D.C. and Montgomery County. I've been in practice for 33 years, private practice.

As we talked about before, a lot of things have been reviewed. But bottom line is, from the clinical standpoint, I had a great drug that worked fantastically well, cisapride or Propulsid. Unfortunately, it was withdrawn from the market because of cardiac issues.

At that point, I was left with Reglan. Reglan to me is a bad drug. It's a dangerous drug. It's an unpleasant drug. And the ability of using domperidone when it came about was a good option for my patients.

Any time I prescribe a medication, I will run through -- particularly with Reglan or metoclopramide -- the possible side effects. And I will tell you, when I tell people that it may cause a tremor; it may cause uncontrolled motions of

their tongue, their neck, and their jaw; and, worst case scenario, it causes tardive dyskinesia, which is a permanent motor disorder, two-thirds of my patients will say, "I'm not taking that drug." It also causes depression, which is a major issue with a lot of patients as well. So pretty much my hands are tied. The drug is bad. It is a bad drug.

I then tell people, well, the other option I have is domperidone, which you can get from Canada or compounding pharmacies. But it's not FDA-approved. And the point of it not being FDA-approved scares people away. They think that FDA approval means something fantastic, and boy, it must be a safe drug, which we know there's dangerous drugs out there. But that makes people reluctant to take the drug as well.

So sometimes I'm left with people who do nothing. All right? And as Dr. Birns had reviewed, there are a whole host of patients who benefit from prokinetic motility drugs. It's not just gastroparesis. It's not just diabetic gastroparesis. But also understand, diabetics also

have enteropathy, small bowel problems. Sometimes they present with diarrhea, which is beautifully controlled with a prokinetic agent.

Parkinson's patients have terrible motility disorders, and you give them Reglan, it makes their Parkinson's disease worse. Scleroderma patients are required to have motility agents. They have dysmotility.

There's cyclic vomiting patients and there's reflux patients who also do well, who are refractory to just proton pump inhibitors, and surgery isn't always the option for them, or gastric pacing surgery should not be the option that we have to turn to because we have a lack of medications.

I would love for the NeuroGastrx people to come up with another drug, which is great and safe as a prokinetic agent, but right now, we don't have it.

So generally speaking, I would like to have the FDA approve the domperidone; allow the compounding pharmacies to distribute it, as they

have been; allow our patients to obtain it from Canada, if that's their last choice.

Understand, the IND process is cumbersome, time-consuming. It takes hours to fill out your papers. Trust me that nobody is going to fill out those papers to get domperidone for their patients. It just isn't going to happen.

So you're actually depriving patients from that drug, and you're requiring them to turn to metoclopramide, which to me is a bad drug. Thank you.

DR. VENITZ: Thank you very much. We had three registered presenters. I want to make sure there is nobody else that wants to take the opportunity to speak up.

(No response.)

Committee Discussion and Vote

DR. VENITZ: If not, then I want to thank all of the three presenters for their contributions. And after getting feedback from the committee, I think we've decided to skip our break and continue the discussion towards the ultimate

vote at the end of the meeting.

So I'm now opening the discussion for general comments or questions about any of the presentations that we had the opportunity to listen to. Go ahead, Dr. Vaida.

DR. VAIDA: For the FDA, the investigational drugs, there isn't any charge for those? Are they available free? Like if you go under the Access IND? I'm just trying to get to --

DR. KORVICK: I believe they charge a small fee to cover costs, and that's permitted under the IND system for the domperidone. Is that what you're asking?

DR. VAIDA: Correct. If you get this drug compounded, you have to pay for it. It's not covered by insurance because it's not approved.

DR. KORVICK: Oh, I heard somebody say that.

DR. VAIDA: But if you get it -- if you go through the IND, is that then available free?

DR. KORVICK: You still have to pay for it.

MS. AXELRAD: We don't really know the answers to these questions. I believe that

Dr. Korvick said that we believe that the pharmacy charges enough for the drug to recover its costs of supplying it. But we don't know, and I don't think you can assume, that insurance doesn't pay for the compounded drug or for -- we don't know what insurance does or doesn't pay for with regard to this.

I guess it really isn't something that we would take into account in deciding whether to put a drug on the list that can be compounded or not. We don't usually consider cost issues. We don't know how much it costs, even, or what the differential in cost is between a compounded drug. And we wouldn't take that into account in looking at this here.

DR. VENITZ: Any other comments? Dr. Pham?

DR. PHAM: From the institutional perspective, then, for the inpatient setting they will have a cost. But that's no different than if we decided to use Reglan. They would still get the cost of the Reglan charged to the patient as well.

Usually there's an acquisition cost for

whatever it is. If we're getting it through an IND and there's a pharmacy that had sent it or a drug company, drug from the supplier, whatever the case, there's still a cost.

There might be a standard dispensing fee on the institution side, which may or may not incorporate any extra diligence in getting the paperwork. And usually a clinical pharmacist is helping fill out the IND as well.

So that may not be reflected in the dispensing fee, but there's usually a drug plus dispensing fee for products. And the only time it's not that is if they're actually through an IRB-approved investigational study, where the product was already supplied and the costs are driven through another mechanism.

But if it's something like an IND for patient care, it will be similar to whatever the drug costs would be if it was a readily available, commercially available drug.

DR. VAIDA: I'm taking for granted that the nonapproved drug will not be covered by insurance.

And that's why I was just mentioning with the compounded, if this drug is compounded, I'm taking for granted that an insurance company won't pay for it because it's a nonapproved drug.

MS. AXELRAD: I don't think that's necessarily the case. We have seen reimbursement for compounded drugs by various insurance companies. And there have been, in fact, big issues in the news about companies that have suddenly seen their reimbursements for compounded drugs go through the roof in terms of the topical pain medications, and they're trying to pull back and give more scrutiny to claims for compounded drugs.

So I don't think you can assume that. But again, I would say what the costs of this are or anything, we don't take that into account. This is an issue using the four criteria, none of which include cost, to decide whether this drug should or shouldn't be put on the list. And we really don't consider cost in making our judgments with regard to this.

DR. VENITZ: Dr. Pham?

DR. PHAM: I just thought I would provide some comment on the use in pediatrics. Gut motility is definitely a big issue, especially with neonatal reflux. And in the past, Reglan was used readily, not as much.

Then we found ourselves now using a lot more erythromycin as the prokinetic agent of choice, also strongly discouraged since I usually remind my physicians that is what we try to keep in our armamentarium for pertussis treatment. So trying to bring that in and develop resistance for motility is probably not preferred.

But we find ourselves also looking for alternatives. However, looking at just even the two studies that were presented today and trying to look a little bit more in detail at those articles, even though it may not seem like there was any significant difference, I don't think that they were very well powered to detect a difference.

So I would be cautious in extrapolating a lower safety risk from those studies in particular.

But I would comment that, in general, we would still, from the pediatric side -- despite the lack of alternatives, we would still like to see a drug go through the NDA process and have the FDA approval.

Keeping this as available for compounding -- and sorry if I'm extrapolating incorrectly -- I feel like that would probably provide less incentive for there to be a product that would actually have FDA approval. And institutionally, we would adopt that product much more readily than a compounded product.

DR. VENITZ: Any other comments?

(No response.)

DR. VENITZ: Then maybe kind of a general statement. I think this is our third meeting that we have as a committee, and I don't know how many votes we had on various compounds. And this is probably the compound that we have, as opposed to in the previous cases, more information than we can digest.

It's a drug that's approved elsewhere, so we

do have clinical data both on safety and efficacy, with limitations as it is not approved in the United States. It is being used, apparently to a large extent, for indications that are approved elsewhere, but also for the lactation enhancement, an indication, which apparently is not approved elsewhere as well.

Getting back to our four criteria that we're using, we do have a strong safety signal of QTc prolongation. There's a mechanism. There are some postmarketing data that suggest an increased risk. But as Dr. Pham pointed out, the actual extent of that risk is not really known.

The alternative treatment, and there's only one approved and one off-label in this country, but the approved treatment, metoclopramide, has its own warts, as Dr. Day put it -- a severe risk, CNS, not related to cardiac toxicity but equally concerning and apparently limiting its use.

We do have some information on comparative effectiveness, again in the gastroparesis only. And it looks at least there are no major

differences in clinical effectiveness.

So really, in trying to summarize as I'm thinking through this, it comes down to how can we make sure that this drug continues to be available? Is the existing process, going through an IND application and doing everything associated with it, is that sufficient, allowing a patient access to this drug, or is the current use, as one of to-be-compounded drug substances, whether that's what needs to be done.

Any discussion? Yes?

DR. DIGIOVANNA: John DiGiovanna. I'm a little bit concerned when we have the four criteria that you mentioned for placing a drug on the bulk substance list, but part of the equation becomes whether or not it is available by an alternative IND process.

I think the availability of the drug to those individuals who need it, needs to be something that we consider. I think a drug that goes through the IND process and is marketed as a regular drug is marketed. Large numbers of people

are sold that drug.

I don't know that this drug, if available through compounding for individual patients who do not respond well to other drugs, is going to be marketed in the same way. And I also get the sense that probably fewer people will be exposed to it.

To use in the equation that the expanded IND is an acceptable alternative really suggests to me that that's coming from someone who hasn't tried to get an expanded IND. My personal experience of being a director of dermatopharmacology at Brown University for 13 years means that I have filled out what the FDA has said, a 1572 form, a 1571 form, and multiple IRB approvals.

Even though there is a protocol available for that, I cannot imagine any IRB that I've ever submitted to would accept another protocol without their own tweaking and a substantial amount of activity that goes with it and changes. So to expect that to be something that is possible for a physician's office, I think, simply is not reasonable for most physicians.

So I think the real question then depends. Is this drug going to be available throughout an appropriate process within the U.S. without having someone import it from someplace else and maybe actually not get an active drug? I think, from that perspective, the way to keep it on the market may be to actually have it in the system.

I take what the FDA said initially about those four criteria to heart in that, yes, is the compound physically and chemically characterizable? Are there safety issues? Is there a history of use of the substance, and is it efficacious? But also that no single of these criteria is dispositive. So I think that should be part of our understanding.

The one issue I have here that's difficult for me is that I'm a dermatologist. I'm not a gastroenterologist. And I wonder if the member that we have who's had some of that experience could enlighten us a little bit as far as the utility of this when there are no other medications available.

DR. VENITZ: Dr. Chang, do you care to comment?

DR. CHANG: Yes. I definitely recognize the information that was provided on the safety issues, and I do think that these are low-quality studies, unfortunately. And if you limit the patient population that you're going to treat with domperidone to under 60, no cardiovascular disease or evidence of QT prolongation, there's a substantial number of patients with very impactful disease that would benefit from domperidone with metoclopramide as an alternative.

Erythromycin, honestly, is not an effective drug. It doesn't last long. There's really not much alternative. I personally don't think this works so much in lower GI, but I think there are a host of upper GI disorders where this can be useful.

Domperidone's been around for a long time. I don't think any company is ever going to present this as a drug to get approved by the FDA. I just think that we're dreaming about that. I don't

think it's going to happen.

So in the meantime, there's a lot of patients out there, and I can't give you a denominator. I do recognize that it's not a huge, large patient population, but it's a significant one.

I don't think primary care physicians use it. I think it's gastroenterologists. And I even think it's gastroenterologists that subspecialize in these motility and function GI disorders more so, although you've just heard from community gastroenterologists who use it.

So I feel that there is a substantial group of patients who would benefit. I recognize that in a subgroup of patients, they are not the right patients to use this agent. And I do believe it should be available; however, I think we all need to be educated on the proper indications and exclusions, and also monitoring the patients. But I definitely feel it fulfills an unmet need.

DR. VENITZ: Thank you, Dr. Chang.

Dr. Wall?

DR. WALL: I appreciate the effort of the FDA to try to make this available through INDs. But where I work in the hospital system, we have a large GI population. It's a GI center. And I know that there's a multitude of patients, not within the hospital but who walk out with a script, with the directions of "go to Canada."

I also know there are some pediatrics with the same directions. And I can't see that with all of these drug interactions that need to be monitored, how are we taking care of those patients and keeping them safe if we're telling them to go to Canada and we don't have an accurate record of the things that are going on.

I'm really struggling with it. I understand the safety concerns. But I know these people need to be monitored, and clearly the IND isn't working for the specialized practitioner.

So I think I would really like to see if there is a different way that this can be worked, whether it's through a REMS with special pharmacies, if we go that way, or something to

allow a little bit more flexibility but still appropriate monitoring so we can get some help for these patients but we monitor for these drug interactions and side effects.

DR. VENITZ: Dr. Sewell, I think you wanted to -- oh, I'm sorry.

DR. NGUYEN: Actually, I'm kind of glad you brought up the REMS issue. A couple of points of clarification. I know there's been a lot of comparison with Reglan. And I think one thing that's really important is Reglan has been improved.

We've determined that there was substantial evidence of efficacy, such that it outweighs the risk. When FDA approves a drug, we are very well aware that a drug is not perfectly safe, and that's why we have labeling. And labeling includes the risk and benefits, and that information is very important to ensure the safe and effective use of a drug.

When we're talking about domperidone, we're talking about an unapproved drug. I know it's

approved elsewhere, but it's not approved in the United States. And it's not approved for whatever reason it may be. So I just caution you in that comparison because you're really comparing apples and oranges.

The second thing that you brought up is patient access, and I think that's really important. But on the flip side, we want to make sure we keep our patients safe. And if we don't have labeling, if we don't have other forms of communication, if we don't have a REMS, which is attached to an approved drug, how are we going to ensure that in a compounding setting? We won't know. And I think that's the other side of the balance to patient access.

DR. VENITZ: Thank you, Dr. Nguyen.

Any other comments?

MS. AXELRAD: I just wanted to add one thing to what Dr. Nguyen said, which is that because a REMS is only attached to an approved drug -- this drug is not approved -- the only mechanism we have is under an IND.

As we presented at the last meeting when we talked about expanded access INDs, we talked about the reasons why it's important to have that. It's for informed consent. It's to make sure that they're warned. It's to make sure that they're monitored.

All of those protections, as Dr. Nguyen said, are there to protect the patient. Yes, we want the patients to have access to drugs, but we also want them to be protected.

When you're dealing with an unapproved drug that has never been shown to be safe and effective, there's no labeling to say what the appropriate dose is. There's no guarantee that they're going to be told about the drug interactions and all of those things.

So I think that it's really important to keep in mind that the process that we have versus allowing it in a compounding setting with none of those protections or controls, that is what we have to deal with here. If we had an NDA, if we were talking about an NDA, it would be a very different

type of discussion. But we're talking about uncontrolled use by a compounder.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: What she said.

(Laughter.)

DR. VENITZ: Okay. Dr. DiGiovanna?

DR. DIGIOVANNA: I'm glad you two agree. I think we need a better process. I think in the discussions we've had over these three meetings, we've realized that there's a gap here, that it would be very nice to have drugs available for individual situations related to the specific practice of medicine, but also be able to extract information over time, quality information, about adverse events related to those drugs, perhaps information about potential uses of those drugs that might encourage sponsors to want to submit an IND for those uses. And right now that doesn't happen.

But I think we've identified that there's a gap in the system. The expanded IND process is too difficult for everyone to be able to use, and

probably for most people to be able to use. And I think that's not an easy thing to suggest to the FDA, that they should request more regulation. But I think it would be helpful if people who are more knowledgeable about the mechanisms could try to address the gap.

MS. JUNGMAN: I'll just add, it seems to me that there is a tension, though, between this idea that we want to have more information about the use of these drugs and we want to be able to control the use of the drugs.

But then if providers aren't willing to submit information and participate in the IND process, then I don't know how we accomplish that because it seems to me that it could be very difficult to both allow open access to the drug and also track the data that we want to track to understand how they're being used in real practice.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: I asked inappropriately a while ago, would this drug be eligible for an emergency IND? Just reading the process on the

web, it seems like that would be a very expeditious, somewhat easy way for physicians to get drugs for individual patients.

MS. AXELRAD: If the division can't answer it, I think --

DR. NGUYEN: Actually, Dr. Griebel --

MS. AXELRAD: Oh, good.

DR. NGUYEN: Dr. Griebel will address that question.

DR. GRIEBEL: I'm Donna Griebel. I'm the division director for the Division of Gastroenterology and Inborn Errors Products.

An emergency IND is just another expanded access version. So of course, if we're allowing expanded access to this under single-patient INDs or intermediate access INDs, certainly it would be available as an emergency IND.

The emergency IND, if we're talking about the same thing, is a single-patient IND in which the patient's in an emergency situation. You still have to have a 1572. You still have to have a plan of treatment. Really, the only difference is that

you can submit to the IRB after the fact.

Because you're taking out that part of the patient protection part of it, it has to be an emergency. So the division has to scrutinize situation to see if this is truly an emergency situation for the patient because you're taking away the IRB component until after the fact.

So certainly it would be eligible for that as long as the patient is in an emergency situation.

DR. VENITZ: Thank you.

Any further questions? Any further discussion? What about our committee members and colleagues on the telephone?

DR. GULUR: I would like to ask a question. This is Dr. Gulur.

DR. VENITZ: Go ahead.

DR. GULUR: I share everyone's concerns, which is this drug, while it does have significant side effects, also seems to be widely used in the country right now without approval.

I'm just wondering if we could get more

clarification. If this drug is something we say should be added to the list, I share everyone's concerns that it will be unmonitored, less structure around it. And how does that play into the fact that the FDA puts out a warning saying that this is an unapproved drug and it's against the law? How would that work out?

DR. VENITZ: Dr. Axelrad, do you want to comment?

MS. AXELRAD: Well, obviously neither the warning nor the import alert seems to be particularly effective because it's obviously being used. So I don't know what else to say about that.

If you do not recommend that it be put on the list and if we decide not to put it on the list, then obviously we would continue to do what we have been doing for a number of years. When we find someone who is compounding it, we've been citing them for compounding a drug that they shouldn't be compounding with.

Let me just say we've been doing that because of our concerns about the safety. We have

really consistently been citing people for this when we see it.

DR. VENITZ: Thank you.

Dr. Davidson?

MS. DAVIDSON: Just one more comment about availability. It is approved in this country for use in horses, and I get calls in my world every week asking about Equidone gel because if people Google domperidone, the first thing that comes up is domperidone gel. And so they approach their veterinarian and try to get it for their horse or whatever.

So it goes back to the gap that we've all described between an uncontrolled situation like an IND, which appears to be inaccessible, according to the mouths of the physicians in the room, versus the uncontrolled compounding environment, which I think is more controlled than going to Canada and getting it, and going to your equine veterinarian and getting it online in equine form.

So I'm really struggling with that gap between patient access and total uncontrolled

availability of it by going to the equine product and going across a border. That's really a paradox.

DR. VENITZ: I'm looking around. Yes, Dr. Pham?

DR. PHAM: I feel like I'm getting confused by our own advisory committee because I swear in previous meetings we've had votes where we voted no based on the fact that there was an IND process. I remember that being people's justification.

So I don't know if this is different because of it being more widespread use. It certainly it isn't the safety aspect because QT prolongation to me is just as severe as some things that we had hesitations on in previous meetings.

Also, the fact that you've got an entire class of drugs that typically get prescribed with this drug, H2 blockers that also prolong QT, so inherently you've got this magic combo of QT prolonging agents that are typically prescribed together.

So I don't know why the conversation seems

to be changing for this agent aside from the fact that we do feel like there is more widespread use and we do have a lot more people in the public hearing and nominator presentations that speak to its use.

But at the same time, the conversation in the past has always been if there's a way to get it through an IND, go that route and hope for the FDA-approved process to -- especially if there is such a compelling need that there are going to be providers that will be looking to create a product that's going for FDA approval.

Those same conversations happened in previous meetings of this advisory committee. So I'm just confused as to why this particular drug seems to make us backtrack in our logic.

DR. VENITZ: Because we know much more about it. It's approved elsewhere. It's being used worldwide, including Canada, right across the border. And most of the other drugs that I remember, we had to extrapolate.

We had to have some human use information,

but we didn't have controlled clinical trials. We had safety signals, maybe even preclinical. Here we have human data that at least seems to suggest there is a QTc risk. As I said, the magnitude in my mind, at least, is not clear.

So we know much more than we have in the past. That's why my mind, like most of you, I'm struggling where to draw the line because we know so much. We don't have to guess any more. In a lot of the other drugs, especially some of the topicals, we could extrapolate even though we didn't know.

Here we can't. We have information that's been provided to us both from the nominators and from the FDA, and we have to figure out where we are and strike the right balance between making something that is apparently meeting an unmet need available, and at the same time making sure that patient safety is safeguarded.

DR. PHAM: I guess my response to that is we still have the precedent of Sabril. There was still vigabatrin that was also only available,

approved elsewhere, that we still went through an IND process. And eventually it went through the right route, as far as I know, and we now have it more readily available. There are going to be precedents for all of these examples, I guess.

DR. NGUYEN: Actually, if I may try to address some of your questions there, Dr. Pham. We are very well aware that this drug has been approved overseas for over 30-something years. And it is notable that recently there has been a lot of restrictions on its use.

Whenever you have a drug that's been on the market that's approved for that many years and you start seeing restrictions around it because they are looking at the data, the safety data, that says a lot.

The second thing is different regulatory agencies have different criteria for approval. We approve drugs that's not approved overseas and vice versa. And some of that has to do with the different healthcare systems, different control of drug access. So again, that's just something I'd

like for all of us to keep in mind.

DR. VENITZ: Go ahead.

DR. KORVICK: Dr. Korvick, GI. I just wanted to also highlight what's been said before, I'm not ascribing to people shipping this from Canada, but presumably what they're getting in Canada is an approved, formulated product that has quality controls.

That is somewhat different from a compounded product -- not to say that people don't try to do that well, but that we were also concerned about the dosages that were delivered. So there may be a difference in quality and the dose that's actually delivered.

DR. VENITZ: Thank you.

Yes, Dr. Wall?

DR. WALL: A question for my FDA colleagues. And maybe I'm hallucinating, but didn't this drug come through a manufacturer at one time and presented before the FDA and the FDA turned it down? Did that happen with domperidone?

DR. KORVICK: Domperidone was submitted to

the FDA, and there's one public disclosure about what has happened. And the remaining disclosures are not public, so we can't talk about those.

DR. WALL: But it never went before a committee and voted up or down?

DR. RAJPAL: Yes. It did go to committee in 1989. There's a published article. There were a few small trials at that time.

DR. WALL: Is there anything in this discussion today that we may have missed from that initial meeting or any discussion of that committee?

DR. RAJPAL: I don't believe so.

MS. AXELRAD: There's been a lot of data since 1989. A lot of the data that was presented is much more recent.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. I think it's likely had the FDA approved the product when the NDA was submitted, based upon the experience with other drugs that have since been withdrawn from the market after their approval because of the cardiac

toxicity of QTc prolongation, likely domperidone would have been withdrawn from the market, and this drug would be on the do-not-compound list, and it wouldn't even be being considered for nomination to the list we're talking about.

DR. VENITZ: Okay. Any final questions before I'm going to call for the vote? Yes, go ahead, please.

DR. MCKINNEY: I would just add one other comment, which is that the mechanism of action that's come out from all the nonclinical studies has just gotten so strong over the last 10 years. And again, I think your comment is very pertinent. I don't know; it would be difficult to see it getting approved with this strong of a -- and depending on the clinical signal.

Also, I think that speaks to the attribution of any adverse events, that as you understand the mechanism more, then physicians may be more likely to ascribe a clinical event to a particular mechanism of action, which they might not have done in the past.

DR. VENITZ: Thank you.

Any other comments?

(No response.)

DR. VENITZ: Okay. Ladies and gentlemen, then let's proceed to the vote. I have two things I have to read, voting instructions.

This panel will use the electronic voting system for this meeting. During this session, voters are instructed to depress the selected voting button. The vote results will be displayed on the screen.

I will read the vote from the screen into the record. Then we will go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted the way they did.

We will now begin the voting process. Please press the button three times on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. Please press the flashing button firmly three times. After you have made your selection, the light will

continue to flash. If you are unsure of your vote, please press the corresponding button again.

The question that you're voting again is in front of us: Should domperidone be placed on the 503A bulk list, yes or no? Please go ahead and vote. And our colleagues on the phone, please email or call on the phone.

(Vote taken.)

DR. HONG: For domperidone, we have 3 yeses, 8 nos, and zero abstain.

DR. VENITZ: Let's go around the table. Let's start with Dr. Carome.

DR. CAROME: I voted no because of the significant safety concerns.

DR. WALL: I reluctantly voted no because they still have the IND. But I would encourage folks to see if there was a way that there could be a little more flexibility with it, so that we can have it more readily available.

DR. DIGIOVANNA: John DiGiovanna. I voted yes, somewhat reluctantly also. I think that the dictum of "First, do no harm" works in two

directions. Being unable to treat selected patients is just as difficult sometimes as thinking that your actions will expose individuals to risk.

I think that the physicians who are going to use this need to take the responsibility for it. I wish that the FDA had a way of attaching a black box warning or a REMS program to compounds that they're concerned about. But to encourage individuals to go to another country and get a reputable source of it from there I don't think is acceptable.

What I would prefer is that there is a more streamlined, user-friendly way, like the expedited IND, version 2, that allows private physicians to be able to easily comply with that system yet be required to review their patients in an organized way.

MS. DAVIDSON: I voted no, for all the same reasons that you voted yes, reluctantly. I feel like compounding, as I said before, is a considerably more controlled environment than going to Canada or using the horse-based.

But we do have the IND process in place, which does educate and does inform and does monitor patients. And I feel like it not going on the 503A list will force a closer look at the IND process and maybe increase awareness on the part of physicians to lobby, or whatever the word is, to get the process streamlined so we can close that gap.

MR. HUMPHREY: William Humphrey, and I voted no because of the safety concerns that were expressed. I do recognize that there is a clinical need for this drug, but you can get it through the IND process.

I may be somewhat a little biased because of where I work, but we deal with expanded access drugs nearly every week. And while the process is cumbersome and onerous when you first do it, after a few times it gets a lot easier.

DR. PHAM: Katherine Pham. I voted no due to my concerns about the QT prolongation, especially with commonly prescribed concomitant H2 blockers. I also felt that it was available

through the IND, and echo Dr. Humphrey's comments about the process. And once it's been done, it is something that becomes a little bit more routine each time.

We've never seen a patient not be able to get a product needed through the IND process; and also, that if there's such a widespread need, that this again should compel the industry to move a product forward through the NDA process.

MS. JUNGMAN: Elizabeth Jungman. I also voted no. I think, given the safety considerations, that the protocol and patient protections of the IND process are important. I am sympathetic to the needs of patients who have a need for this kind of an option. But I want FDA to have visibility into how it's being used and the outcomes.

DR. VAIDA: Allen Vaida. I voted no, for some of those same reasons, that there is an IND process, and hopefully that will at least track some of the reactions and also some of the safety characteristics of the patients.

That was even in my questions on the cost. I was hoping that that was also going to be another reason that it was going to be safer and also more cost-effective. But I really don't think at the present time this should be added.

DR. VENITZ: I voted yes, and I think, as Dr. DiGiovanna already stated, I'm worried about not protecting the patient safety, but protecting the patient from potentially effective treatment and making it much less available by the IND route that I recognize exists.

It's a reluctant yes vote, and I would wish obviously, like most of us, that with the compounding, there would be some way of labeling or risk communications to the patient and the prescriber before dispensing it.

Dr. Chang?

DR. CHANG: Yes. I voted yes. I agree with everything that was said in the past for the people who did say yes. I definitely do think there is a safety risk, but I think that the data is showing that it's more for patients who are elderly, who

have comorbidities, and it's not for a large group of patients who actually it serves an unmet need with very poor alternatives that we already discussed.

I do agree that I wish that there was some safeguards that could be placed with the compounding pharmacy because I don't think it should be prescribed in every individual. And I use alosetron on restricted use, and I know exactly what the guidelines are for that, and I think it's something that should be done with this.

But I also know that from a pragmatic standpoint, it's available in so many countries, has been approved for so long, this IND process that you may use for drugs that are very rare and not available, it's just not pragmatic in clinical practice.

If it was easier, that's definitely what I think people should do, but I don't think it's that easy.

DR. VENITZ: Thank you, Dr. Chang.

Dr. Gulur?

DR. GULUR: I voted no. I think all of us potentially share the same concerns whether we voted yes or no. We would all like patient access for this medication, which has some clinical efficacy. However, it is also a drug with significant side effects, and monitoring is really important with this drug.

Just adding it to the compounding list does not make it too much better than the Canada option. Neither of those options are really good because, again, we will not have an adequate monitoring process.

The IND does offer that, so there is that opportunity. But I also recognize that it's not easy for individual physicians to go through. I would second what has been said, that we need a better process for this. Thank you.

DR. VENITZ: Thank you, Dr. Gulur. And this does conclude the main topic for this afternoon.

Dr. Axelrad, you may have some final words for us?

MS. AXELRAD: Yes. I just wanted to say

thank you very much to the committee for your thoughtful discussion, your questions and comments today. I think this particular drug this afternoon was the most difficult that you've had to face of the 19 drugs that we've covered, and I think you did it carefully, thoughtfully, and you had a lot of information to go through in order to reach a decision.

So thank you all for your work. And I personally have said that I will go back and see if there's anything that we can do in terms of looking at the IND and whether there is anything that can be done, although I do see a tension between what you were saying, Dr. DiGiovanna, and what Elizabeth was saying also, about in order to protect the patients, you have to have certain things on it. And if you loosen it up, then you loosen the protection.

So I think there is a balancing. But we can take under advisement whether there is anything that we can do with regard to this particular IND to make it easier. But thank you all for your time

and your work on this.

Adjournment

DR. VENITZ: I want to add my thanks to everyone. I hope you all have a safe trip home, and the meeting is adjourned.

(Whereupon, at 3:30 p.m., the afternoon session was adjourned.)