FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Topic 3

Ipamorelin Acetate and Ipamorelin

Tuesday, October 29, 2024

12:00 p.m. to 1:53 p.m.

Meeting Roster

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C O N T E N T S

P R O C E E D I N G S

(12:00 p.m.)

Call to Order

Introduction of Committee

DR. GULUR: Welcome back, everyone. Before we begin the FDA presentations and the ipamorelin acetate and ipamorelin free base topic session, panel members who will be in this topic will introduce themselves by stating their names and affiliations.

We will begin with Dr. Cooke.

DR. COOKE: I'm David Cooke. I'm the Clinical Co-Director of the Pediatric Endo Clinics at Johns Hopkins.

DR. GULUR: Dr. Lee?

DR. LEE: Brian Lee. I'm a gastroenterologist and hepatologist at University of Southern California.

DR. GULUR: Dr. Solga?

DR. SOLGA: Steve Solga, gastroenterologist and hepatologist at the University of Pennsylvania.

DR. GULUR: And virtually, Dr. Yanovski?

DR. YANOVSKI: Hi. Jack Yanovski, Chief of the Section on Growth and Obesity at the Intramural NICHD. I'm a pediatric endocrinologist.

DR. GULUR: Thank you. We will proceed with an FDA presentation on Immunogenicity Risk of Compounded Peptides from Dr. Daniela Verthelyi, immediately followed by an FDA presentation on bulk drug substances from Russell Wesdyk.

FDA Presentation - Daniela Verthelyi

DR. VERTHELYI: Good morning, or good night, wherever you are. My name is Daniela Verthelyi. I'm going to be talking about immunogenicity risk of compounded peptides. I have no conflicts. This is what we're going to be discussing, what is product immunogenicity, then we're going to describe what are the concerns regarding clinical immunogenicity for peptides; do a brief introduction to the mechanisms involved in generating an immune response for products; and then discuss what are the concerns for peptides, in general, and also complex peptide products.

What is immunogenicity? It is the unwanted

development of an immune response, usually antibodies that are elicited by a product. On your right, you see a graph that very simply illustrates what it takes to make an immune response to a peptide drug. Basically, it needs to be taken up by some cells of the immune system that we usually call antigen-presenting cells. These in turn activate other cells of the immune system, the T cells, and those T cells can help B cells make antibodies. What we usually measure are antibodies, and those antibodies can bind or can neutralize the product, and as a result they can impact the safety and efficacy of the product.

Do they always result in changes in safety and efficacy? No. Many times when antibodies are developed for the product, there are no apparent effects on safety and efficacy, but there are also other times when they can alter pharmacokinetic and pharmacodynamics of the product. And as a result of that, because either they accelerate the clearance or they delay clearance, they can result in loss of efficacy and/or toxicity, accumulation

and toxicity.

They also have been linked to severe adverse events such as hypersensitivity and anaphylaxis, whether it's IgG or IgE mediated immune complex disease; neutralizing antibodies that reduce the efficacy of what usually would be an effective therapy; and cross-reactive neutralization of unique endogenous counterparts, and that's probably one the biggest concerns. The other concern is that when there's neutralizing antibodies that develop, they can be elicited against the drug, but also other drugs that have the same type of sequence.

What are the immunogenicity risk factors for a product? A lot of them have to do with the patients that take them, whether it's the type of patients; what disease they have; how the drug is administered; the dose, the route, the regimen, et cetera; or the underlying characteristics of the patient, whether it's their concurrent medication, et cetera. But many of them have to do with the quality of the product, API, and the impurities.

API, by the way, is the active pharmaceutical ingredient.

Now, it turns out that our immune system is geared towards the development of what's called tolerance to self. So it won't mount an immune response unless you have an autoimmune disease towards any peptide or protein that's present in the body that it can see during what's called the T-cell indication in the thymus.

So the degree of tolerance is going to be measured with the homology to self in terms of the sequence, but also the concentration and distribution of this peptide in the body. So when we have impurities of the product where there's a change or shift in that structure or in that sequence, you could be making those T cells present antigens that are different from what the body has developed tolerance to.

The other type of impurities that is a concern are what we usually call innate immune response modulating impurities, and those are impurities that are going to act as adjuvants.

They can be aggregates, they can be process-related impurities, contaminants, excipients, leachables, all kinds of different things that can enhance an immune response.

This slide is fairly complicated, but please bear with me because we're going to go step by step. Usually when a product is administered, let's say what's here is this subcutaneous space, it goes into a space that is usually populated by immune cells already. Most of the tissues in our body have immune cells that are embedded in the tissue. So when you inject a product, most of it's going to immediately drain to the lymph nodes, through the lymphatics, and in the lymph nodes there's going to be antigen-presenting cells, so T cells and B cells in high concentration so they can interact and talk to each other, as I mentioned before.

When a product is administered in the presence of impurities, what happens is that this process can magnify. The impurities at the site of injection can call in and attract immune cells that

are going to take up more of that antigen, more of that peptide that was co-administered with impurities, and there's going to be local inflammation with dendritic cells, and macrophages, and monocytes, and neutrophils, creating a site that is ideal for an immune system to occur.

Those impurities are also going to help what are the prime cells that initiate an immune response, the dendritic cells. It can help them take up the antigen and present it to the T cells in a framework that allows the T cells to respond. Those are called costimulatory molecules, and they're called cytokines and other soluble proteins and peptides that are going to help that T cell become an effective T cell in helping B cells turn into plasma cells, which secrete antibodies. And when they produce antibodies, that's when we get those changes to PK, and we can have those changes to efficacy and deficiency syndrome.

When we add to this the potential presence of product aggregates, aggregates are an extra layer of concern because they not only are taken up

differently and maybe more efficiently by those antigen-presenting cells that illustrate there is a DC, a dendritic cell, but they can also bypass that helping hand to the B cells and activate B cells directly through the B cell receptors. Because of this, most peptides that are capable of inducing an immune response, if there are impurities present, that can change the quantity and quality of the immune response.

Because of this, when there are no clinical studies to evaluate a peptide, there are a number of studies that are done to characterize these factors, both the aggregation profile, the process-related impurities, and the product-related impurities; and these are really complex assays such as LC-MS, MS, peptide mapping, and in vitro assays to look at whether those peptides are presented by the antigen-presenting cells to the T cells, as well as in vitro assays to look for those impurities that can be active even when present in very low amounts.

So why are we talking about the

immunogenicity risk of peptides? The level of concerns with peptides is different than with small molecules. Peptide sequences can elicit an immune response, particularly if they're aggregated or presented within scaffolding. Peptides administered via subcutaneous, intravenous, intramuscular, intradermal, inhalation, and intravitreal routes, all those have higher immunogenicity risks than oral or transrectal.

Product formulation is critical to the quality and stability of a peptide product. Formulation differences can modify peptide stability and immunogenicity. Peptide-related impurities can also modify the target of the antibodies that are developed, changing the target on the peptide; and then impurities or contaminants that activate immune cells may increase the immunogenicity of the API or result in immune responses that target new sequences that may cross-react with endogenous counterparts.

Peptide-related impurities can be difficult to detect, analyze, and control because these

impurities can have similar amino acid sequences to the peptide itself, and that requires advanced analytical techniques such as liquid chromatography-high resolution mass spectrometry to detect, identify, quantify, and control. Impurities and contaminants can activate immune cells where the product is deposited, increasing the immunogenicity risk at trace levels.

As I've mentioned before, very low levels in the picograms to nanograms can have this effect, and assessing the immunogenicity risk of immunomodulatory impurities in peptides requires complex in silico and in vitro studies, and mitigating the immunogenicity risk of peptides requires sensitive assays in control of product and process-related impurities.

I would like now to show some data that was generated in our lab. You have two graphs. The one on the left is showing the response, the NF kappa beta activation. This is just the activation of cells. There's a reporter for activation of these antigen-presenting cells. You

see to the far left your control, a positive control, which we're using LPS at 100 picograms, and that's about 1 EU, then eight different drug substances that are being tested. The first six are from commercial samples and the last two are for compounded samples, and you can see the degree of activation of the immune cells is different.

But I really want, actually, you to focus on the graph on the right, which we submitted all of these drug substances to filtration, sterile filtration, using a 0.2 PFTE filter. You can see that some of those impurities that are causing innate immune activation were reduced by that filtration, while others were not.

Product immunogenicity constitutes a risk for peptides, including compounded peptides, especially when delivered via certain routes of administration, which may result in significant risks of harm, including life-threatening reactions such as anaphylaxis. Controlled impurities, including aggregates, can mitigate the risk, but it requires sophisticated manufacturing and testing

strategies. And as you saw in my last example, it is important that when the drug product is generated, there are sufficient controls and the strategies are in place to mitigate this risk.

With that, I'm going to thank you, and I believe the next speaker comes in. Thank you.

DR. GULUR: Thank you.

FDA Discussion - Russell Wesdyk

MR. WESDYK: Good afternoon. My name is Russell Wesdyk. I'm the Associate Director for Regulatory Affairs in the Office of Pharmaceutical Quality II. I'm going to be talking to you about bulk drug substances, the nomenclature, the regulations, and the implications for your patients. So we've gone from an immunogenicity high science, all the way down to the regulations here. Bear with me, though; this is going to be a relevant topic as we get to some of the substances we need to talk about this afternoon. I have no conflicts of interest to disclose.

So why are we here and why are we talking about this? Well, in at least one of the

substances we're going to talk about this afternoon, we need to basically have you guys vote on some related substances within a nomination. How did we get there? This is not a case where we have two different nominators presenting two different materials. These are instances where we have a single nomination that has conflated bulk drug substance information contained within it. In other words, there are multiple bulk drug substances referenced within a nomination for what should be a single bulk drug substance. That makes our job a little more challenging from an FDA perspective.

So the goals of this presentation are to help explain our situation to you and why we analyzed both of those substances; talk through the regulatory definition of a bulk drug substance, an active pharmaceutical ingredient and an active moiety; and explain how those differences actually have implications for the drug products made with them; and provide you with some additional relevant background. Thank you.

I'm going to start with a thought experiment here. We promise we won't ask the question and we won't make you vote on this one, but we wanted to start with what I tried to come up with, the most humdrum, plain vanilla example I could, non-controversial.

So the question is, how many bulk drug substances, APIs, and active moiety, are shown in the example below? And hopefully, by the end of this presentation, you will understand why there are six bulk drug substances, six APIs, two different active moiety, and if we wanted to have all of these put on the 503A Bulks List, we would need to receive six distinct nominations. Unfortunately, we're not always in that situation, but hopefully you'll understand that further as we go through.

Here's where it gets a little boring. My apologies. What is a bulk drug substance? According to the CFR, if you go to the sections that talk about compounding, a bulk drug substance is, basically -- not basically; it says it's the

same as an API. "Alright, Captain Obvious." I know you're asking me, "So then what's an API?" Let's return to the CFR again. An API, per the CFR, is any definition that is intended for incorporation into the finished drug product and is intended to furnish some pharmacological activity. Basically, it's the aspirin and the aspirin tablet, or more appropriately, using my examples before, it's the diclofenac sodium in the diclofenac sodium tablet, but that's different than diclofenac. Those are two distinct and different bulk drug substances.

So what does that mean in practical terms? Well, generally, the specific form of an API that's used in a formulated product, it may be the free base form, but it's often the salt or the ester of that free base form or active moiety, and each of those are distinctive APIs or bulk drug substance. And that form that's chosen is typically picked for its physical, chemical, or various other characteristics, which render them more or less suitable for drug product processing. And

generally speaking, when you get down to the desired dosage form, the CQAs that are relevant for that dosage form drives what bulk drug substance form you're going to use.

For example, if I'm manufacturing an injectable dosage form, I'm probably more concerned with solubility; whereas if I was formulating, let's say, a tablet, I might be less concerned with the solubility and more concerned with the physical characteristics: how does it flow, is it the right crystalline form, and so on and so forth. Something else I might be concerned with is how stable it is in a heated environment. So, all of those characteristics that the bulk drug substances can have, the different ones, are relevant, especially as I go to pick my formulation.

I should also spend a little bit of time on what is an active moiety. And again, my apologies; we're back to the CFR here. So what is an active moiety? An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, or a salt, or

other noncovalent derivative. And that last part is really important here. Once I start covalently bonding different things onto the substance, it's no longer the same active moiety; it's a different active moiety.

So going back to our example of diclofenac and naproxen, if you were to look at the chemical structure, they're not that close, but they're not radically different. There's some different things appended to them. Even though they do similar things, they are different active moiety; whereas the various salts of diclofenac are all salts of the same active moiety. And that's why in this case we have six distinct BDSs and two distinct active moiety, and we would need six different nominations in order to evaluate and put all of them on the list.

Why does this matter? Well, again -- I think this is my last regulation slide -- it's not just a matter of regulations, but we've made very clear, and our regulations make very clear, that when a salt or an ester of an active moiety is

listed on the 503A Bulks List, only that particular salt or ester may be used. The base compound or other salts and esters must be evaluated separately for eligibility.

And why does this matter to your patients? Well, because each one of those different forms will have very different properties, and these distinctions are important in compounding just like they are in conventional drug product manufacturing. It's not just important from a regulation standpoint, but it's really critical to patients that these different chemical structures will have different physical/chemical properties, different PK/PD profiles, different pharm-tox profiles, and all of that impacts on patient safety, product efficacy, and so on and so forth.

I should also mention how we start to tell them apart. There are various unique identifiers and related databases that help us. One of them is called the Global Substance Registration System, often referred to as GSRS. That's the home of what's called a UNII code or a unique ingredient

identifier. It's used by many worldwide regulatory agencies, as is the Chemical Abstract Services, which is the home of the unique identifier known as a CAS number. But what's important for the committee to understand is these databases are generally populated by manufacturers and suppliers. They provide the structures and related information and request the unique identifier. The regulators don't own that data or police that data they're in.

The other thing I should mention here is -- and again, this is also more just for the committee -- from a public service standpoint, the use of common names not relevant today, but for future reference. The use of common names can be highly problematic and cause widespread confusion. Common names are often used when a USAN name doesn't yet exist because a drug may have crashed during early studies, so the innovator never even bothered to get a USAN name. But those common names can be really problematic because they can mean different things to different people.

So again, to sum this up, we're doing

physical and chemical characterization on a bulk drug substance, and if you look at the definition that's shown up there for how we do that, it talks a lot about the properties and toxicities of the BDS. If you're talking about different BDSs, they naturally have different properties and toxicities. So again, it can't then be well characterized if we're talking about two different things, so we need to focus on one.

In conclusion, a bulk drug substance is defined as the same as an API for purposes of our regulations. A free base form, as well as each of the salt forms, are distinct bulk drug substances, each with unique physical, chemical, PK/PD, pharm-tox profiles, all of which can impact on safety and efficacy. We ask that nominators, bulk drug substance manufacturers, and compounders please be aware of what single bulk drug substance you're nominating, manufacturing, and using to formulate your compounded product.

Now, the point, UNII code and CAS numbers, again, are unique identifiers, but they're not

controlled by the FDA. And finally, our physical and chemical characterization evaluation and conclusion is specific to each individual and unique bulk drug substance. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the FDA presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

(No response.)

DR. GULUR: Virtual?

(No response.)

DR. GULUR: Alright.

We will now proceed with the FDA presentation on ipamorelin acetate from Dr. Katie Park and Russell Wesdyk.

FDA Topic 3 Presentation

Katie Park

DR. PARK: Good afternoon. My name is Katie Park. I'm a clinical analyst with the Pharmacy Compounding Review Team in the Office of New Drugs, and I'll be presenting ipamorelin-related bulk drug substances with our OPQ colleague, Russell. I would like to recognize the entire evaluation team, as well as the contribution of many other FDA colleagues, and also special thanks to the Division of Gastroenterology and General Endocrinology in OND.

Ipamorelin free base and ipamorelin acetate were nominated for inclusion on the 503A Bulks List. Wells Pharmacy Network nominated ipamorelin acetate and LDT Health Solutions nominated ipamorelin free base. These nominations were later withdrawn on September 19th of 2024; however, FDA

is electing to proceed with a presentation of this evaluation.

In the next couple of slides, we will present these two different forms of ipamorelins nominated in detail. Both ipamorelin free base and ipamorelin acetate were evaluated for the growth hormone deficiency and postoperative ileus. The proposed dosage form is subcutaneous injection in 2000 microgram per mL. The criteria we consider in our evaluation for the 503A Bulks List are physical and chemical characterization; historical use in compounding; available evidence of effectiveness or lack of effectiveness; and safety.

Now, I'll turn over to the OPQ colleague to discuss differences in nominations submitted and physical and chemical differences between two ipamorelins.

FDA Topic 3 Presentation

Russell Wesdyk

MR. WESDYK: Thank you, Katie.

So this is one of those instances where we received nominations that had conflated bulk

substance information contained within them. And again, we don't mean we've got two nominators nominating two different substances. We mean that the nominator themselves have multiple substances within a single nomination. So we're first going to spend some time describing what do we know about ipamorelin free base and what do we know about ipamorelin acetate.

What you see in front of you is the UNII code; CAS number; molecular formula; molecular weight; and chemical structure for each of those two substances. And again, those are unique drug substances or bulk drug substances. In terms of what we received in the nominations, for the first nomination, the substance named was ipamorelin acetate; however, the UNII code, CAS number, and chemical name don't correspond to ipamorelin acetate; they actually match up with ipamorelin free base form.

The certificate of analysis that we received did name ipamorelin acetate, so we started to feel a little better and thought, we're on solid ground.

But when we looked at that C of A deeper, we realized that the molecular formula, and molecular weight, and the C of A itself did not match up with what it named ipamorelin acetate; it actually matched up with ipamorelin free base. So it wasn't included what the nominator was nominating, or even what the tester was testing, or the drug substance supplier was actually supplying, so we were not sure what we had.

For the second supplier, the second nominator, they named ipamorelin. And again, the UNII code, CAS number, and chemical name matched up with ipamorelin free base, so we think we're in pretty good shape. But the C of A provided was for ipamorelin acetate. When we looked at the test contained within that certificate of analysis, we could reasonably conclude it probably was for ipamorelin acetate; but again, that leaves us with a real challenge. What is actually being nominated here? It's not immediately clear. Because of our safety concerns associated with these substances, we decided to evaluate them both.

I'm going to start with ipamorelin acetate. This is the acetate salt of the free base form. Free base form ipamorelin is a pentapeptide; that's a peptide that contains 5 amino acids, and it contains unnatural amino acids as well. It presents as a white to off-white lyophilized powder and it's soluble in water. There is no USP drug substance monograph, drug product monograph, nor is there any other monograph.

It's reported to be stable at minus 20 degrees, and the impurities that we would expect to see are both peptide related and peptide synthesis related impurities from the starting materials, residual solvents, so on and so forth. We of course don't know what the process is to produce this stuff. We don't have a synthetic pathway.

So because of that, we looked to the certificate of analysis to see, ok, well, what's present in this material and how does that relate to what Daniela was talking about with respect to the potential for immunogenicity?

We both looked at the C of As that were provided by the nominator, and then we looked more broadly out into the public literature and public domain to see what we could find on the market and what that might tell us about the about the substance. Unfortunately, we did not find a lot. The C of As generally gave us identification, assay, water content, and acetate content, but no other critical information such as impurities, aggregates, bioburden, or endotoxin levels, for example. And this was, again, nominated for an injectable dosage form.

We therefore concluded ipamorelin acetate is not well characterized. Because of that lack of certain critical chemical characterization data; as I've already mentioned, impurities, aggregates, BET, and so on and so forth. We're also concerned with the potential for immunogenicity, especially when formulated in an injectable dosage form for subcutaneous administration. And finally, the unnatural amino acids may add to the complexity of characterization of ipamorelin acetate.

In the interest of time, I'm not going to repeat all that information. I'll try to note what's different in the case of ipamorelin free base. The biggest concern here, in addition to all the concerns we've already expressed, is under the second bullet. This is really not soluble in water, and if you're talking about manufacturing injectable dosage form, that would appear to present an additional challenge, which leads us to the next slide, please, the conclusion that ipamorelin free base is also not well characterized for all the reasons we mentioned prior, but also because the limited water solubility makes it difficult to understand how they would manufacture the proposed dosage form.

I'll now turn back to Katie. Thank you for your attention.

FDA Topic 3 Presentation

Katie Park

DR. PARK: Thank you, Russ.

Here's what we found on historical use in compounding. Literature shows that ipamorelins

were first identified in 1998 and have been used in the past; however, there's insufficient information on how long they have been used in compounding. Based on the outsourcing facility reporting data, compounding with ipamorelin can be traced back to at least 2017. Ipamorelins have been studied for postoperative ileus and used for patients with growth hormone deficiencies.

Ipamorelins have been used extensively in medical spas and wellness clinics. Although it is unclear if compounded ipamorelin was used, one medical clinic reports that they partnered with FDA-regulated compounding pharmacies. Ipamorelins have been compounded in injectable, oral, and nasal formulations and marketed online for various uses. They also have been compounded in combination with other peptides such as sermorelin and CJC-1295.

Ipamorelins have also been used in sports as doping agents, which is now on the list of prohibitive substance under World Anti-Doping Agency. Ipamorelins are not recognized in the national medical registries; European Medicines

Agency website; European, Chinese, Indian; or Japanese pharmacopeias.

In conclusion, there's some evidence of compounded ipamorelin use in humans. Internet search results show that compounders have been preparing ipamorelin in injectable, nasal, and oral formulations marketed for a variety of uses and are increasingly being marketed by medical spas and wellness clinics.

Now, I'll move on to general the pharmacology and pharmacokinetics of ipamorelin. Ipamorelin acts as an agonist of ghrelin receptors. When ipamorelin activates ghrelin receptors, it releases growth hormone from anterior pituitary and stimulates both gastric acid secretion and gastric motility in the stomach. Nonclinical studies assessing the pharmacokinetic and toxicological profile of ipamorelin delivered via subcutaneous route were not identified. A PK study conducted in adult male rats showed that intravenous ipamorelin had a short half life, was resistant to metabolism, and was excreted in urine.

We identified one pharmacokinetic, one pharmacodynamic study by Gobburu et al., which was a randomized, placebo-controlled, dose-escalation study conducted in 48 healthy adult male subjects. Five groups of six healthy male subjects per group received ipamorelin from 4.21 to 140.45 nanomole per kilogram over 15 minutes IV infusion and 2 subjects per group received placebo. Study showed that ipamorelin exhibited linear pharmacokinetics with short half-life of 2 hours. It also showed a linear pharmacodynamic of growth hormone release dependent on the concentration of ipamorelin. Maximum plasma growth hormone concentration was reported as 465 milli-international units per liter, and all concentrations declined to very low at all doses by 6 hours.

These couple of slides contain same overview of growth hormone deficiency information that has been presented earlier for ibutamoren. FDA has not identified data to support effectiveness of ipamorelin for a diagnosis or treatment of growth

hormone deficiency in children or adults. Although a previous study in healthy subjects who were administered single doses of IV ipamorelin showed increased growth hormone levels, there are no effectiveness studies in subjects with growth hormone deficiency. There are also no data on whether ipamorelin will increase growth hormone levels in partial or complete growth hormone deficient patients. There are currently FDA-approved therapies with established efficacy for growth hormone deficiency.

Now, I'm going to talk about postoperative ileus. Postoperative ileus, abbreviated POI, is a transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents or tolerance of oral intake. If not treated, POI is associated with significant postoperative morbidity, reduced patient satisfaction, and prolonged hospitalization. The pathophysiology of POI involves a combination of pathways and mechanisms, including opioid use, paralytic enteric

nervous system reflexes, and inflammation following surgery. Clinical signs and symptoms are listed below.

The main objectives of treatment of POI are accelerating GI recovery and decreasing hospital length of stay. Nonpharmacological treatments include early reintroduction of nutrition; gum chewing; laparoscopic surgery; epidural anesthesia; and limited excess fluid. For pharmacological treatment, there's only one FDA-approved drug, alvimopan, which is used for accelerating time to upper and lower GI recovery following bowel resection. Other medications such as methylnatrexone, metoclopramide, neostigmine, or celecoxib may be used for symptomatic management.

There are no clinical studies for the treatment of POI via proposed subcutaneous route. Beck et al. study was the only available study that we identified, which was a proof-of-concept, phase 2, multicenter, randomized, double-blind, placebo-controlled trial evaluating upper GI recovery in 117 hospitalized adults following

abdominal surgery by either laparotomy or laparoscopic.

Fifty-six subjects received IV ipamorelin 0.03 milligram per kilogram and 58 subjects received placebo twice daily, started on postoperative day 1 until postoperative day 7, or hospital discharge, whichever occurred first. The primary endpoint was the time from first dose of study drug to first tolerated meal without nausea or vomiting. This endpoint is measuring the recovery of upper GI tract. Other secondary and additional endpoints are also listed below.

Study showed at the medium time to first tolerate meal from first dose of study drug was 25.3 hours in the ipamorelin group, whereas 32.6 hours in the placebo group. This primary endpoint was not statistically significant. Secondary endpoints and additional endpoints also had no differences between study groups. When stratified by the surgery types, shorter bowel recovery times were limited to subjects undergoing open laparotomy.

A separate review article by Ishida et al. left comment on this POI efficacy study. The article mentioned that, quote/unquote, "In patients undergoing bowel resection, ipamorelin did not shorten the time to first meal intake compared with placebo. This phase 2 clinical trial did not show any significant differences in measurable colonic function between ipamorelin and placebo. Due to these disappointing results, its development was discontinued."

In conclusion, clinical trial did not demonstrate effectiveness of ipamorelin in the treatment of postoperative ileus. There is currently an FDA-approved drug with established efficacy for the management of postoperative ileus following bowel resection surgery.

I will now switch gears to discuss safety. There were no nonclinical acute toxicity, repeat-dose toxicity, genotoxicity, or carcinogenicity studies found in the literature. In rodents, ghrelin receptor activation in brain region that processes reward can potentially induce

reinforcing and addictive behaviors; however, nonclinical studies are lacking to demonstrate whether ipamorelin has reinforcing and addictive properties. Developmental and reproductive toxicity studies with ipamorelin are also unavailable; however, systemic administration of ghrelin to mice resulted in negative effects on fertilization, implantation, and embryofetal development. It is unknown whether ipamorelins can negatively impact fertilization and embryofetal development.

In conclusion, ipamorelins may have behavioral reinforcing properties that can contribute to development of addiction and may negatively affect reproductive health and pregnancy outcomes; however, nonclinical toxicity studies were too limited in scope and duration to inform safety considerations for potential clinical uses of ipamorelins.

For clinical safety, we considered the FAERS database. There were two reports of adverse events associated with compounded products, including

increased lacrimation and headache after using nasal spray containing ipamorelin, and arthralgia with left elbow joint pain after using injectable product containing ipamorelin and sermorelin. The reports from FAERS were, however, limited in interpretation due to several factors such as insufficient case details and concomitant medications.

From the earlier study by Beck et al., study reported adverse events that were mostly mild to moderate in severity. Most common adverse events were nausea, vomiting, and abdominal distention. These were similar in both treatment groups; however, ipamorelin-treated group had a higher percentage of hypokalemia, insomnia, and hyperglycemia at discharge. Serious adverse events such as infection, anastomotic leak, and readmission due to complication of wound healing and death occurred after completion of therapy. In regards to 2 fatalities in the ipamorelin-treated groups, it is unclear whether deaths were related to ipamorelin, as causalities were not provided in

the article.

This slide contains the same information as ibutamoren that discussed some of the potential risks associated with elevated growth hormone and IGF-1 levels. There are insufficient data to conclude that ipamorelin would not raise safety concerns similar to those associated with approved products that stimulate growth hormone release.

As described earlier, immunogenicity is a concern for peptide products. This immunogenic response may be enhanced when peptides are given via subcutaneous route. The nomination did not include, and FDA is not aware of, information about ipamorelins to suggest that the substances do not present this risk.

In conclusion, we did not identify safety data for ipamorelin administered by subcutaneous route of administration; however, based on previous POI study, adverse events from IV administration of ipamorelin raised safety concerns about the use of ipamorelin in compounding. There are also insufficient data to conclude that ipamorelins

would not present safety concerns similar to those associated with FDA-approved products.

Although ipamorelin contains only 5 amino acids, FDA is concerned about potential risk of immunogenicity when giving subcutaneous due to potential for aggregation and impurities. Lastly, there are currently available FDA-approved drugs for the diagnosis of growth hormone deficiency in both children and adults, treatment of growth hormone deficiency in adults, and treatment of short stature in children due to inadequate secretion of endogenous growth hormone. There's also an FDA-approved product for the management of postoperative ileus.

In balancing for evaluation criteria, we recommend not adding ipamorelin-related bulk drug substances to the 503A Bulks List. Ipamorelins are not well characterized from a physicochemical perspective and have lack of endotoxin testing for injectable route of administration. Although there is some evidence of compounded ipamorelin use in humans, there's lack of nonclinical and clinical

safety data, and lack of clinical effectiveness data for ipamorelin-related bulk drug substances delivered via subcutaneous route for growth hormone deficiency or POI.

There are potential serious safety risks associated with ipamorelin, and these are particularly concerning given the existence of drugs approved by FDA for growth hormone deficiency and POI, which are serious conditions; therefore, after considering the information currently available, a balancing of the four evaluation criteria weighs against ipamorelin-related bulk drug substances being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to the presenter, if you can. Finally, it would be helpful to acknowledge

the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

(No response.)

DR. GULUR: Virtual?

(No response.)

Open Public Hearing

DR. GULUR: We will now begin the open public hearing session.

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 open 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 the 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 in 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 for 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.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing for the record. You have 20 minutes.

DR. ROSEBUSH: Thank you.

Again, my name is Lee Rosebush. I'm here on behalf of a coalition of pharmacy compounders that I represent, including FarmaKeio. For the record, I do not represent Wells, nor do I represent LET from this perspective. I do want to mention a couple of things since we've had three presentations that were just given from this perspective. We had an immunogenicity, we've had BDS presentation, and we've had the ipamorelin

presentation. I do want to start out with the immunogenicity presentation.

It was quite interesting because, in this perspective, a clinical trial was mentioned, and we saw a chart comparing commercially available product to compounded available product. Notice, you didn't hear the name of the product associated with that, and was that ipamorelin from that perspective. I would argue in that side, if it's not, just like it's been told often in multiple occasions, it's irrelevant from this perspective and should be considered misleading moving forward.

Second in this, if it truly was ipamorelin, I would beg the question as to why it was labeled as a commercially available product; because if it was approved ipamorelin, we wouldn't be here. We'd have the ability to compound from that product. Accordingly, from that perspective, it couldn't be commercially available ipamorelin. It had to have been something else. Obviously, that's misleading, at best.

Therefore, if that presentation was just

simply made to talk about the risks of immunogenicity, that would apply to all products, not particularly ipamorelin. If that's the case, FDA has put forward FDA guidance documents, as well as ICH guidance documents that we're going to talk about that explicitly allows for APIs to be tested for things, including impurities, including things along aggregates, and including things around endotoxins.

Second, from this perspective, we've heard several COAs that were just mentioned in the BDS presentation. I think that is also misleading from the agency, at best. As the agency has mentioned, those presentations and nominations were withdrawn. That's not my words; that's FDA's words. Also from that perspective, it is quite clear, as you've heard from the last two presentations, that I have given, that we submitted a re-, quote/unquote, "nomination" for this product. We also provided COAs for these products. Our COAs and renomination was for ipamorelin acetate, period. If the COAs that we have provided in writing to the docket were

reviewed, that would be clear as to which product in that perspective we have been talking about.

So again, from this perspective, moving forward, I think it was misleading to be able to make pharmacy compounding look bad because of two folks not associated with these discussions, nor are they presenting today. However, there are people in the room from Wells who could answer that, including potentially on the PCAC, which I haven't heard from, from that perspective of some of the disclosures available who do know about what Wells did during that process, period. Accordingly, from that side of it, I would ask that the conversation, please, from that perspective again, be stricken, as those nominations were withdrawn, period.

Now, coming back to the review of this, quote/unquote "nomination and discussion associated with ipamorelin," there are four factors, as we've discussed on multiple occasions: 1) is the substance well characterized physically and chemically; 2) has the substance been used

historically in compounding; 3) are there concerns about whether a substance is effective for a particular use; and 4) are there concerns about the safety of substances for use in compounding? Again, you see nothing in here about superiority comparative analysis, inferiority analysis, et cetera.

As we move forward on this one, I think it's extremely important to point out, ipamorelin, as you will see, has the same side effect or profile as semorelin. Semorelin in this perspective can be compounded by 503As, period. It's a proponent of an FDA-approved product, and in fact there are some benefits associated with using ipamorelin as compared to semorelin, for example, the half-life of the product.

It was just mentioned during the study that it's 6 hours. I would beg to compare that to semorelin. For those that understand GHD, there's a potential benefit for having a longer half-life and the potential increase of growth hormone, from that perspective, with that product.

As we've mentioned, those four factors come from FDA's regulation 21 CFR 216.23. Accordingly, as I've mentioned before, there is a Federal Register notice from 2019, and all of those comments in quotes that I read from earlier today with the L-theanine presentation I would ask to be included in the record here, as well as the comments associated with choice, including those of a woman's choice, be included in this conversation as well.

I would also point out in this perspective, it is quite clear in the regulations when we are talking about a substance versus a product. Going to the BDS discussion, notice here when a substance is highlighted; notice when a product is highlighted. I think that is quite important to remember as we start going through some of these factors as to the approval and whether or not it should be considered or not be considered for the list. Any other considerations of when you would look at a product, for example on the first, when it should be the substance, things like endotoxin

testing for what's considered for subQ injection, is improper, period.

Now, on those four specific factors, is the substance well characterized physically and chemically? As you've heard this earlier from FDA themselves, FDA has a database called the GSRS system. FDA's own GSRS system specifically links to ipamorelin -- that has been provided -- and NIH's own PubChem also links to ipamorelin. Interestingly, when you go to NIH's document, they actually say ipamorelin is synonymous with ipamorelin acetate. So if there really truly is a question, from the industry perspective, as to ipamorelin versus ipamorelin acetate, the NIH may want to clean up its own website.

Moving forward, it has a detailed listing for ipamorelin that includes information on the characterization of ipamorelin both physically and chemically. We have provided COAs in the written materials that show endotoxin testing, purity testing, et cetera, all based on what FDA and ICH guidance documents relate to, and we're going to go

through those here in just a second; and they're based on FDA's own guidance when it comes to peptide testing and ICH standards.

In addition, FDA's packet -- and I would note this to you, and you also didn't hear this in the presentation -- did not include or address oral uses of ipamorelin. One of the things you're going to hear about -- you've heard the first one was 76,000. The second one you heard was 560,000. Anybody got a guess what this one is? It's even more. We're going to go through the prescription history with that in just a second.

Specifically, are there concerns about whether a substance is effective for a particular use? In this case, ipamorelin has been used over 675,000 times, 675,000 dispenses, and that again is a limited number of pharmacies. And I understand from real-world evidence, that has been pointed out multiple times now, that a pharmacy may not be required to report. The pharmacies have said they would have reported. We're going to go through what those adverse events are.

I would also point out, if we want to go through what can be reported and what can't be reported, all of you as physicians aren't required to report. All of you as hospitals aren't required to report. So should we take your data and throw it out as well, and not consider that as real-world evidence? Again, arbitrarily picking a standard, when it applies and when it doesn't apply, leads to legal challenges.

Four, are there concerns about the safety of the substances for use in compounding? Our real-world evidence and retrospective analysis found that out of over 675,000 prescriptions, only one adverse event was reported, and it was non-life threatening. Further, as discussed later, a clinical trial found that adverse effects associated with the treatment were rare and similar to those, as I mentioned, reported with semorelin, which can be used for compounding by 503As today.

So let's go through the first requirement and criteria. The issues, as I've mentioned on several occasions now, raised by FDA related to

things about immunogenicity, endotoxin, purity, we've heard it with chiral aspects, et cetera, relate to the API itself. They do not relate to compounding. Why is that important? Because if FDA's really truly concerned -- and this is about patient safety with the API -- they can simply put forward a guidance document saying how this should be done. And, in fact, there are guidance documents on how purity testing, endotoxin testing, et cetera, can be done, and those are literally listed on the next slide.

FDA in that perspective should release guidance for APIs and not prohibit compounding for those that properly require and test the API. We have provided written COAs showing that that testing has been done to the written record and they are not the COAs that FDA has continually referenced inside the slide decks here.

API manufacturers are also testing for potency, purity, and impurities, including aggregates that were mentioned and endotoxin testing. I've provided a link here.

Unfortunately, because of our limited amount of time, we can't go through it, but that is a common test. For immunogenicity, for example, you could simply do an HPLC or UPLC machine, run it through from that perspective, and do additional testing to determine. They lay it out specifically in that article published on NIH to be able to determine that if you needed to. In addition, the National Center for Biotech Information, the PubChem as I've mentioned, there is a link to it, and FDA's GSRS listing for ipamorelin.

Now, as was mentioned, we've also included this information. As I wanted to make clear, our COA says it's for ipamorelin acetate, and from this perspective, our, quote/unquote "renomination materials" that we have provided written-wise also say it is for ipamorelin acetate. In addition, the COAs that we provide say it's for ipamorelin acetate, and the testing done shows it's from ipamorelin acetate.

Here is FDA's own guidance documents and from ICH on how to test. Notice, impurities is

there from that perspective, and you can go down the list; solvents, which was raised as well. This testing for the COA included all of these requirements. The physical and chemical characteristics of the substance -- notice it's not drug product, however -- even if looking at the finished product for impurities, it includes from that perspective testing that is no more than 0.5 percent of the drug substance. As you can see, that meets FDA's own ANDA requirements for this specific testing.

The aggregates, as I mentioned before, this product can be taken orally, and from that perspective, we provided an additional quote showing from a testing perspective how it could be done. Endotoxin, the peptides can be taken orally, and alternatively, there is testing for endotoxin; it is on the COA. Unnatural amino acids were raised. I will give you two examples that use unnatural amino acids that FDA has approved previously. Immunogenicity, in this case, testing for aggregates and impurities can and are being

done.

Now, in the historical data, as I've mentioned, oncology approvals over a 5-year period included a sample size from 14 to 908 patients. In addition, as we mentioned on multiple occasions, NDAs and BLAs, from that perspective, 13 examples of real-world evidence were used for approvals. In this perspective, we're aware of any serious, let alone unexpected, adverse events directly attributable to drug products compounded from ipamorelin. This includes real-world evidence from pharmacies who have dispensed over 675,000 prescriptions. And yes, this included going back and looking at patient histories, from that perspective, as to what was dispensed, and medical records. FDA is included in these materials. FDA's review of its FAERS and CAERS system further -- you heard that today as well -- 675,000 prescriptions, and we had less than a few known adverse events. I would also point out, as we pointed out previously, an approval process doesn't necessarily mean it has to be safe. It doesn't

mean zero from that perspective.

Here's our data, 675,709 prescriptions that have been dispensed. Yes, that has been provided in written material to the agency. Notice you didn't hear any of those materials discussed today when it came to historical compounding. Yes, they received it previous to this.

Are there concerns about whether a substance is effective for a particular use? And with that, I'm going to turn it over to my colleague, Jim.

MR. LaVALLE: I'm here representing FarmaKeio. FarmaKeio did pay for my travel and lodging here. I want to point out, as the chair of the International Peptide Society, we've trained several hundred physicians under CME accredited education on peptides specifically, so there are a lot of different areas that it's been at least reported to be used, but I want to point out where it's most used in that clinical setting; in the real-world, what are clinicians using and what are they reporting back, at least through the society?

Postoperative ileus, I don't see a lot of

reporting on that from our clinicians, but are they using it for IGF-1 improvement? Yes. Do they note there are no big spikes in cortisol, or prolactin, or ghrelin? So alterations and other hormones, not seeing anything there. Increase in lean body mass; and lowering body fat, probably one of the more relevant uses for ipamorelin in the clinical setting. Bone density, to a certain extent, but also I'd like to point out improving sleep and memory. Sleep is probably one of the biggest things that our clinicians report; that their patients see an improvement in sleep.

I think this study was gone over. There wasn't that much of a difference in secondary outcomes and only a few days difference in terms of time to first meal, and totally in agreement with that. It's not the use that we see that clinicians are using, at least from the education that we've done and what we get reported back, with about six meetings a year with our clinicians that are getting education.

Once again, just to reiterate the safety,

safety and issues raised at the use of the substance and compounded product, reports peer-reviewed medical literature about the substance; pharmacology; acute toxicity and repeated-dose toxicity; mutagenicity; and reported abstracts and literature about adverse reactions in humans. Once again, we know that it's not complete but we have contacted at least 9 pharmacies and, yes, they're not required. At the same time, compounding pharmacists have the same desire that all other medical professionals have. If something's wrong, they want to report it.

Let's move forward. This was in hypogonadal males. The review here examined the literature on the use of secretagogues to explore the potential complementary role in the management of hypogonadal and eugonadal males with metabolic syndrome or subclinical hypogonadism. Conclusion was that it was a potent selective stimulator growth hormone, significantly influenced the GI system and influenced body composition and adiposity. Adverse effects associated were rare, similar to those

reported with sermorelin.

In terms of ordering ACTH or cortisol levels, there was no significant difference on that at all, and the lack of any kind of stimulation of ACTH, or cortisol and plasma, even at a 200-fold higher dose than the ED50 for GH release.

We've already went through this. Lee presented this. One adverse event reported, and from the side effects side, maybe injection irritation is probably the most common thing that was reported by clinicians through the society. And once again, conducted the search on the FAERS and the CAERS database for the period of September 30th of 2023, and found no additional adverse events reported since 2023. And once again, just to reiterate the conclusion, I believe Lee went through this already, and that's it. Thank you for your time.

Clarifying Questions from the Committee (con't)

DR. GULUR: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer

take comments from the audience. We do have some additional time. We can do some clarifying questions if anybody in the panel has questions or if the FDA would like to make any comments.

DR. GANLEY: Hi. I'm Charlie Ganley. As I noted in previous sessions, I just wanted to make a comment regarding real-world evidence. Real-world evidence is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data. Various sources of real-world data can be analyzed in non-intervention studies such as registries, electronic health records, and medical claims.

The information provided in the presentation are simply numbers of prescriptions filled by unidentified pharmacies over an unknown period of time. It does not identify the use, dose, route of administration, and duration of exposure. It does not provide any data related to safety, and most importantly, effectiveness of the drug. Thank you.

DR. GULUR: Thank you.

MS. BORMEL: Hi. I'm Gail Bormel, FDA. I

wanted to talk a little bit about API and why we're so concerned with it. APIs are the starting materials for use in compounding. That's what we're talking about, the bulk drug substances. When you're not in the compounding world, if you're in the outsourcing facility world or you're in the conventionally manufactured drugs world, they're subject to CGMPs, current good manufacturing practices; and part of that requirement is that they have to test the APIs that come in and make sure they are what they say they are, particularly with identity. There is no such requirement on pharmacies to do this testing.

So part of our responsibility when we're looking at the bulk drug substances is to look at what exactly the bulk drug substance is. That's why we talk about that BDS, the bulk drug substance, or the API. And in the particular case of ipamorelin, there are complications because there can be impurities, there can be aggregates, and that is what we were talking about, because it would be important to how that particular drug

would act in terms of the safety issues that were raised.

In addition, I just wanted to also let you know that there are, as I've mentioned before, thousands of pharmacies who use bulk drug substances in compounding, so there's not a uniform way that all the bulk drug substances are evaluated by the thousands of pharmacies across the United States.

DR. GULUR: Thank you.

Dr. Cosel, virtually?

DR. COSEL: Thank you very much for recognizing me. I just wanted to make a couple of additional clarifying points. The first OPH speaker noted new information that was submitted to the agency, or raised this, and questioned the agency's consideration of information in a nomination that was recently withdrawn. I just wanted to clarify that FDA may continue to evaluate a substance at its discretion, even if the nominator submits a comment requesting withdrawal of the nomination. In this case, the nominator

submitted comments requesting withdrawal of their nominations, and FDA did continue to evaluate ipamorelin free base and ipamorelin acetate on its own initiative.

Second, it's our understanding that the new information submitted to us is not a new nomination, and FDA's initial assessment is that this new information does not provide any new clinical data that would weigh in favor of its inclusion on the 503A Bulks List. Finally, we will consider any relevant information according to our normal process for comments submitted to the docket, which would include considering the information in advance of any notice of proposal making.

DR. GULUR: Thank you.

DR. SOLGA: Hi. This is Steve Solga. Just a question to the last person who spoke from the FDA. Can I understand more about the motivation to continue to evaluate after the withdrawal?

DR. COSEL: I mentioned the withdrawal was recent, and FDA had initiated its evaluation and

done quite a lot of work to provide it, and we wanted to share our consideration with the committee and proceed on, on the substance. I'll ask if Gail or others would like to add to that.

MS. BORMEL: I can just say you can see that pharmacies are making it anyway as per the comments in the open public hearing, so it's important that we had done the work and we proceeded with the evaluation, which we're allowed to do.

DR. SOLGA: Thank you.

DR. DEVEAU: Again, Ian Deveau, Deputy Director, Office of Compounding Quality and Compliance. Just to follow on to what Dr. Bormel had indicated about the GMPs or lack of GMP requirements for 503A, they're also not required to do any clinical trials to demonstrate whether or not any impurities have any immunogenicity or any other responses. So there is no requirement for this, and that possibility is a complete unknown.

DR. GULUR: Any other questions?

Go ahead.

DR. SOLGA: Well, as long as we're all here,

for anybody at the FDA, when you consider efficacy, do you distinguish when you look at conditions, potential indications, in treating a putative disease versus a syndrome? I mean, the conventional drug world, that's all about whether we're on that pathway or not.

DR. GANLEY: Our evaluation of efficacy is limited primarily to what was in a nomination at one time. There are a lot of examples of where these drugs may be used for other conditions and we can't evaluate everything. There is a burden on the nominator, or in this case the open public hearing, to present information in clinical empirical trials that would support their position.

So we don't make any distinction. If someone wants to treat a syndrome or a specific disease, that's determined by the information we receive in the nominations or in an open public hearing here. But there still is a burden, if we haven't reviewed it, for them to provide some information that would support it. Simply because it's prescribed for that doesn't necessarily

indicate that it's effective for that.

DR. SOLGA: Thank you.

DR. LEE: So my understanding is the nominator had --

DR. GULUR: Please state your name.

DR. LEE: -- submitted this drug for two specific indications for growth hormone --

DR. GULUR: Dr. Lee, would you mind stating your name?

DR. LEE: -- sure, Brian Lee -- deficiency and postoperative ileus.

Now, it's clear from the presentations today that there's actually widespread use and that it's marketed to the public for a variety of conditions. Is there any sense from these prescriptions that are prescribed what the proportion is for what diseases and whether they're related to the two indications that we're talking about today?

DR. GANLEY: Hi. This is Charlie Ganley. As I noted, they provided information on prescriptions but nothing on information about the use, route of administration, dose, or duration of

use, so we have no information on that. We're working in the blind here because all this information is not readily accessible for FDA. We depend on individuals submitting information to us that would help support their position.

DR. SERUMAGA: Brian Serumaga. Just out of curiosity, the original nominators, did they submit any information to the FDA as to why they withdrew the nomination?

MS. BORMEL: I don't think we can discuss that. This is Gail Bormel, FDA.

DR. GULUR: Thank you.

I want to, just for the process, indicate that once the public hearing component is closed, we cannot entertain any further comments from the public. I'll repeat myself. Once the public hearing component is closed, we cannot entertain questions or comments from the public.

Yes, Dr. Lee?

DR. LEE: One more question. Brian Lee. We heard in the presentation from the open hearing that there have been over 500,000 prescriptions but

only one adverse event reported. Can the FDA describe a little bit about what the adverse event reporting system would be that would be cited in this case?

DR. GULUR: Go ahead.

MS. BORMEL: Gail Bormel. For pharmacies, pharmacy compounders on pharmacies, there's no affirmative requirement of adverse event reporting under 503A, so anything that they would report would be voluntary. Oftentimes, with respect to compounded drugs, we receive voluntary reports from consumers, from practitioners, and sometimes from pharmacies, but mostly from consumers, et cetera. So since there's no adverse event reporting requirement of 503A, we may get something; we may not.

This is really unlike the rest of the law for outsourcing facilities under another section of the Act, which is required to report serious adverse events to the agency. In addition, manufacturers of approved drugs are also required to report. When you're dealing with compounding

pharmacies, it's voluntary reporting, and they don't have to report under 503A.

DR. GULUR: Thank you.

Dr. Desai, online?

DR. DESAI: Thank you very much. Seemal Desai, member of the committee, dermatologist, UT Southwestern and Innovative Dermatology. I'm struggling a bit here in particular -- I've been on PCAC for many years, but one of the things that I'm struggling with a little bit with this particular situation is the concept of adverse event reporting in the setting of a wide amount of use by physicians that's documented through clinical applications, and I understand the difference between real-world and also between scientific evidence.

Is there any scope on the FDA side to use the clinical experience, based on the number of years that this has been already in circulation or been used as a compound, to determine more about the efficacy of these products? I guess the other way to ask this question is, where is the line

that's drawn between those that have robust data versus those products that we use clinically as physicians, off label and in compounded indications, based on clinical trials, as well as case reports and observational studies?

DR. GANLEY: Yes. This is Charlie Ganley. As we noted in the presentation in the open public hearing, FDA will consider real-world evidence. I can generally state, however, there's usually an enormous amount of other information available to us, whether it be mechanistic information, natural history of a disease, and other empirical information that we rely on. And then depending on what the purpose of the real-world evidence is, that can help us support a decision.

I don't know specifically what applications the open public hearing was referring to, but when you think about it, real-world evidence in those cases generally would be something that possibly was already approved and they're getting a supplemental location. I don't know specifically offhand. And generally, when real-world evidence

is going to be taken and considered by FDA, the applicant will come to the FDA and make a proposition that this is what we would like to do in terms of collecting real-world evidence, and this is how we intend to analyze it, and we're going to use that to help support this use.

So simply having prescription data and use data without information about who it was used and what it was used for is not necessarily going to provide information on the safety or efficacy if you have not collected it in an organized fashion. That's why I was very clear, when we're looking at real-world evidence, when we're looking at electronic health records, for example, or for medical claims data, it depends on what information you're trying to obtain from that real-world evidence. So simply because you write a prescription and give a dose to an individual, we don't have that information. We have to make a decision based on information provided to us.

DR. GULUR: Go ahead.

DR. GURA: Hi. Kathleen Gura. Just a

question, and it just came to me as you were talking. Can the FDA do something like a REMS situation for these kinds of compounds to collect the data that we don't have?

DR. GANLEY: This is Charlie Ganley. No, we don't. REMS really apply to applications that are submitted to FDA for approval, whether it be a new drug application or biologic application. These drugs are not approved; they're marketed.

DR. GULUR: Go ahead.

DR. COOKE: David Cooke. Help me understand a little bit better; ipamorelin has not been approved for an indication, but there's over 600,000 dispensations of this, so some number of prescriptions for it. What's the basis for the dispensing that medication without either the approved indication or the compounding approval that we're discussing here today?

MS. BORMEL: Gail Bormel, FDA. There are situations, and as I've mentioned before, there are thousands of pharmacies. And we do have a law in Section 503A that specifies what bulk drug

substances are to be used in compounding. We also have an interim policy which describes those bulk drug substances that are in Category 1 that could be used while we're evaluating things, but that doesn't mean that everyone complies with that. So there may have been a lot of pharmacies using this, or just using it and not looking at what bulk drug substances could be used under the law and what the agency has considered to be appropriate. These are pharmacies across different states.

So I really can't speak to that because I don't know why they would be using it or why they thought that it was appropriate. But, in general, the primary regulators of the state-licensed pharmacies are the state boards, and we don't get information at FDA about what state-licensed pharmacies are making, nor do we get, as I've mentioned before, adverse event reports, necessarily, because they're not mandatory under 503A. So I can't really answer that.

DR. COOKE: Thank you.

DR. WEISS: Rita Weiss with the NABP. My

question is, is FDA aware of any state boards that mandate reporting to FDA?

MS. BORMEL: Yes. Gail Bormel, FDA. Do you mean mandate reporting of adverse events?

DR. WEISS: Yes.

MS. BORMEL: Yes. Well, there's one state that requires adverse reporting to the state that I'm aware of, and that is California, but that's a reporting requirement to the state, not to the agency, of adverse events that a pharmacy would find out about.

DR. WEISS: Thank you.

DR. GULUR: I'm going to take this opportunity to just summarize the discussion so far. Obviously, the concerns have been raised as far as the processes and how we identify. One of the big questions brought up was how do we reconcile, I should say, the information that this substance is currently being prescribed, compounded, and dispensed to patients, and yet a review of the substance, based on a nomination, which was subsequently withdrawn, however, still

initiated by a nomination, indicated that it would not otherwise have been considered safe or have enough data to support its safe or efficacious use. Other concerns raised were whether there were some processes that could be put in place to proactively identify these practices.

Another point that was raised was the real-world evidence has come up many times as can we use prescribing data with no major reports coming in as evidence of safety. I think I'll just clarify and comment there that all of us in practice and in history here are fully familiar with the fact that there have been drugs, many that come to mind, that have been prescribed for years before their serious side effects and serious impact on the population were realized, to much of the detriment of many in our country. So the standards for evidence exist for a reason. Anecdotal lack of reports does not equal safety, necessarily, so I just wanted to put that out there as well.

Any other comments?

DR. GANLEY: Yes. This is Charlie Ganley. I just want to make it clear that when we think about drugs, there's a dose/route of administration, how much is safe, and we don't have access to any of that information. There's an opportunity for the open public hearing speakers or the compounding industry to provide this information to us ahead of these meetings, and we're willing to accept that information so we have a better understanding. But we're looking into what's in the public record, what's in the internet, and as you saw in this presentation, there are different wellness clinics marketing these things. We have no information on that.

So I think the burden is somewhat on the industry here to provide information that would support this. But I would have no idea as to what the regular dosing regimen would be for this or what data would actually have supported that because we have not found empirical evidence of it.

DR. GULUR: I would just like to -- before I call on you -- remark on one other aspect. The

number of prescriptions does not equal use. As we all know, prescriptions are not always utilized for one thing. There are also the automatic refills, as we're all aware of, where things are sent repeatedly to patients who may have stopped using it, et cetera.

So getting more detail would be extremely helpful. And if we are to use that information well -- and it sounds like it is a voluntary process; there's no reporting required, again. But it sure sounded, in hearing our open public hearing speakers, that they have their own policies for transparency and would like to share this information. So perhaps if it's not mandated, at least there should be a voluntary reporting of prescriptions, the utilization, and any reported events that come through.

Again, reporting, the other issue, of course, is that patients take multiple medications. They may not even realize which one is causing what effect for them, so their providers should also hopefully keep these kinds of instances importantly

reported.

With that --

DR. COOKE: So if after this meeting, FDA decides not to put this substance on the 503A list, but a sponsor in the future decides to ask for it to go on the list, either for the same route in indication or a different route in indication, and provides more information, that would be reconsidered; correct?

DR. GULUR: Yes?

MS. BORMEL: The process for the 503A Bulks List is after the committee votes, then the agency takes that information into consideration, and then would issue a proposed rulemaking, either putting it on the list or not putting it on the list. And after that time, there would be opportunity for public comment before a final rule is issued and the final decision is made.

DR. COOKE: Okay. So there's an opportunity in that comment.

MS. BORMEL: Correct.

DR. COOKE: But even after they make a final

decision, is it possible for a different sponsor to come back in the future with more information and reapply?

MS. BORMEL: I believe it's possible. It may be a different process to do so, but it's possible. But there would be a final rule at that point. So it would be possible, but I believe it's a citizen petition process, yes.

DR. BOGNER: Gail, you mentioned -- Robin Bogner --

DR. GULUR: Thank you.

DR. BOGNER: -- an interim policy until there's a final list. Can you talk about that at all to us?

MS. BORMEL: Yes. Gail Bormel, FDA. It's taken a while to develop the list for both 503A and 503B, so we had issued interim policies under Section 503A and 503B, but we'll only talk about 503A. And during the time period during which we were developing the lists, we said we would categorize the bulk drug substances nominated for the 503A list into three categories, Category 1,

Category 2, or Category 3.

Under Category 1, if things were nominated with what we consider to be sufficient support, and they were placed in Category 1, we wouldn't object to the use by compounders of these bulk drug substances until we evaluated it formally through the evaluation process and the PCAF process. We've since that time issued another draft guidance to stop the categorization process, but that isn't a final guidance yet.

So we're still categorizing, generally, as things come in. But that's what I was referring to, that Category 1 list that allows for that particular use of bulk drug substances on Category 1 until we've finalized our decision making via a final rule in the case of the bulk substances for 503A.

DR. BOGNER: Thank you.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Virtual?

(No response.)

DR. GULUR: Alright.

So I'll just summarize again the remaining part of what we just discussed for the record, which is, essentially, that there is a strong conversation and request that information be shared voluntarily by compounding pharmacies with the FDA on prescriptions, dose, route, and dispensation so that there could be more informed decision making moving forward, which would also allow us to protect the health of our citizens.

Any other comments? Anything else that folks would like to make sure is recorded?

(No response.)

Committee Discussion and Vote

DR. GULUR: So with that, this is going to be a slightly different voting process, so please bear with me as we go through this.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our third question, which is a voting question with subsections. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote after you've pressed it, you may press the button that is corresponding to your current vote until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who

voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

For question 3, do committee members agree to vote on ipamorelin-related bulk drug substances discussed today, which is ipamorelin free base and ipamorelin acetate, as a group; yes or no? If any member of the committee votes no, FDA will take individual votes on each of these substances.

Any questions? So again, just to state, do committee members agree to vote on ipamorelin-related bulk drug substances discussed today, ipamorelin free base and ipamorelin acetate, as a group; yes or no? We do have virtual voters who will be emailing their responses, so please bear with us.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 12 yeses, 1 no, and zero abstentions.

DR. GULUR: Since one or more panel members voted no, we will proceed with questions 3b and 3c.

For question 3b, FDA is proposing that ipamorelin free base not be included on the 503A Bulks List. Should ipamorelin free base be placed on the list? If you vote no, you are recommending FDA not place the bulk drug substance on the 503A Bulks List. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

If there are no further questions or comments concerning the wording of the question -- go ahead.

DR. BOGNER: Robin Bogner. I have a quick question. If we abstain, if the majority were to abstain, would that smooth the way to reevaluating this when there's more information available?

DR. GULUR: No? Does the FDA wish to comment? I don't believe so. I would recommend

you vote based on the information provided.

DR. BOGNER: Thank you.

DR. GULUR: Yes?

DR. VAIDA: I just voted wrong again.

DR. GULUR: Oh, you did? You can continue. It's open. I haven't even opened it yet, so you could go ahead and keep voting. Feel free to press as many times as you like.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

For purposes of clarity, I will repeat the question. FDA is proposing that ipamorelin free base not be included on the 503A Bulks List. The question is, should ipamorelin free base be placed on the list? If you vote no, it will not be placed on the list. If you vote yes, it will be placed on

the list.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are zero yeses, 12 noes, and 1 abstention. Thank you.

DR. GULUR: Now that the vote is complete, we will go around the table and have everyone who voted, starting with that end of the table, state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

DR. SOLGA: This is Steve Solga. I voted no. I don't see any strong rationale for placing on the list anywhere in the provided information. As a newcomer to this committee -- I should say first-time temporary voting member -- I appreciated the discussion we had after the presentations, notwithstanding all of the FDA's context prior to the meeting and here. I felt like I didn't fully understand the context and consequences of a no vote, but after the discussion, I felt I was closer to that, so thank you.

DR. LEE: This is Brian Lee. I voted no. I'll make a comment that there are different levels of evidence to evaluate safety and efficacy in science, and there's a general paucity of high-quality data to inform this decision. But something that's widely prescribed and used doesn't mean that it's safe and effective. And there are plenty of examples, or cautionary tales rather, that would say that it's important to judge things based off of high-quality evidence.

The randomized clinical trials that have been performed with this substance show that there is lack of efficacy, and there are real safety concerns that have been raised. And I'll note that the randomized clinical trials did have signals of adverse events, so I find it concerning that the safety surveillance system by the industry only noted one adverse event amongst over 500,000 prescriptions. So that needs to be noted and could potentially be improved upon in the future.

DR. COOKE: This is David Cooke. I voted no because of the lack of adequate safety and efficacy

data.

DR. WEISS: This is Rita Weiss. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. DURHAM: Todd Durham. I voted no.

DR. GULUR: Dr. Yanovski, online?

DR. YANOVSKI: Yes. I voted no for the same reasons everyone has already stated. Thank you.

DR. GULUR: Thank you.

Dr. Desai, online?

DR. DESAI: Thank you. Seemal Desai. I abstained from this vote due to some conflicting comments that I felt I had heard during the discussion, which I also felt was robust and helpful but somewhat confusing in the deliberation between the data presented and some of the other evidence that I reviewed in preparation for the meeting. Thank you.

DR. GULUR: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello. I voted no

for the reasons that have been stated previously.

DR. GULUR: Thank you.

Padma Gulur. I voted no for reasons that have already been stated, in which I will summarize. I would like to start by summarizing that panel members appreciated the robust discussion and the comments from the FDA helping to clarify many questions, so we'd like to thank the FDA for that.

The primary reasons people voted no appear to be a lack of safety and efficacy data. Related to this, comments were also made on how widely prescribed medications do not equal safety and that randomized-controlled trials should be conducted; and further, that the randomized-controlled trials that had been presented had indicated safety signals, which the prescription data that was provided would indicate do not exist, which may be a signal of underreporting.

So with that, we will end this topic and -- oh, sorry. We do have the second question. My apologies.

On slide 5, we have the next question, which is, FDA is proposing that ipamorelin acetate not be included on the 503A Bulks List. Should ipamorelin acetate be placed on the list? Again, it's the same instruction as last time. If you should vote no, you're recommending it not be placed on the list. If you vote yes, you are recommending it should be placed on the list, and of course you have the option of abstaining as well.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For

the record, there are zero yeses, 12 noes, and 1 abstention. Thank you.

DR. GULUR: Now that the vote is complete, we will go around the table similar to the last time and have everyone who voted state their name vote, and if you want to, you can state the reason why you voted as you did into the record.

We could start with you.

DR. SOLGA: Steve Solga. I voted no. To my understanding of the regulatory standard, the threshold was not met.

DR. LEE: Brian Lee. I voted no for reasons I stated previously.

DR. COOKE: David Cooke. I voted no for the same reasons as for the base.

DR. WEISS: Rita Weiss. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. VAIDA: Allen Vaida. I voted no for reasons before.

DR. DURHAM: Todd Durham. I voted no.

DR. GULUR: Dr. Yanovski, online?

DR. YANOVSKI: Jack Yanovski. I also voted no for the fact that safety and efficacy hadn't been sufficiently shown. Thank you.

DR. GULUR: Dr. Rebello, online?

DR. REBELLO: I also voted no. Elizabeth Rebello. I voted no.

DR. GULUR: Dr. Desai, online?

DR. DESAI: Seemal Desai. I abstained for the same comments as before.

DR. GULUR: Thank you.

Padma Gulur. I voted no. As has been stated by all the panel members, the reasons for the vote this time are the same as they were for the free base.

Adjournment

DR. GULUR: With this, we will be concluding the ipamorelin acetate, ipamorelin topic. Thank you, everyone. We will take a quick 10-minute break. We will reconvene at 2:05 pm. Panel members, please remember that there should be no discussion of the meeting topic during the break

amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 1:53 p.m., the topic 3 session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Topic 4

Kisspeptin-10

Tuesday, October 29, 2024

2:05 p.m. to 3:13 p.m.

Meeting Roster

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C O N T E N T S

P R O C E E D I N G S

(2:05 p.m.)

Call to Order

Introduction of Committee

DR. GULUR: Welcome back, everyone. Before we begin the kisspeptin-10 topic session, panel members who will be in this topic will introduce themselves by stating their names and affiliations. We will begin with Dr. Alukal.

DR. ALUKAL: I'm Joseph Alukal from Columbia University. I'm a urologist.

DR. GULUR: Dr. Dmochowski?

DR. DMOCHOWSKI: Roger Dmochowski. I'm an urologist from Vanderbilt Medical Center.

DR. GULUR: Welcome. Thank you. I would like to state into the record that we do not have a nominator presentation for the kisspeptin-10 topic. We will now proceed with the FDA presentation on kisspeptin-10 from Dr. Elizabeth Hankla.

FDA Topic 4 Presentation

Elizabeth Hankla

DR. HANKLA: Good afternoon. My name is

Elizabeth Hankla. I'm a clinical analyst with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting kisspeptin-10. I would like to recognize the evaluation team, as well as the contribution of many other FDA colleagues. Special thanks to the Division of Urology, Obstetrics, and Gynecology in OND.

Kisspeptin-10 was nominated for inclusion on the 503A Bulks List. It was evaluated for the treatment of secondary hypogonadism in men. Products proposed in the nomination are 1 mg per mL solutions for injection for subcutaneous and intramuscular administration. The criteria we consider in our evaluation for the 503A Bulks List are physical and chemical characterization; safety; historical use in compounding; and available evidence of effectiveness or lack of effectiveness.

Kisspeptin-10 is a synthetic peptide containing 10 amino acids that can be synthesized through a solid-phase peptide synthesis process. The water solubility of kisspeptin-10 is 2 mgs per mL. Regarding stability, it is reportedly stable

as a powder for up to one year when stored at minus 20 celsius; however, peptides such as kisspeptin-10 can be extremely sensitive to product formulation, process, and environmental conditions, which may lead to the aggregation and degradation of peptides. This could, for example, result in loss of their biological activity.

Potential impurities in kisspeptin-10 include peptide-related impurities, peptide synthesis process-related impurities, and starting materials. The solid-phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions.

These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Based on the COA provided in the revised nomination, the total impurities are not more than 2 percent, but there is no information on the nature and level of individual impurities in the

nomination. Information is lacking about the nature and control of individual peptide-related impurities.

In conclusion, kisspeptin-10 is not well characterized from the physical and chemical characterization perspective because certain critical characterization data such as likely impurities were neither found in the publicly available scientific literature, nor were provided in the COA. FDA is concerned about the potential for immunogenicity of kisspeptin-10 when formulated as injectable dosage forms for subQ and IM administration due to the longer amino acid chain and potential peptide-related impurities and aggregates.

We will now discuss safety information. This slide presents some of the nonclinical safety information we identified. In terms of acute toxicity, an in vitro study suggested that acute exposures of vein endothelial cells and arterial smooth muscle cells to high concentrations of kisspeptin-10 trigger the development of

atherosclerosis.

In a repeat-dose toxicity study, the IV no observed adverse effect level, or NOAEL, in dogs was 1 mg per kg after 14 days of daily treatment. In another repeat-dose toxicity study, kisspeptin-10 administered for 4 weeks by a constant subQ infusion accelerated the development of aortic atherosclerotic lesions and vascular inflammation in atherosclerosis-prone mice.

FDA did not identify nonclinical genotoxicity, developmental and reproductive toxicity, or carcinogenicity studies with kisspeptin-10. In conclusion, although the pro-atherosclerotic effects of kisspeptin-10 are concerning, their clinical relevance remains unclear. Importantly, nonclinical toxicity studies available at the time of this evaluation were too limited in scope and duration to inform the safety considerations for potential clinical uses of kisspeptin-10.

In terms of clinical safety, FDA's search of the FAERS database for reports of adverse events

for kisspeptin-10 retrieved one report from a 17-year-old male with hypogonadotropic hypogonadism who was treated with compounded kisspeptin-10. The subject gained weight and his estrone increased. Interpretation of this case is limited by an unclear temporal relationship and insufficient information.

As described earlier this afternoon, immunogenicity is a concern for peptide products. This immunogenetic response may be enhanced when peptides are given via the subQ route of administration. The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions.

Kisspeptin-10 may pose a significant risk for immunogenicity, potentially amplified by aggregation and peptide-related impurities. The nomination did not include and FDA is not aware of information about kisspeptin-10 to suggest that this substance does not present these risks.

We identified several small studies that

administered kisspeptin-10 to humans mostly via the IV route of administration. In addition, one study administered kisspeptin-10 as a single subQ bolus to 35 healthy adult women. No serious adverse events were reported in these studies; however, these studies were of short duration, had small sample sizes, and often did not include information on adverse events. No published clinical trials were found that assessed the safety of kisspeptin-10 when administered chronically or on a fixed schedule for over one day. Many studies administered only 1 or 2 bolus doses.

In conclusion, based on available data, there's a lack of information about whether kisspeptin-10 can be safely used in the intended population, the appropriate dose range, and frequency and duration of dosing for the proposed routes of administration. In addition, as a peptide with 10 amino acids that is administered through the subQ and IM route of administration may pose a significant risk for immunogenicity.

Here's what we found on historical use in

compounding. Kisspeptin-10 was first described in the 2004 article; however, there's insufficient information available to determine how long it's been used, specifically in pharmacy compounding. Based on published studies, kisspeptin-10 has been studied for its effects on gonadotropin-releasing hormone, or GnRH, and luteinizing hormone, or LH, in the reproductive system. Of note, it's unclear whether the kisspeptin-10 products were compounded in these studies.

As discussed in the safety section of this presentation, a FAERS case report described the use of a compounded injectable kisspeptin-10 product for the treatment of hypogonadotropic hypogonadism. Kisspeptin has been marketed online for a variety of uses. A Google search for kisspeptin generally identified websites of compounding pharmacies, med spas, and clinics in the United States that are compounding and/or marketing kisspeptin for a variety of uses. The most common uses on several clinics' websites are for weight loss and fertility. One website referred to kisspeptin-10

as an alternative to human chorionic gonadotropin, or HCG, which is not eligible for the 503A Bulks List.

Kisspeptin-10 has been compounded as an injectable product and as a troche. Kisspeptin-10 is not a component of an approved product in any country, nor is it found in the European or Japanese pharmacopeias.

Here, we present some information on the pharmacology of kisspeptin-10. Kisspeptin-10 is one of several endogenous isoforms of kisspeptin. Natural and synthetic forms of kisspeptin-10 bind to and activate the G-protein coupled receptor, GPR-54, also known as the kisspeptin receptor. It's shown here in this figure to the right and labeled KiSS1. GPR-54 activation in GnRH-expressing hypothalamic neurons increases the pituitary secretion of gonadotropins LH and FSH, which in turn can increase the secretion of sex hormones from the gonads.

Of note, the frequency of administration of kisspeptin-10 impacts the pharmacological outcome.

In nonclinical studies, tachyphylaxis has been observed. For example, a continuous IV infusion in male monkeys with a high dose of kisspeptin-10 triggers an acute stimulation of LH release followed by a rapid drop to baseline levels. Nonclinical pharmacological studies have provided evidence that tachyphylaxis can be avoided by intermittent administration of lower doses of kisspeptin-10.

Lastly, we would like to point out some information on GnRH, also shown in the figure to the right. GnRH is a key regulator of the hypothalamic pituitary gonadal axis, and its pulsatile secretion initiates puberty and maintains overall reproductive function. Abnormalities in GnRH frequency are associated with reproductive disorders. Tachyphylaxis induced by continuous administration of kisspeptin-10 disrupts this pulsatile release of GnRH. It's been proposed that agonist-induced GPR-54 desensitization may account for this tachyphylaxis.

In most studies published in the literature,

which will be discussed in the remainder of this presentation, kisspeptin-10 was delivered via the IV route of administration; however, we would like to remind you that kisspeptin-10 has been nominated to compound injectable formulations for the IM and subQ route of administration for the use in secondary hypogonadism.

Here, we present some information on the pharmacokinetics of kisspeptin-10. In rats that received an IV injection of kisspeptin-10, the half-life of the peptide was found to be extremely short. The nonclinical PK profile of kisspeptin-10 delivered via the subQ and IM routes are unknown at this time. In healthy men that received an IV infusion of kisspeptin-10, the half-life was about 3.8 minutes.

We identified one study that administered kisspeptin-10 via the subQ route of administration in healthy women. As may be expected, peak levels were lower after subQ administration at similar doses; however, authors did not report the absolute bioavailability of kisspeptin-10.

I'll now switch gears to provide a brief overview of hypogonadism. Hypogonadism is a clinical syndrome that results from failure of the testes to produce physiological concentrations of testosterone and/or a normal number of sperm due to pathology in the HPG axis. It is classified as primary or secondary. Secondary hypogonadism, which is what we'll focus on, is dysfunction arising from the level of the hypothalamus or pituitary. Men have low testosterone and low or inappropriately normal LH and FSH. It is also called hypogonadotropic hypogonadism.

There are several possible causes of secondary hypogonadism. Here, we describe idiopathic hypogonadotropic hypogonadism, or IHH, briefly, as this is the patient population that received kisspeptin-10 in studies. IHH results from the failure of normal episodic GnRH secretions leading to delayed puberty and infertility. IHH was previously thought to be a permanent condition, but it's now known that a subset of patients spontaneously recover function of the reproductive

axes. Reversal of IHH is not always long-lasting, and some patients experience a relapse to a state of GnRH deficiency.

Treatment of hypogonadism depends on the underlying etiology and a patient's goals for fertility. Products approved for the treatment of secondary hypogonadism include testosterone, HCG, and FSH. Because exogenous testosterone can impair spermatogenesis, it is not recommended in males interested in current or future fertility. In men with IHH, spermatogenesis can be initiated with exogenous gonadotropins.

Now, I'll present information on the effectiveness of kisspeptin-10 for secondary hypogonadism. We identified four published studies using kisspeptin-10 in subjects with IHH. Some of the studies included subjects who had IHH with reversal. In these exploratory studies, kisspeptin-10 was administered as an IV bolus or IV infusion. None of the studies administered kisspeptin-10 intermittently over a prolonged period.

Authors measured LH, FSH, testosterone, and estradiol concentrations after kisspeptin-10 administration. Importantly, study objectives were not to treat subjects with IHH, rather, investigators aimed to probe the kisspeptin GnRH pathway in this population. Results from these studies are mixed, but generally there was no LH response after exogenous kisspeptin-10 administration in non-reversed IHH subjects.

Here on this slide, we want to note that kisspeptin-10 was nominated for hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies, and we evaluated preservation of spermatogenesis with testosterone therapies in the context of the treatment of secondary hypogonadism in men.

We identified a single study that administered kisspeptin-10 as an IV bolus to 6 men with IHH on their prescribed clinical sex steroid treatment of exogenous testosterone. We touched on this study in the previous slide. In this study,

no participant responded to kisspeptin-10 with an LH response, and sperm concentrations or pregnancies were not measured as an endpoint in the small study.

In addition to the four studies discussed in the previous two slides, we identified one additional proof-of-concept study using kisspeptin-10 in 5 men with type 2 diabetes and low testosterone levels and seven age-matched healthy men. It is unclear if men in this study had a diagnosis of hypogonadism because according to authors, subjects had no symptoms at recruitment.

Subjects received kisspeptin-10 as a single IV bolus injection or a single IV infusion. In the IV bolus study, subjects received GnRH at their first visit and kisspeptin-10 at the second visit. Testosterone was not measured because according to authors, transient rises in LH response to acute kisspeptin administration are not associated with sustained increases in testosterone. LH concentrations increased following kisspeptin-10 administration with a similar change in LH in both

men with type 2 diabetes and healthy men. Following GnRH administration, LH also increased in both groups with a greater LH stimulation compared to kisspeptin-10. After an IV infusion of kisspeptin-10 for 11 hours, mean LH, LH pulse frequency, and total testosterone increased.

Of note, while a single IV infusion of kisspeptin-10 could increase testosterone concentrations in this study, it's unclear if kisspeptin-10 administration could maintain testosterone release for longer periods of time.

In conclusion, there is insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism. Based on the studies we identified, it's not possible to draw any meaningful conclusions on effectiveness due to the small number of subjects included, the exploratory nature of the studies, and the dosing of kisspeptin-10 used in the studies.

We are not aware of studies that administered kisspeptin-10 via the proposed routes

of administration in men with hypogonadism. In addition, it's unclear if chronic IV administration of kisspeptin-10 would confer any clinical benefit in this patient population. At the time of this evaluation, there are several FDA-approved treatments that are indicated to treat secondary hypogonadism in men.

On balance, the physiochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for kisspeptin-10 weigh against inclusion of the substance on the 503A Bulks List. In particular, FDA's proposal regarding this substance is based on the fact that it's not well characterized from a physiochemical perspective. There's a lack of information about whether kisspeptin-10 can be safely used in the intended population and on immunogenicity risks. There's insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism, and there are FDA-approved products that are indicated

to treat secondary hypogonadism, a potentially serious condition. After considering the information currently available, a balancing of the criteria weighs against kisspeptin-10 being added to the 503A Bulks List. Thank you. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the presenter. When acknowledged, please remember to state your name for the record before you speak and direct your question to the presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenter? Yes?

DR. STAAS: Hi. Donnette Staas, Jazz

Pharmaceuticals. I did have a question for the FDA regarding the nonclinical safety package for this particular molecule. I noticed that for this one, unlike some of the others, you do have a little bit more information on the acute toxicity and repeat-dose toxicity. So I was just wondering, or just wanted to clarify, if perhaps what's still missing, then, is the immunogenicity assessment perhaps, and is there other nonclinical data that you would have liked to see?

I noticed that you didn't have any reproductive toxins. I was wondering whether, for example, just an evaluation based on structural alerts would have been enough for that. I'm just trying to get a sense for what the complete package would look like for a molecule like this. Thank you.

DR. HANKLA: Elizabeth Hankla, FDA. I want to refer this question to our nonclinical colleague.

DR. GULUR: Could you hold on until they turn the mic on for you?

DR. ALBUQUERQUE: Thank you so much for the question. Edna Albuquerque, nonclinical reviewer supporting PCRT. We did review the data that are available in the literature. Yes, we have a little bit more. In terms of acute toxicity, all that we have, really, is an in vitro study where the authors report destroyed atherosclerotic type effects in cell cultures. So we don't really have much in terms of in vivo acute toxicity.

For the repeat-dose toxicity studies, which would be very relevant to understand the safety of this substance on long-term treatment, I would like to point out that in that particular study, although we do have a NOAEL, which is the dose that we would take as a benchmark to understand safety margins, in that study, the treatment lasted only 14 days. So for long-term treatment, we really have no data to support safety in the long run.

We're also missing gene tox, missing carcinogenicity studies. We have no repro or developmental studies. So in terms of the battery of studies that we would normally consider in an

evaluation of safety, for understanding safety margins for proposed clinical doses, what we have is still very minimal. So I hope that helps.

DR. STAAS: That is very helpful. Thank you, and that's what I suspected your answer would be. I just wanted to confirm.

DR. ALBUQUERQUE: Thank you so much.

DR. STAAS: Thank you.

I did have one other question, if I may --

DR. GULUR: You can follow up, yes.

DR. STAAS: -- related to the the typical rises that you would see in testosterone on administration of GnRH. You mentioned in that last study, on slide 86, that the LH stimulation was greater with GnRH. I just wondered if you could give a measure of what the testosterone increases would look like for GnRH versus kisspeptin. Thank you.

DR. GULUR: Give us a minute while we pull up slide 86.

DR. HANKLA: Elizabeth Hankla. Yes. Can you pull up slide 86, please? So in this study,

kisspeptin-10 was given as an IV infusion for 11 hours in 4 subjects, and the testosterone levels are indicated here. They went from an average of about 245 nanograms per deciliter to 328 nanograms per deciliter. I might have to defer to my DUOG colleagues, if they have any information about after stimulation with GnRH, what testosterone levels would be. I know in terms of LH secretion, it's more robust for GnRH. I just don't have particular numbers right now; and if not, we might have to get back to you.

DR. GULUR: Go ahead.

DR. GASSMAN: Hi. I'm Audrey Gassman. I'm the Deputy Director for the Division of Urology, Obstetrics, and Gynecology. It's an interesting question as to whether this is different than GnRH agonist, but it's very difficult to tell because you can't do cross-study comparison because the assessment of testosterone varies so much from study to study.

So although this is some preliminary data, I think we'd need more to really see whether this

provides a different response or not. These are very initial investigative studies in a few patients, so I don't know that we could give you and say that kisspeptin was 10 percent more, or 20 percent more, or 20 percent less; so apologies.

DR. STAAS: Understood. Thank you very much. I have no other questions. Thank you.

DR. GULUR: Any other clarifying questions from panel members? Yes?

DR. WEISS: Rita Weiss. On slide number 77 -- tell me when you've got it -- you had mentioned the fact that there was a website that referred to kisspeptin-10 as an alternative to HCG, and then you made the comment that HCG is, obviously, an active ingredient of an FDA-approved drug, but it is not allowed to be compounded.

Would you please expand on that?

MS. BORMEL: Gail Bormel, FDA. HCG has been deemed to be a biologic, and that was on our 2020 list. It was converted from an NDA to a BLA, and biologics are not eligible from the enforcement discretions under 503A. So they can no longer be

compounded in accordance with 503A and be eligible for the exemptions. We have a website on that, and it might be a little bit easier, but generally, the thing to remember is that biologics are not eligible for compounding under the law.

DR. WEISS: Then by way of example, something like insulin.

MS. BORMEL: I believe, yes.

DR. GULUR: Alright. Any other questions?

(No response.)

DR. GULUR: Virtual?

(No response.)

Open Public Hearing

DR. GULUR: We will now begin the open public hearing session.

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 open 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 the 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 this 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 in 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 for 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.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing for the record. You have 15 minutes.

DR. ROSEBUSH: Sure. If we can start with slide 19, please. For the record, my name is Lee Rosebush. I'm a pharmacist and an attorney, specifically a Doctor of Pharmacy and registered pharmacist here, and represent a coalition of pharmacies who compound this product, including FarmaKeio. If we can start on slide 19.

While they're looking up the exact slide so we can get that from that perspective, the reason why I'm going to raise this is there's going to be a study that specifically talks -- and it was published in JAMA articles that talks about the use of this product in female reproductive and sexual health. Notice you did not hear anything in the last presentation about reproductive and sexual health.

As has been mentioned, now, three and four times, specifically, the last nominations have been withdrawn. We've provided additional information to the agency prior to this in written material, and including in this slide, that included additional uses of this product that aren't even being considered today in this situation, in JAMA articles, if we can find this slide, slide 18. Sorry. It specifically talks about the use in reproductive and female health.

As we've talked about before and as I've mentioned previously, my understanding from the administration in this perspective is that it will

specifically not get between a woman and her reproductive health, specifically sexual and reproductive health, and obviously there's a caveat for that now when it comes to compounded-based products. We'll get to it very quickly. I'm not sure what the issue is with finding that slide, but if we can start back at slide 2, I'll go quickly so we can make sure we hit that slide.

Secondly, from that perspective, on the last go-round, there were several specific questions, and I would like to answer those specifically very quickly. Again, these apply to all four substances, so this wouldn't apply just to the last substance, but it would apply to this one as well.

The FDA, again, is misleading you. Several of you asked why are we doing this and why are we doing this now? Let's be blunt. There was a lawsuit. Specifically, FDA is being sued over this topic. I cannot discuss the settlement discussions, but that settlement is publicly available on the court documents, and it specifically will give you the reasons for your

questions being asked.

Two from that perspective, there were many questions about why aren't the compounding pharmacies providing additional information associated with this. It's important to remember, compounding pharmacies aren't the ones who provide diagnoses and dispenses for particular reasons. Healthcare providers and practicing physicians are the ones who do that. We receive your prescriptions, take those prescriptions in, and dispense medications for the reasons that you've decided and described.

Third from that perspective, there's been a lot of talk in those discussions specifically about the length of time and the usage of these materials. These are compounded medications. These compounded medications typically last less than 30 days. It's pretty hard, from that perspective, if your treatment regimen is less than 30 days, from that perspective, to be able to address that.

Fourth and finally, as we get to the female

reproductive study, again, we'll raise this issue. My understanding of the reason for the PCAC discussion was for you to make a decision, not for the FDA; and what we heard earlier when I raised this issue is that you weren't provided, as a PCAC member, with all of our materials; that they decided, in that perspective, it wouldn't change their mind. That doesn't give them the right not to provide you those materials. Again, it goes to the arbitrary, and capriciousness, and the misleading of this nature, to be able to show that PCAC wasn't provided with all of our written materials.

Coming back to this regulation in this perspective, it's also important to show that the statute here that we are talking about simply requires the FDA to maintain a list of drugs that are not components of FDA-approved drugs or subject to a USP monograph. It doesn't require a nomination for the discussion of these materials, and that's why they're moving forward today and why these nominations have been withdrawn; again,

misleading answers to you all from that perspective, and I think you should know the true answers from that.

As we've also discussed with 21 CFR 216.23, specifically, if you look at the answer for B Part D for that regulation, it discusses specifically the lack of information associated with those molecules that can be compounded underneath the 503A Bulks List. That same exact standard, in that perspective, applies to these, as you hear, and lack materials, again, showing the arbitrary and capricious nature of these materials not being provided.

The last question that was asked, how many substances have actually been approved by PCAC in this period of time? Does anybody actually know? PCAC's been around, and the nomination process has been around for 10 years. There's not one injectable medication that's ever been approved here. There's also never been one oral medication that's ever been approved on this list. You don't believe me, just go to 21 CFR 216.23. It'll tell

you the 6 substances that have been approved in 10 years. All five of them are topicals, one being Brilliant Blue for ophthalmology-based use.

There was a question of could we just simply go through this process again? They could have. They simply could have just came to us and asked us for more information; hence, why the lawsuit continues on to this day. That request never occurred to us.

Now, if we can go back to our slides? From slide 2, as we've talked about previously, these are the four factors. Is the substance well characterized physically and chemically? As we've mentioned on multiple occasions, FDA's own GSRS and NIH's own PubChem specifically provide this material here.

In addition, we have provided COAs that have not been provided to you. They were not the COAs that were provided in this perspective and discussed in this presentation that show that endotoxin testing, purity testing, et cetera, can be done and are being done based on ICH guidelines;

2) historically -- we've talked about this multiple times -- this substance, in this situation, has been dispensed in over 71,000 prescriptions for kisspeptin-10; 3) kisspeptin-10 has been used over 71,000 times for issues, including female reproductive sexual health, which would now be denied and removed; and 4) our real-world evidence, regardless of what's being said, and retrospective analysis found that in over 71,000 prescriptions no adverse events were reported.

Yes, there are multiple states that an adverse event requires that to be reported to the agency. In addition, why it may not be required, my understanding is that NABP and FDA have regular communications on these types of materials.

The issues raised by FDA, as we've said on multiple occasions, relate to the API itself, not the compounding concerns. And again, these could be addressed via guidance documents simply on how the API manufacturers test for potency, purity, et cetera, for COAs. As was mentioned earlier, 503As don't have to go through CGMP. That is a

true statement. API manufacturers, though, could be subject to an FDA guidance document that could require them to do this type of testing before they could sell the product. That is also a true statement and could be done.

As previously mentioned, here is the PubChem and the GSRS listing. Here is the ICH guidance -- again, as we've mentioned previously -- that could be done to ensure impurity testing, potency testing, et cetera. For the actual physical and chemical characteristics, as we've said before, this peptide can be, based on the studies that we have provided, and have shown to be taken orally.

In addition, spectromic techniques are commonly available in most chemistry and biochemistry research labs, and together they are a powerful approach for initial, as well as routine, evaluation of protein and peptide self-analysis. We've provided the link there specifically to the study.

Has this substance been used historically in

compounding? As we've talked to multiple times now, in real-world evidence, this slide, again from this side of it, is showing that FDA has accepted as little as 14 patients, yet we have over 71,000 prescriptions this time. Last time, it was over 600,000 prescriptions, from the side of it, again, to show real-world evidence associated with us. Yes, we looked at patient medical records; yes, from that perspective, pharmacy history records were looked at; yes, in that perspective, each of these were requested by a physician via prescription.

We are unaware of any serious, let alone unexpected, adverse events directly attributed to the drug products compounded from kisspeptin-10. This includes real-world evidence from pharmacies who have dispensed over 71,000 prescriptions involving kisspeptin-10. FDA has included in these materials FDA's own review of FAERS and CAERS system, and you saw very little, from that perspective, as to what they actually were reviewing.

Here is real-world prescription data from that perspective, again, involving kisspeptin-10 itself, orally and injectable. And I would point out, if historical data, for example, is not supposed to be used as real-world evidence, then why in the world does FDA include that as one of the four factors for reviewing this analysis? That is an explicit requirement under FDA's own regulation to look at historical compounding, and with that, I'll turn it over to Jim.

MR. LaVALLE: Jim LaValle, pharmacist, Chair of the International Peptide Society, and I've had the pleasure to write a couple of databases with the APhA and Lexicomp. And now knowing the extent of the information that's needed, we have 100 monographs written on small molecules, as well as peptides, with level of evidence that's reported on various peptides, which I'm going to be very happy to share since we spent a lot of time writing those.

This was effects of kisspeptin on sexual brain processing and penile tumescence in men with

hypoactive sexual disorder, and that was the first clinical evidence that showed kisspeptin in men with low sexual desire. So it's one thing to raise testosterone in a hypogonadal male or a eugonadal male, but the other side to kisspeptin is that there are a couple level 3 studies, and there's at least a randomized-controlled trial, that shows evidence that there is an improvement in sexual desire and penile response, so up to 56 percent more than placebo, and associated behavioral measures of sexual desire and arousal also were improved.

There are concerns for safety and substance on the compound. A 2021 study was obviously a canine study, but it was looking for toxicity post-administration after a 14-day washout, and no overt signs of drug-related toxicity on clinical signs; body weight; food consumption; clinical pathology; histopathology; urinalysis; ECG; or respiratory rate; obviously, just a first study to to validate that. A 2023 study, once again, no adverse events or side effects reported. This is

in reference to other side effects. In addition, it had no significant clinical effects on blood pressure or heart rate.

This was in women with hypoactive sexual desire disorder. I know that it wasn't listed in the nomination. I would say, from the clinicians, as I had mentioned in a previous talk, we have hundreds of clinicians and physicians that are trained under continuing medical education credit and certification. Most of them are applying this for women who've failed other options for pregnancy, including IVF, and in addition to that, dysmenorrhea.

DR. ROSEBUSH: And if I can, this is the study that I was referencing a minute ago related to sexual and female reproductive health.

MR. LaVALLE: And no reported adverse events. I did pull up a couple of both level 3 and level 4 evidences based off our monographs that we've written that I just want to include: modulation of human resting; brain connectivity by kisspeptin; and enhancing sexual and emotional

function. This was a 2020 study, where it showed that kisspeptin modulates resting brain connectivity and enhances sexual or emotional processing. So it may not have a direct hormonal effect and may have a more emotional well-being effect. I think that's what we're missing on it for men.

Once again, now I know for the IPS, we're going to be calling out to our physicians to provide the information that will show the level of adverse events or side effects that occur from their prescribing. We do also have within our monographs the recommended dosing based on the level of evidence cross-referenced from that, so that should also be helpful in the future.

Once again, 2023, found no additional adverse events reported. I know there was one report on a 17-year-old hypogonadal male. Once again, conclusion, like all drug substances, any testing recommended by the agency can be performed; and, yes, literature supporting historical use is present. Are there concerns about whether the

substance is effective for a particular use? No literature supporting effectiveness in RWEs; then once again, concerns for safety, a few human studies that were published have not shown a concern for human safety. Thank you.

DR. GULUR: Thank you.

I would have some questions for the speakers. You've mentioned the 9 pharmacies multiple times, and in this recent slide, one pharmacy was significantly prescribing this compared to the others, pharmacy number 7. Would you be able to tell us, where are these pharmacies? Which states are they in? And are they required by state law in their states to report adverse events, and to whom, the state or the FDA?

DR. ROSEBUSH: There are multiple states, from that perspective, that are included with these pharmacies, and includes one of those pharmacies located in California. As NABP and member of the PCAC mentioned earlier, there is a requirement to report those, and those materials are adverse events reported to the state, which is also

reported on to FDA as well. In addition, there's a separate database for California, where you can go and actually review this material.

DR. GULUR: All pharmacies are in California? You mentioned multiple states.

DR. ROSEBUSH: No, there are a couple of pharmacies. FarmaKeio, which is actually named in the litigation associated with this, is in Texas. But I can tell you, from that perspective, and as was mentioned earlier, even if they're not required to, FarmaKeio takes it upon itself to report these materials. So even if we're not legally required to, it isn't necessarily the standard, that doesn't mean, in this perspective, that they just chose not to provide that material.

DR. GULUR: Could you comment on why one pharmacy in particular has a much higher rate? Are you confirming that that pharmacy is in a state where they're required to report?

DR. ROSEBUSH: I would have to take a look specifically at that pharmacy to see which one was number 7, so I apologize for that. I can tell you

at least one of the pharmacies that was not a zero is in California; so yes, they would be required to report from that side of it. My understanding is there is one pharmacy that specializes more in female reproductive health, particularly for the trans community. This is used, from that perspective, when somebody is transitioning, particularly to increase sexual desire. So yes, this is used for that particular reason and potentially could be taken away from them.

DR. GULUR: My second clarifying question, regarding the APIs that you mentioned, where are these APIs being sourced from; from the United States, outside the country?

DR. ROSEBUSH: Unfortunately, this is part of the problem in the United States, is that 90-plus percent, both FDA-approved manufacturers -- and you can ask the two industry members here as well -- most of their APIs are going to come from outside of the United States as well. Now, when it is brought into the United States, it is brought in through an importer, from

that perspective, and testing is done here in the United States. So yes, it would go through the same processes and channels, from that perspective, that any API distributor would typically go through.

Those API suppliers would be required, as they're producing chemical, to go through CGMP. So from the situation, we as 503As, as pharmacies, aren't required to meet CGMP. The FDA is correct on that process. But from that perspective, that does not mean that the FDA does not have the authority to require API manufacturers who are producing these chemicals to meet certain CGMP standards.

If they wanted to, for example, require that they met chiral testing for one of the earlier molecules, or for this one -- for immunogenicity testing, from that perspective, or whatever, if we would like to go down for purity or endotoxin -- we can follow the ICH guidelines that was provided there and require our API suppliers to meet those.

So yes, I think it's a misnomer and

misleading to be able to say we're not subject to CGMP, and therefore, our API is more dangerous. It's a simple requirement. If it's APIs that concern a question, why are we being told no? Why aren't the API suppliers saying bring up your guidance to meet these certain standards; or why not put a guidance in place to say we as 503As should require our API suppliers to meet certain testing and be on our COAs?

To meet that, our COAs that we provided show -- even though, from that perspective, there have been questions on what those COAs require for 503As -- that they meet endotoxin testing, that they meet purity testing, et cetera.

DR. GULUR: So just to clarify, you're stating that all API, I guess, brokers, or whoever the companies are that are importing it in the United States, have a standard testing for all these products and report them?

DR. ROSEBUSH: I can't speak for everybody, but I can speak for those, from that perspective, that our suppliers are buying from and requiring it

to ensure. There are bad actors everywhere. We can go down how many lists of pharmas who've had recalls. We can talk about all the recalls and 483's that have happened to pharma. So just because somebody's required doesn't mean that they are abiding by. So I can't sit here and swear that every single person who's ever supplied API meets these standards.

DR. GULUR: And to clarify, once the API is acquired by the compounding pharmacies, they are not required to then subsequently test, even after processing?

DR. ROSEBUSH: That would depend on the pharmacy, their testing, the licenses, if they have certain NABP accreditations, from that perspective, especially pharmacy accreditations, testing. There are a lot of contractual requirements that go into that. So again, if it is something that the agency is concerned about -- because I don't want to belittle to say that there isn't an immunogenicity concern across injectable products. I'm a pharmacist first, but if that is the case, simply

tell us the testing that needs to be done. That should be done via an API guidance to say if you're going to be doing this, do this testing.

DR. GULUR: What would you say is the difference between CGMP practice and compounding practice in the pharmacies, and are you suggesting that it should be the same?

DR. ROSEBUSH: So I serve, personally -- even though I'm not here today -- as the chair of the 503B trade association. That's how most people know me. I'm not here to say that 503A and 503B are the same. I'm not saying that. And FDA will tell you this; I normally don't come to 503A hearings. And honestly, for the record -- and I know this is being recorded -- I don't like throwing fire bombs at the agency. A lot of these folks are my friends. I don't want to be here doing this, from this perspective. But I'm also the type of person, and most of these people will tell you, that I am true to my meaning, and when something's not right, I'm going to stand up for it.

In this situation, taking away the right to compound a product, simply because you're concerned about the API source associated with that, is wrong. If the true concern is about API sourcing, and immunogenicity, and the issues with these peptides, then from that perspective, put in place the guidance documents that put those API requirements, and say, in order to do this 503A, or in order to supply these API manufacturers, have those guidance documents there; but otherwise, we're arbitrarily and capriciously picking when this happens and when it doesn't.

I have an active lawsuit as the lawyer against the FDA on this exact topic. That's why we're here. I can't go into any more than that because, obviously, there are confidentiality rules. I would just say read the settlement agreement associated with that.

That's why we're here because of arbitrary and capricious nature. That's why I've thrown so many fire bombs today to say you weren't provided with the information that you should have been

provided. This isn't supposed to be FDA making a decision; this is supposed to be PCAC making a decision. And right now, from what you've told me, many of you in your answers over this response is that you haven't been provided with all the information that I've provided you, so how is that truly a full and right decision? And that's not a blame on you. It's not a hit on you at all. You can only make a decision with the information that's been provided to you.

DR. GULUR: Thank you.

DR. HANKLA: Hi. Elizabeth Hankla, FDA. I just wanted to point out two of the studies that were cited in the OPH, one in men and one in women with hypoactive sexual desire disorder, were done with kisspeptin-54, another isoform of kisspeptin-10.

DR. GULUR: Thank you for that clarification.

The open public hearing portion of this meeting -- sorry.

Yes?

MS. BORMEL: Gail Bormel, FDA. I have to clarify something that Lee Rosebush has said repeatedly, which is that we did not give the information that BakerHostetler submitted to the agency, when in fact we did provide the information that BakerHostetler sent on October 15th to the PCAC, so you should have received that.

DR. GULUR: Thank you.

Yes?

DR. WEISS: Rita Weiss, NABP. I just want to clarify something that was said. NABP accreditation does not require API testing.

Clarifying Questions from the Committee (con't)

DR. GULUR: I'm just going to close the open public hearing before we continue the discussion, if that's ok.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We definitely have the time for more clarifying questions.

DR. GANLEY: Yes. This is Charlie Ganley. I just wanted to make a comment regarding the

real-world evidence issue. Real-world evidence is the clinical evidence of the usage and potential benefits and risks of a medical product derived from an analysis of real-world world data. Various sources of real-world data can be analyzed in non-interventional studies, including registries, electronic health records, and medical claims.

The information provided in the presentation are simply numbers of prescriptions filled by unidentified pharmacies over an unknown period of time. It does not identify the use, dose, route of administration, and duration of use. It does not provide any data related to the safety, and most importantly, effectiveness of the drug. Thank you.

DR. GULUR: Any other comments?

DR. DEVEAU: Ian Deveau, Deputy Director of OCQC. The references to the ICH guidance, I would like to point out at this meeting that those refer to application products, and they are outside the scope of compounded products. They're specifically intended for those seeking approvals from regulatory authorities, including the FDA.

DR. GULUR: Any other questions from the panel members? Virtual?

DR. GULUR: Yes. Absolutely

DR. BOGNER: Robin Bogner. I have a comment. I read USP and go by it quite extensively. In 797 USP, general chapter 797, Section 9.3.1 on component selection, one of the criteria is that you must have a COA that includes specification and test results for the component that show the API meets expected quality.

When I've presented at state meetings in Connecticut, and I've looked at a number of C of As, I don't feel comfortable with them, and a lot of the pharmacists, they were not all compounders by any means and didn't know how to read them. So I would say it's not just ok to have a C of A that says 98 percent pure, but you have to look at the whole thing and feel comfortable with the incoming material. And I'm not sure that a lot of people know how to read them, know how to discriminate between a good test and just a platform test, and know how to feel comfortable

that the incoming API is really of good quality.

DR. GULUR: I'd like to agree with you on that in the sense that we do see a lot of variability, even in the sample of COAs that we saw today. In terms of the information, the testing that is done, is there guidance on this that these groups must follow, or is it left to their discretion?

MS. BORMEL: Gail Bormel, FDA. We do not have guidance on the COAs and what they have to follow.

DR. DEVEAU: There are references in the ICH guidances that give a general statement on what should be there, but it's pretty general; and again, it's intended for products going through approvals, and compounded products are exempt from going through approvals.

DR. GULUR: Yes?

DR. BOGNER: Robin Bogner. I'd like to follow up. I think there's another general chapter -- you should be able to help me with this -- that talks about testing that should be

done for peptides, and it's rather extensive. I just don't see that in the C of As that I see on peptides.

DR. GULUR: Go ahead.

DR. SERUMAGA: Yes. Brian Serumaga, USP. In addition to the comment that Robin just made, in the section of 797 that you referenced, it actually does go on to say that in the U.S., if a compounder is sourcing API, it must be from an FDA registered facility for the API.

DR. GULUR: Could you clarify on the FDA registered facility? Is that the importer or where the API is being manufactured?

DR. SERUMAGA: It doesn't specify, but it does say that if that product is being used in the U.S., it must be from an FDA registered facility. So if it is gotten from a third-party supplier, or whoever that is, they must ensure that they're getting it from an FDA registered facility.

DR. GULUR: Would the FDA be able to shed some light, considering that 90 percent of APIs are procured from external to the United States? What

is that process?

MS. BORMEL: Sure. Gail Bormel, FDA. Even in the law, it does say that the API, the bulk drug substance must be from an FDA registered facility, but there is no clarification on which facility has to be registered. So it may be that the repackager that you obtain it from, who imported it from another manufacturer, that repackager is the one that's registered. But registration in and of itself is not the same as testing or anything along those. It just means that you've registered your facility, and the FDA will come and inspect.

Does that answer your question?

DR. GULUR: Well, it raises another one, if I may. If it's the packager that is the registered facility -- it sounds like there's ambiguity enough that it could very well be a packager -- how does the FDA investigate? I mean, it sounds like the packager can just do a COA testing of what they've obtained, but not necessarily process, and it sounds like there's variability in what they test.

MS. BORMEL: Gail Bormel, FDA. Yes, the

packager could do its own COA and test it, and put it on.

DR. GULUR: I'm sorry?

MS. BORMEL: And use that COA to accompany the bulk substance.

DR. GULUR: So it sounds like they could also use the COA provided by the source, the foreign source?

DR. DEVEAU: I don't know if I'm answering the question, but I will just highlight this. The repackager needs to demonstrate that the repackaging operation does not reduce the quality of the API received wherever. So there is a requirement that they've demonstrated that the repackaging operation, that the quality is transferred to the repackage process. If they get a certificate of analysis from the manufacturer, they have to demonstrate at the end that it meets the same standard.

DR. GULUR: Which means they do have to test.

DR. DEVEAU: They can add additional tests

if they wish.

DR. GULUR: I'm sorry. Could you clarify that? Do they have to test again, or no? Do they have to test it again or just affirm?

DR. DEVEAU: They have to affirm. They have to validate that their process gives the same results; that there is not a reduced quality.

DR. GULUR: Are these COAs in English?

DR. DEVEAU: Not always, not always from the original supplier.

DR. GULUR: Yes, it's an interesting process.

Go ahead.

DR. BOGNER: Thank you. Robin Bogner, one follow-up comment. I was looking at a completely different peptide last month, and went looking for a supplier, and went into the list, and I found an interesting disclaimer that says FDA registration of a facility does not guarantee quality of the drug substance, and that should be noted. Thank you.

DR. GULUR: Any other questions from the

panel?

(No response.)

DR. GULUR: Virtual?

(No response.)

Committee Discussion and Vote

DR. GULUR: Thank you all for a robust discussion. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will now proceed to our fourth question, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and

will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

For question 4, FDA is proposing that kisspeptin-10 not be included on the 503A Bulks List. Should kisspeptin-10 be placed on the list? Again, if you vote yes, it is your recommendation that it be placed on the list. If you vote no, it is your recommendation that it not be placed on the

list.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, we have zero yeses, 11 noes, and zero abstentions. Thank you.

DR. GULUR: Now that the vote is complete, we will go around the table, as we have done before, and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

It would be with you, yes.

DR. DMOCHOWSKI: Roger Dmochowski. I voted no because I don't feel this compound met the criteria as specified.

DR. ALUKAL: Joseph Alukal. I voted no.

DR. WEISS: Rita Weiss. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. DURHAM: Todd Durham. I voted no.

DR. GULUR: Dr. Desai, online?

(No response.)

DR. GULUR: Dr. Desai, online?

(No response.)

DR. GULUR: Dr. Rebello, online?

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. STEVENSON: Takyiah Stevenson, DFO.

Dr. Desai, I do see that you are on mute online. If you could please unmute and state your name and your vote into the record.

DR. DESAI: Are you able to hear me,

Dr. Gulur?

DR. GULUR: Yes, we are, Dr. Desai. Please go ahead.

DR. DESAI: Thanks. Sorry, technical difficulties. I also voted no for the reasons previously stated.

DR. GULUR: Thank you. Considering the length of this meeting, one technical difficulty we can deal with. Thank you.

(Laughter.)

DR. GULUR: So as we can see, the committee has unanimously voted against adding this to the list, and the reasons so far stated have been a lack of convincing safety and efficacy data.

Adjournment

DR. GULUR: With that, we will end the kisspeptin-10 topic. Thank you, everyone. We will now take a quick 10-minute break. We will reconvene at 3:25 Eastern Time for the hydroxyprogesterone caproate topic.

Panel members, please remember that there should be no discussion of the meeting topic during

the break amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 3:13 p.m., the topic 4 session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Topic 5

Hydroxyprogesterone Caproate

Tuesday, October 29, 2024

3:25 p.m. to 4:05 p.m.

Meeting Roster

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Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Voting)

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Professor

University of Connecticut

School of Pharmacy

Department of Pharmaceutical Sciences

Storrs, Connecticut

Seemal R. Desai, MD, FAAD

(via video conferencing platform)

Founder and Medical Director

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Donnette D. Staas, PhD

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(Acting Consumer Representative)

Senior Vice President

Clinical and Outcomes Research

Foundation Fighting Blindness

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Rita Weiss, PharmD, JD

(Acting National Association of Boards of Pharmacy Representative)

Clinical Pharmacist/Compliance

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C O N T E N T S

P R O C E E D I N G S

(3:25 p.m.)

Call to Order

Introduction of Committee

DR. GULUR: Welcome back, everyone. We will now have Dr. Stevenson read the Conflict of interest statement for this meeting's Withdrawn or Removed List topic.

Conflict of Interest Statement

DR. STEVENSON: Good afternoon.

The Food and Drug Administration, FDA, is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the National Association of Boards of Pharmacy, NABP, the United States Pharmacopeia, USP, and the industry representatives, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

During this session, the committee will discuss a revision FDA's considering to the Withdrawn or Removed List. Specifically, the FDA is considering whether to amend 216.24 to add an entry to the list, hydroxyprogesterone caproate: all products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous birth.

As previously explained in the Federal Register of July 2, 2014, 79 FR 37687 at 37689 through 37690, the list entry may specify that a drug may not be compounded in any form.

Alternatively, the list entry may expressly exclude a particular formulation, indication, dosage form, or route of administration from an entry on a list, or a drug may be listed only with regard to certain formulations, indications, routes of administration, or dosage forms. FDA plans to seek the committee's advice concerning the inclusion of this entry on a list. This is a particular matters meeting during which specific matters related to hydroxyprogesterone caproate will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Padma Gulur and Dr. Kathleen Gura.

Dr. Gulur's waiver involves stock holdings in a competing/affected entity. The aggregate value of the stock is between $25,000 and $50,000. Dr. Gura's waiver involves stock holdings of a competing/affected entity. The aggregate value of the stock is between $25,000 and $50,000.

Dr. Gura's waiver also involves stock holdings in two competing firms. The aggregate value of each of the two stocks is between $0 and $10,000.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website on the advisory committee meeting webpage, which can be found at www.fda.gov and by searching for October 29, 2024 PCAC. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

We would like to note that Dr. Rita Weiss is a representative member from the National Association of Boards of Pharmacy, NABP, and

Dr. Brian Serumaga is a representative member from the United States Pharmacopeia, USP. Section 102 of the Drug Quality and Security Act amended the Federal Food, Drug, and Cosmetic Act with respect to the Advisory Committee on Compounding to include representatives from the NABP and the USP. Their role is to provide the committee with the points of view of the NABP and the USP.

Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue; instead, they serve as the voice of the NABP and USP, entities with a financial or other stake in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Thomas Lupton and Dr. Donnette Staas are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any

particular company. Dr. Lupton is employed by On Demand Pharmaceuticals and Dr. Staas is employed by Jazz Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other bulk drug substances or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the topics at issue.

Thank you. I'll hand it back to the chair.

DR. GULUR: Thank you.

We will now proceed with the FDA presentation on the Withdrawn or Removed List process from Gabrielle Cosel.

FDA Presentation - Gabrielle Cosel

MS. COSEL: Thank you very much. My name is Gabrielle Cosel. Again, I'm the Director of the

Division of Compounding Policy and Outreach in OCQC, and I'll be providing a brief overview of our process for identifying drugs on the Withdrawn or Removed List.

One of the conditions that must be satisfied for a drug to qualify for the exemptions under Sections 503A and 503B of the Food, Drug, and Cosmetic Act is that the compounder does not compound a drug that appears on a list of products that have been withdrawn or removed from the market because they've been found to be unsafe or not effective, and we call this the Withdrawn or Removed List. A drug product that is included in the Withdrawn or Removed List is not eligible for the exemptions provided in Sections 503A or 503B. FDA's reviewed and added 85 bulk drug substances to the Withdrawn or Removed List to date.

So how do we do this? Well, we periodically review available information on drugs that were withdrawn or removed from the market because they've been found to be unsafe or not effective to identify new entries for the list, and the

information we review could include Federal Register notices announcing withdrawal of approval of an NDA or ANDA for safety or effectiveness reasons, or notices announcing an agency determination that a drug product that was voluntarily withdrawn from sale was in fact withdrawn for reasons of safety or effectiveness.

We also look at available information to determine whether any new approvals would warrant modifications to existing entries on the list. We work closely with review divisions within the Office of New Drugs to evaluate each identified candidate or a potentially proposed modification to the list, and the review divisions will prepare a review of the information to document its recommendation about whether to include the drug on the list or remove it, or modify an entry.

We use notice and comment rulemaking to update the list. We intend to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed, or if we tentatively determine that changes to the status of

drugs already on the list should result in revision to the listing. And generally, we will finalize any additions or modifications to the list after consulting the advisory committee about the drug and after providing an opportunity for public comments to be submitted on a proposed rule.

So today, as you've heard, we are considering the following entry for the list, hydroxyprogesterone caproate: all drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous birth, and now we will hear more about this particular entry. Thank you very much.

DR. GULUR: We will now proceed with the FDA presentation on hydroxyprogesterone caproate from Dr. Emily Kneeream.

FDA Topic 5 Presentation

Emily Kneeream

DR. KNEEREAM: Good afternoon. My name is Emily Kneeream. I'm a clinical analyst in the Pharmacy Compounding Review Team in the Office of

New Drugs. I will discuss hydroxyprogesterone caproate for inclusion on the Withdrawn or Removed List. I would like to recognize the entire evaluation team, as well as the contributions of many other FDA colleagues who helped with this evaluation. Special thanks to the Division of Urology, Obstetrics, and Gynecology in OND.

Under Sections 503A and 503B of the FD&C Act, FDA is to develop a list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. The Withdrawn or Removed List is codified under 21 CFR. Drug products on the Withdrawn or Removed List may not be compounded under the exemptions provided by Sections 503A or 503B.

Hydroxyprogesterone caproate, trade name, Makena, and its generics were withdrawn from the market due to lack of effectiveness and are being presented at this advisory committee meeting for possible inclusion on the Withdrawn or Removed List. Before issuing a regulation to implement this, the statute states that the Secretary shall

convene and consult an advisory committee on compounding.

Over the next few slides, I will briefly describe the regulatory history of Makena.

On February 3, 2011, FDA approved Makena injection 250 milligram per mL. It was indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. FDA approved Makena based on evidence from Trial 002, which demonstrated an effect on gestational age of delivery less than 37 weeks. This gestational age was an intermediate clinical endpoint. Note that an intermediate clinical endpoint is a measure of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality that is considered reasonably likely to predict the drug's effect.

Makena was approved under the accelerated approval pathway. Note that under the accelerated approval pathway, FDA approves a drug based on an intermediate clinical endpoint that is reasonably

likely to predict the drug's clinical benefit, rather than based on a direct measure of a clinical benefit or on a surrogate endpoint that is validated to predict clinical benefit; therefore, the sponsor was required to conduct a postmarketing confirmatory study to verify and describe Makena's clinical benefit.

The sponsor conducted a postmarketing confirmatory study, Trial 003. The trial evaluated two co-primary endpoints, delivery less than 35 weeks gestation and neonatal morbidity/mortality. The trial failed to verify the predicted clinical benefit of Makena to the neonate, and did not even show an effect on gestational age less than 37 weeks that was the basis of the accelerated approval.

On October 5, 2020, FDA published a proposal to withdraw the approval of Makena in the Federal Register, as the available evidence post-approval demonstrated that Makena was no longer shown to be effective for its approved condition of use. In response to FDA's proposal, the sponsor requested a

hearing later that year.

On October 17 to 19, 2022, the hearing was held. All members of the Obstetrics, Reproductive, and Urologic Drug Advisory Committee present at the hearing voted to advise FDA that Trial 003 did not verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth, and almost all members voted to advise FDA that available evidence does not demonstrate that Makena is effective for its approved indication. The committee recommended FDA should not allow Makena to remain on the market while another confirmatory study is designed and conducted.

On January 19, 2023, following the hearing, the presiding officer issued a report that summarized the legal and factual background, the contents of the hearing, and her analysis and recommendations. The presiding officer stated that she did not think there's a favorable benefit-risk profile to support Makena's remaining on the market and recommended approval be withdrawn.

On April 6, 2023, the FDA Commissioner and Chief Scientist issued a decision withdrawing the approval of Makena and the ANDAs that referenced Makena. On May 15, 2023, FDA published a notice in the Federal Register announcing the final decision to withdraw the approval of Makena. FDA's determination about the unfavorable benefit-risk profile was specific to the condition of use for which Makena had been approved; therefore, the withdrawal approval was specific to Makena and its generic versions indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of spontaneous preterm birth.

It is important to note that withdrawal of approval of Makena does not affect the current approval status of drug products containing hydroxyprogesterone caproate that are currently approved for different indications, which are listed on the slide.

FDA recommends the following entry be added to the Withdrawn or Removed List, hydroxyprogesterone caproate: all drug products

containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Thank you. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the presenter. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

Yes, Dr. Vaida? Go ahead.

DR. VAIDA: So this is just for the one use of the drug, right? The drug could still be used for the other uses that are in there; that you said they may have an effect.

DR. KNEEREAM: This is Emily Kneeream from FDA. Yes, this is just for the specific indication that was listed.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Virtually?

(No response.)

Open Public Hearing

DR. GULUR: We will now begin the open public hearing session.

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

open 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 the product, or 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 in 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 for 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.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, available virtually, please state your name and any organization you are representing for the record, and you have 5 minutes.

DR. STEINBROOK: I am Robert Steinbrook, a physician and the Director of Public Citizen's Health Research Group. We have no financial conflicts of interest. Public Citizen's Health Research Group supports the FDA's recommendation for the addition to the Withdrawn or Removed List

of, quote, "all drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth."

In April 2023, soon after the FDA withdrew approval of Makena and all related generic products, Public Citizen and co-petitioner Dr. Adam Urato, a maternal fetal medicine physician in Massachusetts, filed a citizen's petition with the FDA. The petition called for the prompt initiation of the regulatory process to add hydroxyprogesterone caproate injection for prevention of preterm birth to the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness, and therefore may not be compounded under the exemptions provided in FDA regulations.

As the petition argued, the lack of evidence that hydroxyprogesterone caproate was effective for its labeled indications, as well as a benefit-risk balance that was not favorable for Makena, provided

a strong basis for the FDA to initiate regulatory action to prevent pharmacy compounding of the drug for prevention of preterm birth.

Public Citizen is concerned that unless hydroxyprogesterone caproate is added to the Withdrawn or Removed List, some obstetricians and maternal fetal medicine physicians may continue to prescribe compounded versions of the drug, either now or in the future. Regardless of how frequently compounded versions of hydroxyprogesterone caproate are currently prescribed, the FDA should promptly take the necessary regulatory action to prohibit pharmacy compounding.

We urge the advisory committee to fully support the FDA's recommendation to add hydroxyprogesterone caproate for the prevention of preterm birth to the Withdrawn or Removed List. Thank you for the opportunity to comment.

DR. GULUR: Thank you.

Speaker number 2, please state your name and any organization you are representing for the record. You have 5 minutes.

MR. MOON: Hi. My name is Richard Moon. I'm representing the National Community Pharmacy Association, better known as NCPA. I feel a little awkward. There was a no open-mic conference availability, so NCPA had submitted some technical details about product presentations to the committee, so it's not technically about Makena. The submission is on record, so I guess I'm asking if you still want me to go through and read this, even though you have it.

(No audible response.)

MR. MOON: Well, hearing nothing, I'll go through it real quick.

Again, like I said, my name is Rich Moon from NCPA, and I appreciate the opportunity to share our concerns about the process of the PCAC. Taken from NCPA's longer comments submitted to the docket, basically today's meeting, NCPA wants to say that FDA first announced this meeting on August 30th and posted the event materials on September 20th, giving a month of review. We're also grateful for allowing the remote

participation.

For today's meeting, FDA gave two calendar weeks for the release of the material packets due for nominators, from September 20th, from when the event materials were posted, to October 4th, when the list of information of presenters was due. NCPA expressed its concern regarding the unreasonable condensed timeline and review process of the June 8 '22 PCAC meeting as well, for that meeting is extremely onerous to review the 876-page material packet 1 week before the list of speakers was due to the FDA and 2 weeks before the nominator slides were due. Additionally, NCPA found it unreasonable that the FDA published the material packets only after the NCPA sent a letter requesting the release of this information.

For the June 22 PCAC meeting, the Federal Register notice of the meeting pre-published on May 5th, and FDA sent an official invitation on May 6th. On May 18th, NCPA emailed to FDA requesting the briefing packet with meeting analysis. FDA published a document at 5:37 Eastern

Time on that day, which meant that the stakeholders lost 12 calendar days, from the 6th to the 18th, which they could not have commented. So those nominator slides were due on June 1st. Those seeking to comment had 9 business days, from the 18th to June 1st, to review all the materials, notify stakeholders, experts in the field, coordinate all nominators, and generate, and submit slides.

NCPA also had concerns with the accelerated timeline for submitting materials at the 2017 PCAC meeting. The 2017 PCAC met on November 20th and 21st. The meeting was announced October 25th, giving 3 and a half calendar weeks notice to comment. The meeting had also been scheduled for Monday and Tuesday of Thanksgiving week, with travel required for those participating on Sunday and Wednesday. FDA then released its briefing document on October 30th. Public comments were due November 3rd to be shared with the committee, and gave 4 business days after the materials were available to be able to comment. Slides were due

November 7th, only about 6 business days after materials were made available.

During that 2017 meeting, a psychiatrist was requested to participate via phone, but the FDA denied the request, stating all participants must be physically at the meeting. The psychiatrist recorded the video, was incorporated into the meeting at NCPA's request, but through the in-person only rule, there were no questions that were allowed to be answered. Meanwhile, two of the voting members of PCAC and two staff members participated via telephone; so creating a double standard that we were unable to meet.

I guess, in conclusion, the process of sending the PCAC materials and review was improved in '24 from the previous PCAC meetings, but we'd like to offer a couple recommendations. First, nominators have at least 4 weeks, from the release of the FDA packet to the due date, for nominating of speakers; and second, nominators have at least two calendar weeks from the due date for nominating speakers to the due date for submitting slides.

And lastly, nominators may participate in the PCAC meetings, like this, other than with remote or other than in person. Thank you very much for your time. I appreciate it. And while I realize it's not on 17 HP, I think they're relevant to the topic.

DR. GULUR: Thank you.

Speaker number 3, please state your name and any organization you are representing for the record, and you have 5 minutes.

DR. URATO: Thank you for allowing me to testify today. My name is Dr. Adam Urato. I have no conflicts of interest to declare. I'm a maternal fetal medicine physician from Framingham, Massachusetts. I'm asking that the FDA add hydroxyprogesterone caproate to the list of withdrawn drugs in order to prevent pharmacy compounding and further use in pregnant women. I'd like to thank Mike Carome, Robert Steinbrook, and Public Citizen for their work and help on this.

In 2003, the Meis trial was published in the New England Journal of Medicine, but it wasn't

until 2011 that FDA approved Makena. So the question then is, what happened during those 8 years? From 2003 to 2011, hydroxyprogesterone caproate was widely prescribed by OB providers, exclusively through pharmacy compounding. It was recommended by ACOG and SMFM. There was significant enthusiasm for it, and it was widely used.

So the point here is that it is important to prevent pharmacy compounding so that pregnant women and developing babies will no longer be exposed to this ineffective drug which carries risks to moms and babies, and it is ineffective. The FDA has concluded that there is a lack of adequate data supporting the effectiveness of this drug, and this implicates compounded products, as well as Makena, in its generic versions.

The amount of continued use and support of this product is likely small, but there is always the potential for changes and possible future enthusiasm for it, so I hope that FDA will prevent pharmacy compounding of hydroxyprogesterone

caproate.

I'd just like to make a closing remark about compounding. Hydroxyprogesterone caproate, like diethylstilbestrol, DES, and other medications, is a synthetic chemical compound, and we must not forget that synthetic chemical compounds like Makena and DES -- and these were the advertisements for those -- these compounds have chemical effects and can affect moms and developing babies.

What just happened with Makena is that an ineffective and harmful drug was injected into pregnant women for 20 years, and similar to DES, the Makena saga is not over. We don't know what the long-term effects on the exposed babies may be. There is some evidence of increased cancer risk and effects on brain development.

As a human community, it is crucial that we follow the precautionary principle, especially in pregnancy. We didn't really learn from the DES tragedy, and we basically made the same mistake again with Makena. It is important that we get this right moving forward and really look out for

pregnant moms and their babies. Thank you very much.

DR. GULUR: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We have time for some clarifying questions should the panel members have any, or if the FDA would like to make any comments.

(No response.)

DR. GULUR: Virtual?

(No response.)

Committee Discussion and Vote

DR. GULUR: Seeing no further questions or discussion, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees

may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our last question, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue

in the same manner until all questions have been answered or discussed.

Question 5, FDA is proposing that hydroxyprogesterone caproate, all drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth, be added to the Withdrawn or Removed List under Sections 503A and 503B of the FD&C Act.

Should this entry be placed on the list? If you answer yes, you are recommending it should be placed on the list. If you answer no, you are recommending it should not be placed on the list.

Any questions or comments?

(No audible response.)

DR. GULUR: If there are no further questions or comments concerning the wording of the question -- there are?

DR. VAIDA: Yes, just one more time now. This is, if you vote yes, then you can't use it for this indication. If no --

DR. GULUR: No. It's to place it on the list. So this is the withdrawn list. If it is on the list, it can no longer be used for compounding.

DR. VAIDA: If you vote yes.

DR. GULUR: I will repeat that one more time, too.

Was that clear? Any questions?

Yes?

DR. SERUMAGA: Brian Serumaga. So, if it's not going to be used for combining for this indication.

DR. GULUR: That's correct.

DR. SERUMAGA: That's my understanding; right?

DR. GULUR: That is what they've clarified, yes.

DR. VAIDA: So if you vote yes, then it's going to be on the list not for this indication.

DR. GULUR: Correct.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press

the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 9 yeses, zero noes, and zero abstentions. Thank you.

DR. GULUR: Thank you.

Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

DR. WEISS: Rita Weiss. I voted. yes.

DR. SERUMAGA: Brian Serumaga, USP. I voted yes, the reasons being that the USP does actually have two monographs that are relevant to this

discussion, a drug substance monograph for hydroxyprogesterone caproate and a drug product monograph for hydroxyprogesterone caproate injection.

We saw in the FDA presentation that this product can be used in non-pregnant women for other indications, so that reassures me that there will be a possibility for this to be compounded if it is necessary in non-pregnant women for those particular conditions. The drug substance and the product, the injection monographs show that this product can actually be very well characterized. So for those reasons I voted yes.

DR. GULUR: Thank you.

DR. BOGNER: Robin Bogner. I voted yes.

DR. GURA: Kathleen Gura. I voted yes.

DR. VAIDA: Allen Vaida. I voted yes.

DR. DURHAM: Todd Durham. I voted yes.

DR. GULUR: Dr. Desai, online?

DR. DESAI: Seemal Desai, PCAC member. I voted yes. And in particular, I found the discussion that we had just a few minutes ago

regarding the specific indication for which we are using to put it on the withdrawn list to be very helpful, so thank you.

DR. GULUR: Dr. Rebello, online?

DR. REBELLO: Elizabeth Rebello. I voted yeah.

DR. GULUR: Padma Gulur. I voted yes. And to summarize, this deserves support to put this on the list for the indication that has been clearly delineated.

With that, we have closed all business for today. Before we adjourn, are there any last comments from the FDA?

DR. GANLEY: Yes. I just wanted to thank all the committee members and industry representatives for taking time out of their week. We know you had to travel and get here, and you have to get back to where you're going, and also to Dr. Desai online for participating in this meeting. It's very important to us, and we thank you for that; so thanks.

DR. GULUR: We appreciate that.

Anyone else? Do any of the panel members have any last comments?

(No response.)

Adjournment

DR. GULUR: I will take this opportunity to thank my panel members. Thank you all for robust discussions and your dedication to ensuring that this is a robust process. I'd also like to thank the public and the members who came and spoke at the open public hearings. That is an extremely important and critical component of our ability to ensure that this process is transparent and that all of us are aware as we make decisions.

I would also like to thank everyone from the FDA for all your dedication and support of the process. I know the amount of work that goes into each of these meetings, so I would also like to particularly thank Dr. Stevenson here and all the supporting crew that have made sure that today has been extremely smooth, and except for one Zoom technical difficulty, quite a marvel, actually, in all with a hybrid meeting.

So with that, I would like to thank everyone and look forward to our next meeting in December. We will now adjourn the meeting.

(Whereupon, at 4:05 p.m., the topic 5 session was adjourned.)