FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

CJC-1295-RELATED BULK DRUG SUBSTANCES (CJC-1295 (FREE BASE), CJC-1295 ACETATE CJC-1295 WITH DRUG AFFINITY COMPLEX (DAC) (FREE BASE) CJC-1295 DAC ACETATE, AND CJC-1295 DAC TRIFLUOROACETATE)

Morning Session

Topic 1

Wednesday, December 4, 2024

8:05 a.m. to 10:49 a.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

(8:05 a.m.)

Call to Order

Introduction of Committee

DR. STEVENSON: Good morning. Takyiah Stevenson, DFO speaking. Before we get started, Dr. Galore will be participating virtually and will not be chairing today's advisory committee meeting. Dr. Rebello will be the acting chairperson for today's meeting. I will now turn it over to Dr. Rebello.

DR. REBELLO: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Amanda Hils. Her email address is currently displayed.

My name is Elizabeth Rebello, and I'll be chairing today's meeting. I will now call the December 4, 2024 meeting of the Pharmacy

Compounding Advisory Committee to order. We will start by going around the table and introducing ourselves by stating our names and affiliations. Those participating in all three topic sessions of this meeting will introduce themselves first. Those participating in specific topics of this meeting will be introduced at the start of their respective topic session. Panel members who will be in the CJC-1295 related bulk drug substances topic session will introduce themselves by stating their names and affiliations.

Now, we'll go with the introductions.

DR. SAN ANTONIO: Marianne San Antonio, PCRT, FDA.

DR. SHETTY: Good morning. Daiva Shetty, Associate Director for Pharmacy Compounding, Review Team, FDA.

MS. BORMEL: Gail Bormel, Director of the Office of Compounding, Quality, and Compliance at FDA.

DR. RUPP: Tracy Rupp, Office of Compounding, Quality, and Compliance, FDA.

MR. WESDYK: Russ Wesdyk, Office of Pharmaceutical Quality, FDA.

DR. TU: Mai Tu, Senior Pharmaceutical Scientist, Office of Pharmaceutical Quality.

DR. DURHAM: Todd Durham, Foundation Fighting Blindness.

DR. VAIDA: Allen Vaida, Pharmacist Retired from Institute for Safe Medication Practices.

DR. BOGNER: Robin Bogner, University of Connecticut.

DR. SERUMAGA: Brian Serumaga, United States Pharmacopeia.

DR. STEVENSON: Takyiah Stevenson, DFO, FDA.

DR. REBELLO: Elizabeth Rebello, UT MD Anderson Cancer Center.

DR. GURA: Kathy Gura, Boston Children's Hospital.

DR. McELHINEY: Linda McElhiney, Elevance BioPlus Specialty Pharmacy.

DR. FENSKY: Tim Fensky, National Association of Boards of Pharmacy.

DR. LUPTON: Thomas Lupton, Director of

Pharmacy Services, On Demand Pharmaceuticals.

DR. STAAS: Donnette Staas, Vice President, Regulatory Strategy, Jazz Pharmaceuticals and industry rep.

DR. STEVENSON: I will now ask the online participants to introduce themselves.

Dr. Cosel?

DR. COSEL: Gabrielle Cosel, Director of the Division of Compounding Policy and Outreach, FDA.

DR. STEVENSON: Dr. Ganley?

(No response.)

DR. STEVENSON: Dr. Ganley, if you're speaking, you may be muted.

(No response.)

DR. STEVENSON: Okay. We'll come back to Dr. Ganley.

Dr. Gulur?

DR. GULUR: Dr. Padma Gulur, Duke University.

DR. STEVENSON: Dr. Gupta?

DR. GUPTA: Dr. Anita Gupta, University of California at Riverside.

DR. REBELLO: Panel members who will be in the CJC-1295 related bulk drug substances topic session will introduce themselves by stating their names and affiliations. We'll begin with Dr. Burman.

DR. BURMAN: Kenneth Burman, MedStar Washington Hospital Center and MedStar Georgetown University.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke, pediatric endocrinology, Johns Hopkins University School of Medicine.

DR. REBELLO: Dr. Jensen?

DR. JENSEN: Dr. Kirk Jensen, Lieutenant Colonel, U.S. Air Force at Uniformed Services University.

DR. REBELLO: For topics such as those being discussed at this meeting, there are often a variety of opinions, some which are very strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about this topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until --

(Pause.)

DR. STEVENSON: Good morning. Takyiah Stevenson speaking, DFO from the FDA. We do apologize for the technical difficulties. We had to take an unscheduled break. We will resume. I will hand it back to the chair to begin with the statement. Thank you.

DR. REBELLO: Thank you.

For topics such as those being discussed at

this meeting, there are often a variety of opinions, some which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about this topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch.

Today we will discuss the following bulk drug substances being considered for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with the Section 503A of the Federal Food, Drug, and Cosmetic Act, also known as the 503A Bulks List:
AOD-9604-related bulk drug substances;
CJC-1295-related bulk drug substances; and
thymosin alpha-1-related bulk drug substances.

We note that all nominations for AOD-9604-related bulk drug substances; CJC-1295-related BDSs, and thymosin alpha-1-related bulk drug substances have been withdrawn by the nominators, but FDA decided to evaluate these substances on its own initiative. For each of the substances, we will hear presentations from FDA, have the opportunity to ask clarifying questions, hold an open public hearing, and have committee discussion and voting. We have no nominators presenting today.

The October 25, 2024 Federal Register Notice identified the uses FDA reviewed for each of the

bulk drug substances being discussed at this meeting. Their uses reflect those for which adequate support was provided in a nomination. In certain circumstances, FDA may also review the substances in the context of unnominated or inadequately supported uses because, for example, such uses appear to be widespread, are intended to treat serious conditions or pose serious risks to patients. In addition, nominations and FDA evaluations for the bulk drug substances, which are included in the briefing documents posted on FDA's websites, identify the proposed and reviewed uses, dosage forms, and rights of administration. Thank you.

Dr. Stevenson will read the Conflict of Interest Statement for this meeting's 503A Bulk List's topics.

Conflict of Interest Statement

DR. STEVENSON: Thank you.

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 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.

Today's agenda involves discussion of the three bulk drug substances being considered for inclusion on 503A Bulks List. FDA will discuss the following bulk drug substances and the uses that

FDA reviewed for each: 1) AOD-9604-related bulk drug substances which are AOD-9604 acetate and AOD-9604 free base for obesity; 2) CJC-1295-related bulk drug substances, which are CJC-1295 free base; CJC-1295 acetate; CJC-1295 with drug affinity complex, abbreviated as DAC free base; CJC-1295 DAC acetate; and CJC-1295 DAC trifluoroacetate for growth hormone deficiency; 3) thymosin alpha-1-related bulk drug substances, which are thymosin alpha-1 acetate and thymosin alpha-1 free base for hepatitis B, hepatitis C, human immunodeficiency virus or HIV; coronavirus disease 2019 or COVID-19; depressed response to vaccinations; adjuvant to flu vaccines; malignant melanoma; hepatocellular carcinoma or HCC; non-small cell lung cancer, NSCLC; sepsis; infections after hematopoietic stem cell transplantation or HSCT; chronic obstructive pulmonary disease or COPD; myalgic encephalomyelitis and chronic fatigue syndrome or ME/CFS.

For nominated bulk drug substances, the

nominators of these substances were invited to make a short presentation supporting the nomination. This is a particular matters meeting during which specific matters related to the three bulk drug substances will be discussed.

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

Dr. Gulur is attending all topics. Her waiver involves stock holdings and a competing/affected entity for all topics with an aggregate value between $25,000 and $50,000. Dr. Gulur's waiver also involves stock holdings in a competing firm for the AOD-9604 and the CJC-1295 topics. The aggregate value of the stock is between $25,000 and $50,000.

Dr. Gura is attending all topics, and her waiver involves six stock holdings. The first two stock holdings are in competing/affected entities

for all topics with an aggregate value between $50,000 and $75,000. The other four stock holdings are in competing firms: a competing firm for the thymosin alpha-1 topic; a competing firm for the AOD-9604 and thymosin alpha-1 topics; a competing firm for all three topics; a competing firm for the CJC-1295 and thymosin alpha-1 topics. The aggregate value for each of the four stock holdings and competing firms is between $0 and $10,000.

Dr. Janet Lee is attending the thymosin alpha-1 topic. Her waiver involves stock holdings in two competing/affected firms with an aggregate value of between $25,000 and $50,000 and $0 and $55,000.

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 web page, which can be found at www.fda.gov and by searching for December 4, 2024 PCAC. Copies of these waivers may also be obtained by submitting a written

request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035 in 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 bulk drug substances at issue.

We would like to note that Dr. Timothy Fensky 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 participants to advise the committee of any financial relationships that they may have with the topics at issue.

Thank you, and I'll turn it back to the chair.

DR. REBELLO: We will now proceed with the FDA introductory remarks from Dr. Frances Gail Bormel.

FDA Introductory Remarks - Gail Bormel

MS. BORMEL: Good morning, everyone. I'm Gail Bormel, the Director of the Office of Compounding, Quality, and Compliance, which is the FDA office primarily responsible for developing and implementing policies and compliance strategies, addressing the quality of compounded drugs. I would like to formally welcome you to the 13th meeting of the Pharmacy Compounding Advisory Committee.

As you've heard before, we will discuss three bulk drug substances that have been nominated for inclusion on the list of bulk drug substances that can be used in compounding human drug products

under Section 503A of the Federal Food, Drug, and Cosmetic Act, which is also known as the 503A Bulks List. As you've heard, the substances that will be discussed are, 1) CJC-1295-related bulk drug substances, which includes the free base; the CJC-1295 acetate; the CJC-1295 with drug affinity complex, free base; CJC-1295 drug affinity complex acetate; and CJC-1295 drug affinity complex trifluoroacetate.

The second bulk drug substance is AOD-9604-related bulk drug substances, which includes AOD-96O4 acetate and AOD-9604 free base. The third bulk drug substance is thymosin alpha-1-related bulk drug substances, which includes thymosin alpha-1 acetate and thymosin alpha-1 free base.

We have scheduled time for an open public hearing after FDA's presentation on each of the bulk drug substances. We are glad you were here today to participate in the Pharmacy Compounding Advisory Committee. We do value your input and expertise, both of which are critical to the

success of this process. We look forward to a productive meeting and continuing to work together. Thank you again for joining us.

DR. REBELLO: We have Dr. Charles Ganley, who was able to join us virtually.

Dr. Ganley, will you please introduce yourself?

DR. GANLEY: Hi. Good morning. Charlie Ganley. I'm the Director of Office of Specialty Medicine in the Office of New Drugs at FDA. Thank you.

DR. REBELLO: Thank you.

We will now proceed with the following three FDA presentations: Investigational New Drug Expanded Access presentation from Lori Bickel; Immunogenicity Risk of Compounded Peptides presentation from Dr. Daniela Verthelyi; Bulk Drug Substances Discussion presentation from Russell Wesdyk.

FDA Presentation - Lori Bickel

MS. BICKEL: Good morning. I'm Lori Bickel, and I'm a regulatory counsel in CDER's Office of

New Drugs Policy, and I have no conflicts to disclose. This morning, we're going to look at two ways investigational drug and biological products can be used either for research under an IND or for treatment through expanded access. This is to help inform advisory committee members and the public of ways in which an investigational drug or biological product can be studied or used to treat patients.

First, I'll give a brief overview of the investigational new drug, or IND, submission requirements. This is needed before most investigational drugs can be studied in clinical trials; then we'll move on to expanded access and how it differs from clinical trials, including the requirements for all expanded access and details about the three categories of expanded access. Finally, I'll take a quick look at some of the tools that FDA has developed to help patients and their physicians determine if expanded access is an appropriate option and to streamline the process if it is.

To start, we're talking about ways to use

investigational drugs and biological products. Research on an investigational drug is usually done under an IND. To get to an approved drug, clinical trials provide evidence of the safety and effectiveness of the product and to gather information about the drug that may lead to its eventual approval for commercial marketing and widespread use.

Approval leads to the broad availability for the product, with full labeling for patients and potential third party reimbursement; however, a clinical trial isn't always an option, so in those cases, perhaps expanded access may be an avenue for treatment use using an investigational product if the appropriate conditions are met. This should be a pathway of last resort when other options are exhausted or unavailable. One key difference is that expanded access provides the investigational product for treatment use, not for research.

Both of these pathways are distinct from the 503A and 503B compounding. Whether a product is or is not being studied under an IND is not a

consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List.

I'll start with the IND for research, a clinical trial using an investigational drug or biological product; however, all of the key content of the IND submissions covered here also apply to expanded access submissions.

When I think about the elements for an IND submission, I break the components down into three categories. The first is information about the investigator conducting the study. This person may be a researcher in a large academic institution or it may be a practicing physician within the community. Either way, basic information about the investigator must be submitted to make sure that they are qualified to conduct the research using a drug or biological product on humans. This information can be submitted on the forms that are shown on the slide. These forms are used for the information about the investigator, including all of their qualifications and their CV.

Moving on to the second bucket of information is information about the drug product to be studied. What is its chemistry, manufacturing, and controls information? What is the product identity, purity? How will it be distributed during the trial? In some cases, a Letter of Authorization, or an LOA, may be used to reference information about the drug that is already on file with FDA within an existing IND.

Continuing with information about the drug, it is, obviously, basic information about the safety and efficacy of the drug. Is it reasonably safe at the dose and durations proposed? What clinical or nonclinical data does the sponsor have to justify the dose and duration they've proposed in the protocol? The final piece of information about the drug for the IND submission is about its efficacy. What is the sponsor's rationale to support the intended use of the drug during the proposed investigation?

The third set of information included in the IND is the information about the patient and the

proposed treatment or the protocol for the investigation. This includes a description of the disease or condition being studied. What are the eligibility criteria for the trial, information that's needed about the clinical procedures, and monitoring that will be in place to both evaluate the effect of the product and to minimize any potential risk to study participants? Finally, all INDs will need an informed consent form and IRB approval.

These key content slides don't capture everything necessary for IND submissions, but I hope they've given you an idea of the types of information FDA requires, and why, before a clinical study using an investigational product can begin.

We're going to shift gears a little bit and focus on expanded access. In contrast to a clinical trial, which is primarily the use of an investigational drug for research purposes, expanded access is the use of an investigational drug or biologic for treatment. Expanded access is

use of the product to treat a patient with a serious or immediately life-threatening disease or condition who does not have comparable or satisfactory alternate therapy. As I mentioned earlier, expanded access really is meant to be a last resort. Regardless, all expanded access requests and documentation must meet the requirements for an IND that I covered earlier.

Moving on to the basics of expanded access, the first thing I'd like to point out is actually the asterisks at the bottom of the slide. The sponsor or the manufacturer of the investigational drug must agree to provide it to the patient for the expanded access use. FDA cannot force a manufacturer to provide their product for expanded access. Once a manufacturer agrees to provide the product, there are three different types of expanded access under FDA's regulations.

The first is individual. That's a single patient, which may involve the patient's treating physician. Individual patient access can also be emergency or non-emergency, depending on the

situation. Under an emergency IND, the treatment use of the product can begin after getting the manufacturer's agreement and upon authorization by the FDA reviewing official. Often this can be done over the phone when treatment needs to begin immediately.

The second type of expanded access is intermediate size population. There's no set number for intermediate size, but it's generally more than one and fewer than the number in a treatment IND or protocol. Finally, the third type is treatment use, which is typically larger and widespread. A treatment IND or protocol usually occurs either after phase 3 or compelling phase 2 data analysis.

Now that we have the three types of expanded access, the next set of requirements apply to all three: again, the patient must have a serious or immediately life-threatening disease or condition; there is no comparable or satisfactory alternative therapy; they aren't able to participate in a clinical trial; the risk-benefit analysis must show

that the potential benefit justifies the potential risks; and finally, that providing expanded access will not interfere with the potential development for that expanded access use.

In 2009, FDA published the final rule on expanded access. In 2016, we released a question and answer guidance, which was revised in 2017. In 2022, FDA published a revised draft guidance for public comment with additional clarifications about the program. Public comments are being reviewed, and the guidance is in the process of being finalized.

I'd like to remind everyone at this point that all research is done under an IND, as clinical trials and expanded access come with the full range of human subject protections. These are the citations to the sections of the regulations that apply. Since the regs were published in 2009, FDA continues to take steps to make sure the expanded access program is understood; that its criteria are known and followed so that the program is used appropriately and within its intended scope. These

initiatives included creation of Form FDA 3926 in 2016. Part of that, all INDs, including expanded access, had to use Forms 1571 and 1572, which are the forms for commercial INDs. At that time, FDA also updated the guidances and our website.

FDA has also had an ongoing collaboration with the Reagan-Udall Foundation for the FDA to launch various tools to assist users in determining if expanded access is appropriate and help walk them through the process if it is. Additionally, FDA's Oncology Center of Excellence launched Project Facilitate in 2019, which is a program to help provide one-on-one assistance through the expanded access process.

Here's a screenshot from FDA's website. It's designed to be user friendly with tabs for patients, physicians, industry, and IRBs. I've also provided a link to a series of FDA-produced informational videos. I also wanted to be sure to provide contact information for any questions that members of the committee or that the public may have about either INDs or expanded access. Here

are links to all of the regulations and the guidances that I've mentioned this morning. Thank you for the opportunity to speak with you this morning.

FDA Presentation - Daniela Verthelyi

DR. VERTHELYI: Good morning. My name is Daniela Verthelyi. I'm in the Office of Pharmaceutical Quality Research, and I'll be addressing the issue of peptide immunogenicity this morning. I have no conflicts of interest to disclose. Thank you.

Today, as I said, we're going to be talking about product immunogenicity, describe the clinical immunogenicity concerns that exist for peptides, and give a brief introduction to the mechanisms involved in generating an immune response, and then address specifically, or discuss, the immunogenicity-related concerns for compounded complex peptide products.

Immunogenicity is the unwanted development of an immune response usually marked by development of antibodies for a therapeutic product. Now, as

you can see on the right, development of antibodies is a complex process that involves multiple cells and signals. It is so regulated because their development can impact patients' clinical status. Therapeutic peptides that can induce an unwanted antigen-specific response can impact on the safety and efficacy of the product.

The consequences, the clinical consequences, can be none. Sometimes patients develop antibodies and nothing happens. They can be moderate. They can alter pharmacokinetics and pharmacodynamics. They can lead to loss of efficacy or sometimes even lead to toxicity if there's any drug accumulation. But they can also be severe. They can cause hypersensitivity or anaphylaxis, whether it's IgG or IgE driven. They can cause immune complex diseases. The development of neutralizing antibodies can reduce the efficacy of the therapy, and the development of antibodies that would cross-neutralize the endogenous counterpart can be particularly complicated as it can lead to a deficiency syndrome.

There are multiple factors that are going to impact on whether a product develops or induces an immune response. Some of them have to do with the patient, their genetic structure, their background immune competency, and whether they have any underlying disease. But a lot of them have to do with the product itself, where it's the API or the impurities that accompany that API.

So it is important to understand the tolerance that the immune system has developed towards this peptide, and that has to do with the homology to self. The immune system is trained to ignore or accept peptides that are recognized as their own, but variants of those peptides can produce new epitopes that are recognized as different, and thus can induce an immune response. The other type of impurities that can favor an immune response are things like aggregates, process-related impurities, contaminants, excipients, and leachates; and all of those can act as an adjuvant, and I'll clarify in my next slide, please.

This is a little bit of a busy slide, but as you can see, the idea is that as you introduce a peptide in a tissue -- in this case we are modeling skin -- what happens is that most of the peptide is going to go through the lymphatics to the lymph nodes, and there, depending on what the environment is, the peptide will be taken by cells that present the antigen to the immune cells, or not. If it doesn't, if it's not picking up, there will be no immune response. If it's taken up, the milieu in which this interaction occurs will determine whether there's development of antibodies or the bodies ignore the peptide.

In the presence of impurities, what happens is there's an increase in inflammation, and those antigen presenting cells are getting activated and mature, and are much better able to present the antigen to those immune cells, those T cells and B cells, and induce the production of antibodies. If those antibodies, again, are directed to the drug, they can induce changes in PK, reduce efficacy, but if they cross-react with the

endogenous peptide, they can lead to a deficiency syndrome.

Because of these concerns, usually there is a certain level of characterization that happens that involves the assessment of their aggregation profile, the assessment of process and product-related impurities, and those involve really complex methods for assessment, such as assessment of visible and subvisible particles, measurement of leachables and toxins, residual solvents, and innate immune response modulating impurities, antigen uptake, and so forth. For product-related impurities, LC-MS, MS-MS, peptide mapping, as well as in vitro assays that look at MHC binding in T cell activation are usually used.

In summary, the level of concerns with peptides is different than for small molecules. Peptide sequences can elicit an immune response, particularly if aggregated or present on scaffolding. Peptides administered via subcutaneous; intravenous; intramuscular; intradermal; inhalation; and intravitreal routes

have greater immunogenic risk than oral or transrectal peptides.

Drug formulation is critical to the quality and stability of the peptide drug products. Formulation differences can modify peptide stability and immunogenicity.

Peptide-related impurities may modify the target of the antibodies developed, and impurities or contaminants that activate immune cells may increase the immunogenicity of the API or result in an immune response that targets new sequences that may cross-react with endogenous counterparts.

Peptide-related impurities can be difficult to detect, analyze, and control because impurities can have similar amino acid sequence to the peptide itself, necessitating advanced analytical techniques such as liquid chromatography, high-resolution mass spectrometry to detect, identify, and quantify the impurities.

Impurities and contaminants can activate immune cells where the product is deposited, increasing the immunogenicity risk at trace levels,

picograms and nanograms.

Assessing the immunogenicity risk of immunomodulatory impurities in peptide requires complex in silico and in vitro studies.

Mitigation of the immunogenicity risk of peptides requires sensitive assays and control of product- and process-related impurities.

Here's an example of the studies generated in our own lab, looking at the risk of innate immune response modulating impurities in compounded and commercial samples. You can see on the left is a graph depicting the level of innate immune activation that we detected in cells exposed to 6 drug substance lots from a commercial vendor, then 2 lots from a compounded vendor.

As you can see, the level of immune activation was higher in those of the compounded vendor, but more importantly, when that drug substance was then filtered, sterilized, the amount of innate immune activation achieved by one of the samples was reduced of the drug substance, of the compounded samples, but one was not, indicating

that there are different impurities, and those impurities may be differently purified with the use of usual purification methods.

In summary, product immunogenicity constitutes a risk for peptides, including compounded peptides, especially when delivered via certain routes of administration, which may result in significant risk of harm, including life-threatening reactions such as anaphylaxis. Control of impurities, including aggregates, can mitigate this risk but requires sophisticated manufacturing and testing strategies. Thank you.

FDA Presentation - Russell Wesdyk

MR. WESDYK: Good morning. I'm Russell Wesdyk. I'm the Associate Director for Regulatory Affairs here at FDA. I have no conflicts of interest to disclose. We're going to be talking a little bit today about bulk drug substances and active moieties, and you'll find that this is particularly relevant in all of the evaluations that we're going to be dealing with later on today.

All of these presentations, whether it's

CJC, AOD, or Ta1, we're going to be handling multiple related bulk drug substances because it wasn't clear what in fact was being nominated or presented to us, or even the information contained within the nomination sometimes referenced multiple different substances. Despite the lack of clarity about which bulk drug substance was intended in the nomination, due to our concerns about safety, we decided to evaluate them all, present them to the committee.

The goals of this presentation is to help you understand the regulatory definitions of bulk drug substances, BDSs, APIs, and active moieties. We want to explain how bulk drug substance differences have implications both for the products made with them and for the patients dosed with those products, and finally provide additional relevant background.

So we're going to begin with a thought experiment, and for some of you, I apologize, because you went through this last time; but some of you haven't, so allow me the chance to go

through it again. Take a look at the screen and consider how many different bulk drug substances, APIs, and active moieties are present on that screen, and hopefully at the end of this presentation, you will understand why there are six different BDSs, six different APIs, and two different active moieties.

If a nominator proposes to manufacture or compound one of these things, or all six, they would need to submit six different nominations, each supporting itself. You can't nominate diclofenac, but support it with diclofenac potassium information or even naproxen sodium information. But that's in fact what we're going to be dealing with throughout the rest of his day. It's akin to I'm nominating a Cox 2 inhibitor, and here's all this information on aspirin. That's really not relevant in terms of the public health or the patients that are going to be dosed with these substances. So it's important to understand the differences and follow along with the presentations. Thank you.

So let's start with what do the regulations say about this. An active pharmaceutical ingredient is defined in the CFR, in the portions that deal with compounding, as being the same -- sorry; let me rephrase that again. An active pharmaceutical ingredient is defined as the same as a bulk drug substance. So then you ask me, "Okay, Russ. What is a bulk drug substance -- or what is an API?" Sorry, I'm getting these in reverse.

An API is defined in the regulations as the substance that's intended for incorporation into the dosage form, into the finished product, and is intended to furnish a pharmacological activity. In essence, an API is the aspirin that's in the aspirin tablet, and the BDS, that's the language we use for compounding, is the same thing.

From a practical standpoint, there can be differences in the API forms that are used. There can be various salt forms to a free base, and these tend to be chosen based on the pharmacological activity, based on the PK/PD characteristics,

pharm/tox profiles, et cetera, et cetera, and that selection is usually specific to the dosage form being studied. If I'm a formulator, for example, and I'm manufacturing an injectable product, I'm probably more concerned with the solubility of the API, and I'll select the salt form that aids in solubility. If I'm manufacturing a solid oral dosage form, I'm probably less concerned with solubility, more concerned with other characteristics, and so again, I might select a different salt form.

We've talked a little bit about active moiety, so I should spend a moment or two. What is an active moiety? An active moiety is defined in the CFR as the molecular ion, excluding those appended portions of the molecule that cause it to be an ester or a salt; but if you're covalently bonding something to that structure, you've got a different active moiety. That's why, for example, though naproxen and diclofenac are not terribly unrelated, they are in fact different active moieties, and hopefully that helps you understand

why, here in the example, we have six distinct BDSs and two different active moieties.

Why does this matter? Again, I'll start with the regulations. We've stated on a number of occasions 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. But it's not just regulations. These definitions and distinctions are important in compounding, just as they are in drug product manufacturing. It's not just a matter of regulations or definitions. Those different salts, those different esters, will have different pharmacological properties, different physiochemical properties, different pharm/tox profiles and PK/PD profiles, and all of that is relevant to patient safety and efficacy of the product.

Also for our evaluation, what you see on the screen is the rule that we're supposed to follow in OPQ when we're trying to figure out if something is well characterized, and we're supposed to be looking at the properties and toxicities of the

bulk drug substance that's going to be used in compounding and comparing it to the properties and toxicities of the test material that showed it to be safe and effective, or ideally shows it to be safe and effective. If those properties and toxicities are different, I cannot consider it well characterized. So when we're conflating different salts and esters in our nominations, it almost forces me to conclude it's not well characterized.

I should also mention in terms of related information, there are unique identifiers and databases that are generally used to identify bulk drug substances or APIs. GSRS, or the Global Substance Registration System, is one of them. It's the home of the unique ingredient identifier or known as a UNII code. You'll hear us talk about those a little bit today.

There's also the chemical abstract services, and that's the home of the CAS registry number, but please note, manufacturers and suppliers populate these databases, not FDA, or any other regulatory agencies. The manufacturers and suppliers provide

the structure and related information and request that unique identifier. Regulators like FDA don't own that data or police the data in it, and we don't have the authority to just unilaterally make changes to that data that's owned by those various companies.

So, in conclusion, a bulk drug substance is defined as the same as an API in our regulations. The free base form of a bulk drug substance, as well as each of the salt forms, are distinct bulk drug substances, each with unique physical, chemical, PK/PD, pharm/tox profiles, et cetera, et cetera, and all of that impacts on patient safety and product efficacy.

Nominators, bulk drug substance manufacturers, and compounders need to be aware of what single bulk drug substance they're nominating, manufacturing, and using to formulate a compounded product, and support that specific BDS in their nomination packages. UNII codes and CAS numbers are unique identifiers for APIs and BDSs, but they're not controlled by the FDA. And finally,

our physical and chemical characterization assessment and conclusion is specific to a unique BDS.

Some final thoughts; I'm not going to spend much time on botanical bulks, but for those of us who are following along or might want to nominate a botanical drug substance, please note that they are not like typical drug substances that are a pure substance. Botanicals tend to be mixtures of compounds, and care must be taken to identify a single bulk drug substance. We have guidances on this, and we encourage nominators to look at those guidances if they plan to submit a botanical.

I also want to talk a little bit about the use of common names because that's going to impact us a lot today. The use of common names as opposed to USAN names can be problematic and confusing. This will be highlighted as a concern for the 503 bulks evaluation list evaluations that we present today. Allow me to try to explain this issue using a hypothetical example so we don't need to reference any company confidential information.

Imagine all of you are now suddenly the CEO of the ABC Discovery Company, and you have synthesized a new compound that you think will show promise as an anti-cancer agent. Let's call that compound ABC123, consistent with your company internal naming convention. You get a UNII code for this, you get a CAS number for this, and you file an IND, or maybe you begin your early clinical trials overseas.

During formulation development, you typically vary the salts and counterions and evaluate the solubility and pharmacological effects of the compound. And as the story continues, your early clinical trials identify some significant negative safety signals associated with ABC123 and its various salt forms.

In response to those safety signals, you modify ABC123 free base form and add a binding affinity ligand complex. Let's call it BAL. Now, this is a structurally distinct compound and a different active moiety from the original ABC123, but because you're in an early development phase,

you just keep calling it ABC123. You do some additional studies with this new form of ABC123, and find a lack of efficacy, so you cease development. This is not unusual in a clinical program, in any development program. Most drugs fail in the clinic.

At this point, you, the ABC company, are done with ABC123. You're not going to make it anymore. You're not going to study it anymore. You have no reason to update GSRS or the chemistry abstract services, and you certainly have no reason to seek a USAN name for any of the compounds or variations that you studied. And at this point, there is conflicting information in the public domain, including in the clinical literature, about what ABC123 actually is. Is it the compound without BAL or is it an entirely different BDS and active moiety that does contain the BAL structure? Which salt form or which active moiety is ABC123? The truth is, there really is no right or wrong answer to this question.

Now, if interest in clinical development of

the compound was rekindled in the U.S., a sponsor would have to fix this problem. They'd have to submit information to us and let us know, "Hey, this is exactly what we plan to dose patients with." But if instead of development being reinitiated by a sponsor, a compounder decides to market ABC123 prior to the substance being in the bulks list -- and I am not commenting or suggesting there is any basis for that, but you as PCAC, and we as FDA, and even healthcare providers, have absolutely no way to know what an Rx for ABC123 actually means. We don't know the right chemical structure, the BDS form, or even the active moiety form. It's entirely possible that physician thinks they're writing the script for one thing, or the BDS supplier thinks it's something else, while the compounder thinks it's something else again.

This is a fictional example. It shows what can happen when nominators, BDS manufacturers, and compounders use common names as opposed to seeking USAN names and resolving naming conventions discrepancies. This is a challenge we're all going

to encounter today and have to work our way through.

I also want to spend a little bit of time on synthetic pathway considerations for complex BDSs, and this builds on Daniela's presentation about immunogenicity and impurities. For a complex BDS such as long chain peptides where there's a greater immunogenicity risk, the synthetic pathway and related impurities can matter a lot in terms of product safety, and Daniela just spoke very eloquently to that.

For such peptides, there may be as many as three broad categories of viable API manufacture, including, 1) isolation from the natural source; 2) chemical synthetic pathways; and 3) biosynthetic pathways. And each of these broad approaches can lead to different impurity profiles, which can have downstream impacts on safety and efficacy. There are, of course, further variations to each one of these broad synthetic pathways, and even different in-process controls that might be used for the exact same pathway. The point being, there are

many permeations possible in terms of synthesis and potential variations in BDS quality as a result.

It is for those reasons that in the case of an approved drug product, there is a specific synthetic pathway and very tight controls in terms of API manufacturing to ensure the safety and efficacy of the product, and those specific technical details are company confidential information and not publicly available, nor can we disclose them to the committee.

It's important to note that no such manufacturing constraints or controls can be assumed for a BDS that can be purchased on the open market and used for compounding, and those BDSs can and do have different characteristics and levels of quality. That's less of a concern for a small molecule like aspirin, for example; however, it's a greater concern for a complex BDS, for lack of any ability to ascertain what impurities is in there compared to what impurities were in the tested product really impacts dramatically on whether or not we can consider it a well-characterized

substance.

As the next-to-last slide of Daniela's immunogenicity presentation makes it quite clear, these differences in BDS quality are not theoretical. They do have real-world implications on patient safety and product efficacy. Thank you so much for your time.

Clarifying Questions from the Committee

DR. REBELLO: Thank you, Mr. Wesdyk.

We will now take clarifying questions to the 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 and the slide number, if possible. Finally, it will 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 to the next panel member.

Are there any clarifying questions for the presenters?

DR. GURA: Hi. Kathy Gura. Thank you, first, for some excellent presentations. My question is to Mr. Wesdyk. Where do excipients and adjuvant products fit into this? They're not API, and they're just added sometimes to the final finish formulation. What kind of review do those go through? Thank you.

MR. WESDYK: Gail and others might want to chime in as well from PCRT and/or OCQC. But the evaluation that we do within OPQ is strictly related to the bulk drug substance. Do we think about the formulation? Yes. There can be formulation considerations, but in terms of the evaluations that are presented to you today, our focus is on the BDS.

MS. BORMEL: Gail Bormel. I agree.

DR. REBELLO: We have a question online.

Dr. Gupta?

DR. GUPTA: Good morning. My name is Dr. Anita Gupta. This question is for Dr. Verthelyi's presentation on immunogenicity. My question is regarding the adjuvant reaction that

you had mentioned. You had mentioned that there might be a immune response to these adjuvants, and that there might be a physiological or immune response. Can you clarify exactly what kind of response that might demonstrate clinically in patients or individuals that might use these peptides?

DR. VERTHELYI: Any impurities that would activate the cells of the innate immune system -- and the cells are not only in our blood but are embedded in all of our tissues -- can lead to an increase in the efficacy or the efficiency with which these peptides are taken up by the cells and presented to what we call the professional antigen presenting cells. They present these antigens or these peptides to the lymphocytes in the immune system. That is critical to induce an immune response. That's what adjuvants do in vaccines. When we have a vaccine, for example, there is a peptide. We use something to alert the immune system that it needs to make a response. That's called an adjuvant. Impurities in peptides

can act in that same way, alerting the immune system that this is a substance that they need to make a response to.

Does that address your question?

DR. GUPTA: Yes. Thank you. You had mentioned that there was anaphylaxis in one of your slides. I was just looking to better understand, if individuals are taking these, what kind of response? Is it only anaphylaxis or are we looking at other kind of advanced responses in patients or individuals taking these peptides?

DR. VERTHELYI: There are different events that can happen if antibodies develop. Anaphylaxis is one type of adverse event. The development of antibodies can lead to loss of efficacy, can lead to antibodies that cross-react and that bind to similar structures that are endogenous. We're administering peptides that have a certain structure. That structure can emulate similar structures in the body of the patient, and if antibodies bind to those, it can alter their physiological function.

So if you were to develop antibodies to those, you could reduce their activity. If that activity is non-redundant, it's a unique activity, that could lead to a deficiency syndrome. All of a sudden, that patient cannot perform that function that they used to be able to do because they have antibodies that are neutralizing that capacity.

DR. GUPTA: Thank you.

DR. REBELLO: Are there any more questions for our presenters?

Dr. Kenneth Burman?

DR. BURMAN: Ken Burman; just a question. What are the requirements for biologic effectiveness for the specific disease entity or for physiology to show effectiveness in these regulations?

MS. BORMEL: Hi. This is Gail Bormel. For compounded drugs under the Act, there's no premarket review for safety, effectiveness, or quality. What we do as part of the bulk substances that are nominated for use by compounders under 503A, which are state licensed pharmacies, federal

facilities, or licensed physicians, is we bring those bulk drug substances to this committee, and we review the information that's been submitted, as well as conduct our own review of the literature. That's the type of information that we look at. There's no premarket review of these formulations or of these bulk substances.

DR. BURMAN: Thank you.

DR. REBELLO: Are there any more questions? Yes?

DR. BOGNER: Robin Bogner. If I were to purchase a peptide from two different companies, both of them being lyophilized peptides, and one company uses stabilizers and another company doesn't, are those two different bulk drug substances? I'm starting with two different things, one with peptide with perhaps sucrose or trehalose and the other without a stabilizer. Thank you.

MR. WESDYK: Without knowing more information, it would be hard to answer that question. But generally, I think the answer would

be no, unless there was some interaction between the stabilizer and the peptide that actually changed the structure of the active moiety.

MS. BOGNER: Thank you.

MR. WESDYK: You're welcome.

DR. REBELLO: Are there any more questions?

(No response.)

DR. REBELLO: We will now proceed with the FDA presentation on CJC-1295-related bulk drug substances from Drs. Marianne San Antonio and Mai Tu.

FDA Topic 1 Presentation

Marianne San Antonio

DR. SAN ANTONIO: Good morning. My name is Marianne San Antonio, and I'm a physician in the Office of New Drugs. Mai Tu is a Senior Pharmaceutical Scientist in the Office of Pharmaceutical Quality. We will discuss the evaluation for CJC-1295-related bulk drug substances for possible inclusion on the 503A Bulks List. I would like to recognize the entire evaluation team, as well as the contribution of

many other FDA colleagues who helped with this evaluation. Special thanks to the Division of General Endocrinology.

CJC-1295-related BDSs were nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act. CJC-1295-related BDSs were evaluated for the treatment of growth hormone deficiency. The proposed product route of administration is for a subcutaneous injection in a 2,000 microgram per milliliter concentration. The nominations were withdrawn, and FDA is evaluating the substances at its discretion.

We have evaluated publicly available data on the physical and chemical characterization, historical use in compounding, safety, and effectiveness of this substance. Next, my colleague from OPQ will speak about the physical and chemical characterization.

FDA Topic 1 Presentation

Mai Tu

DR. TU: Hello. Thank you, Marianne, for

the introductions. I would like to start with noting that there appears to be inconsistent naming conventions associated with CJC-1295-related BDSs. The CJC-1295-related BDSs are analogs of growth hormones releasing hormones, or the abbreviation is GHRH. There have been many modification to GHRH over time, and we believe that ConjuChem Biotechnologies may have developed CJC-1295 with drug affinity complex, or DAC originally.

DAC is a maleimidopropionamide-lysine, or MPA-lysine, unit added at the C terminus, which we refer to as CJC-1295 DAC free base in the memo; however, there are other modifications of CJC that may have been studied, including versions without the DAC complex, and we want to note that CJC-1295 are common names and not a USAN name, as discussed in the BDS compounding presentation by Russ. The common names do not follow the current systemic naming conventions and are being used for CJC-1295-related BDSs, as found in literature reports and other public sources.

It's not possible to know which compound or

structure is intended when referenced as common names, and the use of common names can be confusing and potentially cause medication errors. This represents a safety risk for patients, as they may be dosed with an incorrect medication compared to what the physician ordered, and it may also introduce error in chemical testing due to potentially inconsistent reference standards being used.

There is inconsistency in the material provided to us, and for this reason, we evaluated five BDSs within the scope of the nominations and literature due to significant safety concerns mentioned. For the purpose of this evaluation, we will refer to the five known CJC-1295-related BDSs as shown in the table, including CJC-1295 free base; CJC-1295 acetate; CJC-1295 DAC free base; CJC-1295 DAC acetate; and CJC-1295 DAC trifluoroacetate or TFA.

The five structures are distinct BDSs for the purpose of compounding, with unique chemical structures and physical chemical properties. The

five BDSs consist of two distinct active moieties, including CJC-1295 free base and CJC-1295 DAC free base. The information of UNII code and CAS number, if available, are summarized in the table, and the molecular weight and molecular formula are unique to each BDS. Supplier is available for the first BDS in the table.

Due to the common name being used, it's not clear which BDS is being nominated from the nomination package received, which was then withdrawn. The first nominator nominated CJC-1295 free base; however, the UNII code and the active moiety reference and clinical references refer to CJC-1295 DAC free base that is different from the nominated BDS. The CoA, CAS number, molecular weight, and molecular formula were not provided, and chemical name does not correspond to any of the CJC-1295-related BDSs being evaluated.

The second nominator nominated CJC-1295 acetate, and the CoA provided is for the same BDS; however, the UNII code and active moiety and clinical references referred to CJC-1295 DAC

free base that is different from the nominated BDS. The CAS number was a deleted CAS, and the molecular weight, molecular formula, and chemical name matched with CJC-1295 free base, and that is also different from the nominated BDS. The physical and chemical characterization is similar in all CJC-1295-related BDSs, and any difference will be discussed.

CJC-1295 acetate is acetate salt of CJC-1295 free base that is synthetic 29 amino acid of GHRH. Most of the properties are similar in all BDSs and any differences are pointed out below. The BDSs are supplied as white lypholized powder. CJC-1295 acetate is water soluble at 5 milligram per mL. There is no USP drug substance monograph for the BDSs.

In terms of stability and storage condition, manufacturer recommends long-term storage at 2 to 8 Celsius in fridge or freezer, and it would remain stable up to 3 years when stored at negative 20 Celsius. The peptide, in general, is sensitive to product formulations, process, and environmental

conditions, which might lead to aggregations and degradations. The potential impurities are peptide-related impurities and peptide synthesis process-related impurities such as starting materials, residual solvents, coupling reagents, activators, or catalysts. The potential for immunogenicity is similar in CJC-1295-related BDSs and was discussed in more detail in the presentation on immunogenicity by Daniela.

For CJC-1295 acetate, the CoA was provided from a nominator, and it included testing for peptide purity, largest single impurity less than 2 percent, but there is no information regarding the nature of individual impurities, aggregates, and bioburden or endotoxin levels. There's a lack of information on the potential of peptide aggregations, especially when formulated in an injectable dosage form for subcutaneous administration.

We conclude that CJC-1295 acetate is not well characterized due to the concern arising that inconsistent naming conventions exist for the BDS.

There is a lack of certain critical characterization data, including impurities, aggregates, or bacterial endotoxin level, a potential for immunogenicity when formally in an injectable dosage form for subcutaneous administration. We want to note that these concerns are also relevant for all CJC-related BDSs.

For CJC-1295 free base, it has limited solubility in water, soluble in 1 percent acetic acid, which makes it difficult to compound at the proposed solution concentration of 2 milligram per mL in water. For this BDS, there is no CoA provided in the nominations, and there's no information on impurity limits or testing results as critical attribute control in the CoA that's reported in public domain. We conclude that CJC-1295 free base is not well characterized. In addition to the reasons mentioned, CJC-1295 free base has limited water solubility, which makes it difficult to formulate in the proposed injectable dosage form.

For CJC-1295 DAC free base, it's CJC-1295 free base with the MPA-lysine unit added to the C terminus, and the BDS is soluble in water at 2 milligram per mL, which makes it feasible to compound at the proposed concentration. For this BDS, there's no CoA provided in the nominations, and the literature search shows that most of the CoAs for CJC-1295 DAC free base only contain purity testing result, and there's no impurity profile available. We conclude that CJC-1295 DAC free base is not well characterized.

And lastly, for CJC-1295 DAC acetate and CJC-1295 DAC TFA, a salt form of CJC-1295 DAC free base, we have not identified publicly available information for these BDSs, and it appears that there's no supplier for these two BDSs, which likely contributes to lack of data or any CoA available. So we also conclude that CJC-1295 DAC acetate and CJC-1295 DAC TFA are not well characterized due to the reason previously discussed.

Thank you for your attention. I will now

hand over to Marianne, who will walk us through the next section of our talk.

FDA Topic 1 Presentation

Marianne San Antonio

DR. SAN ANTONIO: Thank you, Mai.

Now, we will discuss the historical use of CJC-1295-related BDSs in compounding. The form of CJC-1295 discussed in the references used in this section is often unclear; therefore, the information will be considered for all forms of CJC-1295 as appropriate.

CJC-1295 with DAC appears to have first been identified in 2005 as part of a research program led by ConjuChem Biotechnology, in which derivatives of human GHRH were being developed in an attempt to overcome the short half-life of GHRH. Studies conducted in healthy human subjects were first published in 2006; however, ConjuChem withdrew CJC-1295 with DAC from clinical trials later that year.

CJC-1295 without DAC appears to have first been referenced in the literature in 2010 with the

identification of an unknown pharmaceutical preparation that was seized by Norwegian police and customs. There is evidence that there has been compounding with forms of CJC-1295 since at least 2018, but no studies were identified that discussed the use of a compounded formulation of CJC-1295.

An analysis of online discussion forums to identify trends in popularity of doping products found that CJC-1295 emerged as a topic of discussion after 2005, and the number of discussions regarding its use have continued to trend upward.

Additionally, there are reports of illicit use in professional sports. CJC-1295-related BDSs are marketed online for use in weight loss and muscle building, as well as an anti-aging peptide. It is unclear if any of the products are compounded. CJC-1295 is not recognized in the European or Japanese pharmacopoeias or in any of the national medical registries searched. In conclusion, the extent to which CJC-1295-related bulk drug substances have been used in compounding

is unclear. Currently, available data is too limited to understand the historical use for compounding.

Now, we will discuss the nonclinical safety of CJC-1295-related BDSs Like GHRH, CJC-1295 DAC acts as a growth hormone secretagogue or GHS. CJC-1295 DAC is more stable and has a longer half-life than GHRH, and researchers suggested that the DAC modification accounts for the greater stability of CJC-1295 DAC. In rats, a single subcutaneous injection of CJC-1295 DAC TFA increased plasma GH levels. After peaking at 30 minutes, plasma GH levels declined to baseline by 2 hours post-injection.

CJC-1295 DAC levels could still be measured up to 72 hours post-injection. Researchers suggested that the loss of the GH secretagogue activity in the presence of CJC-1295 DAC in the plasma could be due to CJC-1295 DAC-induced down regulation of GHRH receptors in the anterior pituitary gland, a decline in pituitary GH content and/or CJC-1295 DAC-induced activation of a

negative feedback loop regulated by somatostatin and the insulin like growth factor IGF-1. FDA did not identify pharmacological studies of CJC-1295 free base or CJC-1295 acetate.

Nonclinical studies of the acute toxicity of the unspecified form of CJC-1295 DAC showed that in rats, a single IV injection reduced food intake, increased soft mucoid stools, and decreased activity. In dogs, a single subcutaneous injection induced emesis and transiently decreased activity. In repeat-dose toxicity studies of the unspecified form of CJC-1295 DAC, rats were treated with IV doses and dogs were treated with subcutaneous doses for 14 days.

Safety signals included, but were not limited to, reduced food intake and water consumption; increased soft mucoid stools and decreased activity in rats; emesis and decreased activity in dogs; reduced hemoglobin at all tested doses in both species; increased levels of cholesterol in both species; and injection site irritation with evidence of inflammation,

hemorrhage, and minimal to mild necrosis in both species at all doses.

The genotoxic potential of CJC-1295 DAC unspecified form has been assessed through in vitro and in vivo experiments. These studies showed that exposure to CJC-1295 DAC unspecified form induced DNA damage in the pituitary cells. No embryofetal toxicity was observed in pregnant rats treated with subcutaneous CJC-1295 DAC unspecified form. FDA did not identify studies assessing potential effects of CJC-1295-related BDSs within a complete reproductive cycle and on peri- and postnatal development. FDA did not identify nonclinical, 2-year carcinogenicity studies of CJC-1295-related BDSs .

In conclusion, while CJC-1295 DAC-related substances act as GHSs, it is unknown if CJC-1295 free base and CJC-1295 acetate are pharmacologically active. Safety signals reported in nonclinical toxicological studies of CJC-1295 DAC unspecified form included, but were not limited to, local irritation signals characterized by

different degrees of hemorrhage, inflammation, and necrosis at the site of injection in rats and dogs, and genotoxicity signals characterized by DNA damage in vitro and in vivo.

Due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop due to overstimulation of somatotrophs by different forms of CJC-1295 DAC cannot be ruled out. There is a lack of nonclinical studies to inform safety considerations for potential clinical uses of CJC-1295 free base and CJC-1295 acetate.

Now, we will discuss clinical safety. There was no PK data for children or for adults with growth hormone deficiency. PK data in healthy adults was discussed in two articles. The articles do not clearly identify the form of CJC-1295-related BDS that was administered. It appears that both references refer to CJC-1295 DAC free base as the active moiety, but they do not specify a salt.

Teichman et al. describes two studies. The

first was a study in which subjects received either a placebo or a single subcutaneous injection of CJC-1295 DAC unspecified form. The second was a repeat-dose study in which participants received either placebo or 2 to 3 subcutaneous injections of CJC-1295 DAC unspecified form. In a study by Ionescu and Frohman, 12 healthy adult men received a single subcutaneous injection of CJC-1295 DAC unspecified form.

CJC-1295 DAC unspecified form had a half-life of up to 8 days, and drug concentration was measurable for 10 to 13 days after administration. Elevated serum GH and IGF-1 levels compared to baseline were measured after administration of the study substance. IGF-1 levels exceeded normal levels in subjects who received 250 microgram per kilogram dose.

A search of the FAERS database for reports of adverse events for CJC-1295-related BDSs retrieved two reports which were both excluded. A search of the CFSAN database retrieved no cases. In Study 1 by Teichman et al., 94 percent of

subjects reported an adverse event after a single injection. Injection site reactions occurred in approximately 70 percent of subjects receiving CJC-1295 DAC unspecified form and rarely in subjects receiving placebo. Reactions tended to be more severe and/or prolonged after higher doses. Headache, diarrhea, and systemic vasodilatory reactions were also observed.

In Study 2 by Teichman et al., injection site reactions were reported in all subjects who received CJC-1295 DAC unspecified form. Flushing; headache; nausea; abdominal pain; transient involuntary leg muscle contractions and some loss of coordination; transient dizziness and hypotension were also reported. In a study by Ionescu and Frohman, increased heart rate and transient redness and tenderness at the injection site were observed after a single dose of CJC-1295 DAC unspecified form.

Anecdotal reports of a phase 2 clinical trial of CJC-1295 DAC:GRF in subjects with HIV lipodystrophy were found via an internet search.

Subjects were randomized to receive once weekly injections of a 3-week escalating low or high dose of CJC-1295 DAC:GRF or a placebo, and then continue for 9 weeks. The report states that 2 hours after receiving an 11th weekly dose of CJC-1295 DAC:GRF, one subject complained of chest discomfort, and an ECG confirmed an acute myocardial infarction. The subject died approximately 1 hour later. The attending physician stated that the most likely explanation for the event was that the patient had asymptomatic coronary artery disease with plaque rupture and occlusion. The study was terminated, and the data from that study has not been published. No further information about the other study subjects or about adverse events was available.

Although two of the literature articles reviewed did not report major adverse events, these studies were in healthy adults, and most of the subjects only received one dose of CJC-1295 DAC unspecified form. Study authors reported that increased GH and IGF-1 levels were observed

following administration of CJC-1295 DAC unspecified form. There are known potential risks associated with elevated GH and IGF-1 levels, and these risks are included in all FDA-approved recombinant human growth hormone product labeling and are listed here. FDA has not identified data or information to suggest that the CJC-1295-related BDSs would not present similar risks.

Teichman et al. 2006 assessed the presence of antibodies to CJC-1295 DAC unspecified form in the PK study in healthy subjects, and stated that no significant antibody formation was detected in subjects who received the active study drug; however, the observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay, and the authors do not discuss this. Additionally, it is not known how this assay was validated, making it difficult to interpret the assay findings. Although the authors state that significant antibody formation was not observed, they do not specify whether there was no antibody formation, and this does not mean

that there is no risk for antibody formation because data for long-term repeated exposure is lacking.

In conclusion, the available clinical safety information is derived from studies conducted in healthy adults and anecdotal reports of exposure in subjects with HIV lipodystrophy. Injection site reactions were observed in the majority of subjects who received CJC-1295 DAC unspecified form. Other adverse events are listed here.

Although the authors of one study reported the lack of significant anti-CJC-1295 antibodies in subjects who received 1 to 3 doses of CJC-1295 DAC unspecified form, this does not mean that there is no risk for antibody formation because data for long-term repeated exposure is lacking. The CJC-1295-related BDSs are nominated to treat a chronic condition, but their long-term safety profile in humans is unknown, and there were no data to inform safety for the use in the pediatric population.

Next, we will discuss effectiveness. GHD is

a disorder characterized by inadequate secretion of GH from the pituitary gland. GHD onset can be congenital or acquired during childhood or adulthood. Some cases of GHD have no known cause or diagnosable cause. GHD can be complete or partial. Diagnosis of GHD is based on a combination of criteria, including signs, symptoms, and GH stimulation tests.

Multiple recombinant human growth hormone preparations are approved for children with growth failure due to inadequate secretion of endogenous GH and adults with GHD. In pediatric patients with open epiphysis, GH therapy is used to normalize annual growth velocity and final adult height. In adults with GHD, GH therapy offers benefits in body composition parameters, exercise capacity, and quality of life.

No articles discussed the effectiveness of CJC-1295-related BDSs in humans with growth hormone deficiency. Patients with GHD will most likely not respond to GHSs, including CJC-1295-related BDSs, unless these patients have partially preserved

pituitary function or partial GHD. Patients with complete GHD will not respond to GHSs. Studies conducted in humans were in healthy adults, and it is unclear which substance was used. These studies did not measure endpoints such as changes in body composition in adults or height velocity in children.

In Teichman et al. 2006 and Ionescu and Frohman 2006, the authors stated, "GH has also been used for therapy of disorders in children and adults in which pituitary function is either intact or only slightly impaired, or used in conditions with presumed functional GH deficiency." The authors hypothesized that CJC-1295 DAC unspecified form might be studied as an alternative to GH for conditions such as short stature associated with Prader-Willi syndrome; Turner syndrome; small for gestational age; and idiopathic short stature; or for treatment of HIV-associated lipodystrophy; wasting syndrome; and severe burns; however, there is no information concerning effectiveness to support use of subcutaneous CJC-1295-related BDSs

for the treatment of these conditions. An anecdotal report of a trial in humans with HIV lipodystrophy who received CJC-1295 DAC:GRF was reportedly stopped early after a subject who received CJC-1295 DAC:GRF died, and the data were not published.

In conclusion, there is no information concerning effectiveness to support use of subcutaneous CJC-1295-related BDSs for the treatment of GHD. Professional society guidelines do not discuss the use of CJC-1295-related BDSs for GHD, and there are FDA-approved therapies with established efficacy for GHD.

In summary, for physical and chemical characterization, the CJC-1295-related BDSs are not well characterized due to inconsistent naming conventions, lack of certain critical characterization data, and potential for immunogenicity in injectable dosage forms. For historical use in compounding, although CJC-1295-related BDSs have been compounded, the extent to which they have been used in compounding

and what they have been used for is often unclear. Currently available data is too limited to understand the historical use for compounding.

There are no peer-reviewed references with nonclinical or clinical data to assess safety and effectiveness of CJC-1295 free base or CJC-1295 acetate. Safety and effectiveness assessments discuss CJC-1295 DAC-related BDSs. The salt forms of the CJC-1295 DAC-related BDSs are not specified in the clinical references.

For nonclinical safety, while CJC-1295 DAC-related substances act as GHSs, nonclinical studies were not identified to establish whether CJC-1295 free base and CJC-1295 acetate are pharmacologically active. Safety signals induced by CJC-1295 DAC unspecified form included, but were not limited to, local irritation signals and genotoxicity signals characterized by DNA damage in pituitary cells. Due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop cannot be ruled out.

The available clinical safety information is derived from published studies conducted in healthy adults and anecdotal reports of exposure in subjects with HIV lipodystrophy. Adverse events, especially injection site reactions, were reported in almost all study participants who received CJC-1295 DAC unspecified form. CJC-1295-related BDSs are nominated to treat a chronic condition, but their long-term safety profile in humans is unknown. There were no data to inform safety for use in the pediatric population.

There is no information concerning effectiveness to support use of subcutaneous CJC-1295-related BDSs for the treatment of growth hormone deficiency. Professional society guidelines do not discuss the use of CJC-1295-related BDSs for GHD, and there are FDA-approved therapies with established efficacy for GHD.

After considering the information currently available, a balancing of the four evaluation criteria weighs against the following

CJC-1295-related BDSs being added to the 503A Bulks List: CJC-1295 free base; CJC-1295 acetate; CJC-1295 with drug affinity complex or DAC free base; CJC-1295 DAC acetate; and CJC-1295 DAC trifluoroacetate or TFA. Thank you. This concludes my presentation.

DR. REBELLO: Thank you, Drs. Tu and San Antonio.

We will now take clarifying questions to the 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.

Thank you.

Are there any clarifying questions for the presenters?

(No response.)

DR. REBELLO: Does anyone have questions for participating online?

(No response.)

Open Public Hearing

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

Both the FDA 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 the 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 the 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.

I would like to begin by calling speaker number 1 to the podium. Please state your name and any organization you're representing for the record, and you have four minutes.

MR. D. DeNEUI: Good morning. My name is Dan DeNeui. I'm the Chief Executive Officer of Evexias Health Solutions, which is a national network of over 10,000 medical providers, all representing many different disciplines of medicine. To be clear, we're all sitting here today because of a settlement offer made by the Department of Justice in response to a lawsuit filed against the FDA by our organization. The offer was made by the Department of Justice, as they quickly and correctly recognized the FDA's overreach, as well as their failure to follow their own guidelines by incorrectly categorizing certain peptides as too dangerous to compound.

My question is, based on what? Why are these 17 peptides suddenly too dangerous to compound? Do we have people suddenly dying because they are overdosing on AOD? Do we have a rapid

rise in hospitalizations because of the widespread use of ipamorelin or thymosin alpha 1? Are there centers for addiction for CJC-1295, and why now? Why now is the FDA further restricting?

(Pause.)

MR. DeNEUI: Can I start over?

My question is, based on what? Why are these 17 --

(Pause.)

MR. DeNEUI: I'd like to reclaim some time.

My question is based on what? Why are these 17 peptides suddenly too dangerous to compound, and why now? Why now is the FDA further restricting a medical practitioner's freedom to practice medicine with compounds he or she believes, based upon his or her own clinical training, would benefit a patient?

Medical providers practice the Hippocratic Oath, which is to first do no harm. Unfortunately, it would seem, especially in the case of compounded medication, the FDA is more concerned about protecting other interests rather than looking for

ways to help patients live happier, healthier lives. Let us not forget that every approved recalled drug was at one point deemed safe and effective by the FDA. Many times, the only difference between medicine and poison is the dose.

Many of the peptides that have been placed on Category 2 have been used successfully by thousands of our practitioners treating hundreds of thousands of patients who utilize these compounds to energize cellular function and give the body what it needs to help address sickness and disease, including obesity, diabetes, and addiction, especially when commercially available products have simply not worked.

The real-world result in the FDA's recent reclassification are that thousands of these patients have turned to the black market to obtain peptides. The black market includes fake online, completely unregulated pharmacies, as well as other pharmacies advertising that they are a research facility, many of whom provide little or no direction on how a patient should use a compound.

The agency's action now places patients into harm's way versus protecting patients' rights to a prescription provided by a medical practitioner through a licensed regulated compounding pharmacy. Is the FDA now practicing medicine? Is the FDA interfering with doctor-patient care? Is the FDA infringing upon medical practitioners' freedom to practice medicine, or is the FDA preventing patients from opportunities to get healthy?

This may be a good time to acknowledge that at no time in the history of our country have we ever spent more money on health care, and although we have spent trillions of dollars, our population is sicker and unhealthier than it has ever been. Conversely, pharmaceutical companies boast a $1.4 trillion net profit on an annual basis. Something seems drastically wrong with this picture, and this falls directly at the feet of the FDA.

During the last PCAC hearing, there were concerns about side effects that were reported from compounds, as well as a lack of monographs on some

of these compounds, which again makes me wonder, does this committee truly understand the value and even the rules around compounding? Our trade association, Alliance for Pharmacy Compounding, has offered to create the framework for adverse drug reporting; however, the FDA has yet, after two years, to act on any proposal. It should also be noted that our compounders do currently provide channels for patients and doctors to report adverse events, again, something that the committee seemed unaware of.

It really is no mystery why the citizens of this country are so sick and tired of being sick and tired. It is time for sick care to change to true health care in this country, and I am proud to do my part to make America healthy again. Thank you for your time.

DR. REBELLO: Thank you.

Speaker number 2, please state your name and the organization you're representing for the record. You have four minutes.

MR. LaVALLE: Jim LaValle, Chair of the

International Peptide Society, Co-Chair for the American Academy of Anti-Aging Medicine. On CJC acetate, the first step I wanted to make was that on the dosing, in all the clinical trials, they are drastically higher than what was seen clinically. From the hundreds of thousands of prescriptions that have been written from the 9 pharmacies that we surveyed, the dosing was typically at 100 micrograms once or twice a day. If you look at that on a 100-kilo person, it's drastically lower than the 25-milligram dose that was shown in the animal studies and some of the human studies.

Let's take a look here. I think that the characterization of CJC was well done by the presenter. What are the current uses for? How do we see it in the preventative side? It's more from the standpoint of looking to restore circadian growth hormone. As people age, yes, they make growth hormone; they don't release it. It can disrupt their sleep. It can lead to loss of muscle mass as they're aging.

Improving performance and recovery, I think it was well noted these cannot be used in any type of athletics where they're being tested; that is correct, and then, at least on clinical reporting from practitioners across -- I know Dan had mentioned thousands of practitioners, that people report getting improved sleep by restoring that circadian rhythm.

This is what we do at the International Peptide Society. We write monographs, and then we categorize what the level of evidence is for the studies that are available. For us, this is what we've currently categorized. There are 6 randomized-controlled trials reported: level 3, evidence obtained from the randomized control; level 4, evidence obtained without randomization; of course, levels 7 and 8 lower on the pecking order, evidence obtained from either laboratory animal studies or evidence obtained from opinions or reviews. We do regular education and certification for practitioners to fully notify them of what the dosing should be, as well as

provide all of the full-text studies for the practitioners. Our practitioners would include medical doctors; MDs; DOs; nurse practitioners; or the primary people that get educated through the International Peptide Society.

These were already characterized. I don't think I need to go over these again. Yes, there is CJC with DAC, and then CJC acetate, very accurately talked about earlier. When we looked, in this particular study, at the 30 and 60 microgram per kilogram, which is still a very high dose in relationship to what is actually prescribed clinically, safely well tolerated, particularly at those doses, and noted that we do not have long-term studies. I think that's the purpose of why the International Peptide Society is trying to educate, create a forum, as well as be able to collect data, so that we can see more and more how clinicians are utilizing these products in their practices clinically.

Most frequent adverse events, I think it was fairly well characterized, transient pain; swelling

or induration accompanied by some local urticaria; no serious adverse event reactions in either study reported; estimated half life of 6 to 8 days. I think the two data points that were shown.

DR. REBELLO: [Inaudible - 2:35:38].

MR. LaVALLE: Thank you.

DR. REBELLO: Speaker number 3, please state your name and any organization you're representing for the record. You have four minutes.

MR. WYNN: My name is Tom Wynn, and I'm a pharmacist at FarmaKeio, and I'm here today on behalf of all pharmacists to speak today about -- if you looked at the briefing documents, there was a lot of talk of uncontrolled processes going on in the pharmacies as far as how they manage these bulk substance when they get them in.

When we talk about a bulk powder, it can be an active pharmaceutical ingredient like an API, as they discussed before, and it can be an excipient preservative sweetener and allows us to compound certain entities without adding extra allergens, and that's sometimes what we are asked to do

because there's a reason why we're going to compound. It might be because they actually have an allergy to whatever is out there currently. Anything we're going to do that is going to be sterile has to be from an FDA registered facility, so we have to get the bulk powder from an FDA registered facility.

When we're reviewing the bulk powders, these are just a few things that we're going to look at. We first are going to be able to check if they're FDA registered by going to the FDA drug establishment list. We then can ask them if they've been inspected. We can also check on the FDA warning and see if possibly they have any warning letters showing any 483s or something of that nature that we may want to review that will give us a clue to some of their processes and what they're actually doing.

We do ask about cGMP practices. Although I may not be able to get SOPs from all of them, I will get a table of contents so I can at least review what their policies and procedures are,

getting an idea if they're actually following cGMP in their practices, and, again, FDA inspected. We want them to be FDA inspected, although with our current guidelines through United States Pharmacopoeia, it's only required that they be FDA registered, not inspected, although we want them to be inspected as well.

This is just an example, and I apologize that the name of the actual company's not on there because I wanted to make it large enough that you could see. But in the briefing documents, again, the FDA commented on some C of As that they got. This particular one was actually from Darmerica. It's one that they mentioned, and on here, you'll see that they do peptide purity. They are doing microbial limits, so they're looking at some bacterial bioburden and bacterial endotoxins.

We'll jump ahead. I had another one on there, again, showing similar items, and what I was getting at was the other one was going to be from Biopeptek. Both of those are FDA registered facilities, and they're both FDA inspected

facilities. So if the FDA has a problem with the C of As, then why don't they reach out to them and have them address that and put more information on there? They list the impurities, but they're right that they don't say specifically what those impurities are, but I think they would if they were asked to do so.

Manufacturers are submitting information, though, for the processes. When they say that they're uncontrolled and they don't know what they are, it's not necessarily true because they can't submit a drug master file. A drug master file is confidential detailed information about the facility's processes, articles used in manufacturing processes, packaging, and storing of human products. And I know some peptides have been submitted, not the ones we're looking at today, but they have submitted some GLP-1s. Some companies have submitted those to the FDA to review. So that doesn't mean that they've approved it or denied it; they just review it. But that gives them an idea of the process that these companies use to go ahead

and manage those peptides before they actually send them out to be utilized.

So my question is, why can't we go ahead, for any of the FDA registered and FDA inspected facilities, and say they have to submit a drug master file? Then you'd get all the information you want on the processing and what they do with these particular bulk powders.

Strategies with stability of peptides, I know there was some talk about that, too, and uncontrolled processes; usually you have buffers and pH modulators used to stabilize formulation --

DR. REBELLO: Your time is up.

MR. WYNN: Okay. Thank you very much.

DR. REBELLO: I would invite speaker number 4 to please [indiscernible - 2:40:01].

DR. T. DeNEUI: I'm Dr. Terri DeNeui. I'm a clinician with two clinics in the Dallas Fort Worth area. I'm representing myself and three other peers, all internal medicine, advanced endocrinology, and a pain management clinic. I'm going to present some real-world data. This is

from three internal medicine clinics. We had 508 patients, not prescriptions. Seventy-seven percent of these patients were on therapy for more than 6 months, and greater than 40 percent of them longer than a year. You can see the breakdown of age, gender, and ethnicity.

This is data from a large pain management clinic as well. They were using it primarily to get their opioid patients off opioids, and quite very successfully. There are a few clinical case studies at the end regarding that. If I don't get to it, it can be found in the public documents. But they were using it primarily because it mimics natural body signals for pain control.

It's not addictive; accelerated healing; promoted tissue regeneration in several cases and actually avoiding surgery in several cases; minimally invasive; very well tolerated, especially as compared to opioids and surgeries. The patients also had a bonus that they experienced better sleep and enhanced quality of life.

The primary diagnosis in these four clinics

we used for joint pain; sarcopenia, which is highly linked to increased morbidity and mortality in Americans, probably globally as well; fatigue; insomnia; unspecified bursitis; weight; and, of course, chronic pain syndromes. These are the primary uses in our internal medicine and pain management practices. The dosing regimen, as has already been noted, had much lower doses than some of the negative outcomes in the studies that were presented previously. I would go on record to say aspirin is lethal in the wrong dose, but we don't pull it off market. These doses were 100 micrograms subQ once a night in all these patients presented.

Now, I want to distinguish between side effects and adverse events because these are very different, and they are often interchanged incorrectly. This comes from the VA Center for Medication Safety and VHA Pharmacy Benefits Management. This was an advisory panel that wanted to note adverse events are unintended pharmacological events that occur when a medication

is administered correctly, while a side effect is a secondary unwanted effect. So that is a big distinction, and I'm noticing in several presentations they're used simultaneously.

In these patients' side effects and AEs, this was our process. These patients were followed up 2 to 4 weeks after therapy initiated. They got injection training for at-home use and, also, the pharmacies provided to the patients a QR code with a link to report any side effect or adverse event that the patient may experience. What we found, side effects reported, which, again, different from AEs, 19 percent of these patients presented with this flushing, this vasodilatory effect, within the first 10 minutes of injection, which resolved within 20 minutes or less. This is a common side effect. No action was taken in most cases, but two patients did stop the medication because of it.

There were three adverse events, so 0.006 percent of the patients being reported. Two patients reported itching. One patient had itching and subsequent anaphylactic response after several

months of using them. All patients stopped the medication. The anaphylactic patient did seek medical care in the emergency room. After investigation, it was deemed by the pharmacist and the clinicians taking care of the patient that there was a preservative that could mimic an egg allergy, and this patient had a severe egg allergy, and the outcomes were resolved and, of course, reported to the pharmacy.

These are two pain management cases. One was a 67-year-old female. She had three prior failed surgeries on her right shoulder and was using CJC-1295. In all of these case studies, it is the acetate form that was used, and she also was using BPC-157. The outcome for her and these patients, who were on these for greater than 6 months, avoided right shoulder reconstruction. Her pain was significantly reduced, which leads to a decrease in reliance on her pain medications, and she reported no side effects or adverse events.

DR. REBELLO: Thank you.

DR. T. DeNEUI: Thank you very much.

DR. REBELLO: I now invite speaker number 5 to the podium. Please state your name and any organization you're representing for the record. You have four minutes.

DR. ROSEBUSH: Sure. My name is Lee Rosebush. For the record, I'm a Doctor of Pharmacy, a PharmD, and I'm also a JD and represent the pharmacies inside that lawsuit against the agency. I apologize for the brevity of this. The reason why we have to go so fast today, if this was truly about patient safety, we'd actually have a true hearing from this, and we'd have more than 3 to 4 minutes each. That is basically what we were assigned from that perspective; hence, the brevity aspect of this.

What you're seeing here are the four standards or the four requirements that are actually supposed to be reviewed when it comes to putting these substances on. There was a question earlier related to the amount of data or efficacy that would be required for that. Notice there is not a standard for that. It's just simply supposed

to be that there's an efficacy aspect to this.

Don't take my word for it. Don't take the statute's word for it. You can take FDA's word for it because they've got their own regulation on it. This is the FDA's own regulation on what's required to get approval for the 503A Bulks List. Notice, there are four requirements. Notice also, you heard a whole lot about products, about immunogenicity and risks associated with that, and notice here, the only thing that's supposed to be talked about products is when something's about efficacy. Everything else is about the drug substance.

I would note that because if you actually look at the products that FDA has put on the 503 Bulks List through PCAC, there's never been an injectable product ever put on there. And notice it's not supposed to be based on the product's aspect of this; it's supposed to be based on the substance of these substances.

I've tried to give you a very quick history, a summary, as to each of these substances. I will

note, as was mentioned earlier, FDA does have a GSRS. NIH also has a PubChem. Both of the listings for CJC are on there. This CoA was not mentioned, if you noticed, in the presentation earlier. The reason being is the nominations were withdrawn. We weren't able to give a nomination associated with this, so this CoA has not been included. Do you notice in that perspective that you will see substances such as solvents included, things such as purity included, things such as the amino acid substances and sequences included on this? It is possible to figure out what these substances are, and it can be done.

Again, if there really was truly a concern about these products, it would be simply just release a guidance document as to what's needed for the APIs. These are FDA standards. Yes, these are for approved products. Yes, these could also be required to be done for compounded products. And in fact, these products which you have not heard, and FDA conveniently left out, and which is included in their deck, these have been made by

outsourcing facilities.

For those that don't know, CJC was made by a 503B. It was made under the cGMP criteria, which includes a cGMP criteria for these substances. For those that want to worry about adverse events, you will see there was one adverse event reported to this. 503Bs are required to report their adverse events to FDA; hence, there was one. I would also note that FDA inspected that 503B facility in the same year that these were reported being made. FDA did not issue any type of citation or warning, or observation in their 483, associated with these products.

Real quickly, if you can go to the history, and I'll be done, the reason why I'm going to this, has it been historically used? You will see there's been over 450,000 prescriptions dispensed for this out of pharmacies. That's not including the 503B, which is on top of that. The estimated is over a million doses of prescriptions of this have been made historically from that perspective. If this is removed, you are taking away physicians'

use of this for over 1 million times.

I would also note -- and you heard this at the presentations at the very beginning -- there is no expanded access potential program for this because there's no ongoing study for that, so it's irrelevant. The other thing that is here is from an IND. FDA has reviewed CJC for an IND. In fact, it's listed on clinicaltrials.gov. One of the reviews for INDs, as was noted earlier, is safety. So if this product is too unsafe to be used now, that means FDA when it put forward its IND put forward a product that was too unsafe to be studied at that point as well. If it was ok to be studied at that point, it should be allowed to be used now as well.

Here is the actual data that is used from FDA's own materials. I would also point out, as you just heard, real-world evidence in this perspective has been used to be approved.

DR. REBELLO: [Inaudible - 2:49:24].

DR. ROSEBUSH: I will note real quick, Charlie Ganley last time read what is real-world

evidence and accepted by the FDA. We made sure --

DR. REBELLO: Thank you. We're at time.

DR. ROSEBUSH: -- on that last slide real-world evidence was met what Charlie Ganley read. Thanks.

Committee Discussion and Vote

DR. REBELLO: The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

The committee now will 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 question 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 first question, which is a voting question. We'll 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've entered your vote. Please press the button firmly that corresponds to your vote. If you're 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'll continue in the same manner until all questions have been answered or discussed.

Are there any issues or questions from the panel about the wording of the voting question? The question is, Section 503A Bulk Drug Substances List, CJC-1295-related bulk drug substances. FDA's evaluation addressed five CJC-1295-related bulk

drug substances, which include two active moieties, CJC-1295 free base and CJC-1295 DAC free base, and five different BDSs. FDA proposes to use a single voting question to address them as a group.

Do committee members agree to use a single vote to address the group of CJC-1295-related bulk drug substances discussed today? Yes or no? If any member of the committee votes no, the FDA will take separate votes on each of these substances. If voting yes, the committee members will vote on the substance as a group and will proceed to answer one additional voting question. If voting no, committee members will vote on each of the substances separately and will proceed to answer five additional voting questions.

Are there any issues or questions from the panel about the wording of the voting questions?

(No response.)

DR. REBELLO: Does anyone online have any questions regarding the voting?

(No response.)

DR. REBELLO: 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've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Good morning. Takyiah speaking, DFO. For the record, there are 12 yeses, 1 no, and 0 abstentions. Thank you.

DR. REBELLO: Now that the vote is complete, we'll go around the table and have everyone who voted state their name and vote into the record.

DR. DURHAM: Todd Durham. I voted yes.

DR. VAIDA: Hi. Allen Vaida. I voted yes.

DR. BOGNER: Robin Bogner. I voted yes.

DR. SERUMAGA: Brian Serumaga. I voted yes.

DR. REBELLO: Elizabeth Rebello. I voted

yes.

DR. GURA: Kathleen Gura. I voted yes.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted yes.

DR. BURMAN: Ken Burman, I voted yes.

DR. JENSEN: Kirk Jensen. Yes.

DR. REBELLO: For the panel members that are online who voted for this session, Dr. Gulur, please state your name and your vote for the record.

DR. GULUR: Padma Gulur. I voted yes.

DR. STEVENSON: Dr. Gulur, Takyiah speaking. You may be muted. Please state your name and your vote for the record.

DR. GULUR: I've unmuted myself. Are you able to hear me? Hello?

DR. REBELLO: I can hear you, Dr. Gulur.

DR. GULUR: Thank you. Yes. Padma Gulur, and I voted yes.

DR. STEVENSON: One moment, please.

(Pause.)

DR. STEVENSON: Continuing on to Dr. Gupta, please state your name and your vote for the record.

DR. GUPTA: Dr. Anita Gupta, and I voted yes.

DR. STEVENSON: For the people who are in the room, I believe the public can hear those who are speaking. One moment, please.

(Pause.)

DR. STEVENSON: Hi. Takyiah speaking. I do apologize for the audio issues inside the room. I do believe that the audience outside the room can hear what the virtual panel members are saying. I'm sorry. I'm hearing an echo inside the room. We will continue to Dr. David Cooke. Please state your name and your vote for the record.

DR. COOKE: David Cooke. I voted yes.

DR. STEVENSON: Great. Thank you so much.

DR. REBELLO: Since one or more panel members voted no, we will proceed with questions 1B through 1F.

Section 503A Bulk Drug Substances List,

CJC-1295-related bulk drug substances. FDA is proposing that CJC-1295 free base not be included on the 503A Bulks List. Should CJC-1295 free base be placed on the list? If voting yes, you're recommending FDA should place CJC-1295 free base on the 503A Bulks List. If voting no, you're recommending FDA should not place CJC-1295 on the 503A Bulks List.

Are there any questions or issues from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: If voting yes, you're recommending FDA should place CJC-1295 free base on the 503A Bulks List. If you vote no, you're recommending FDA should not place the bulk drug substances on the 503A Bulks List. If substances are 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 National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

DR. STEVENSON: Oh. Dr. Burman has a question.

DR. BURMAN: I'm sorry. Maybe it's just me, but that's different from what the question says in part B. Part b says FDA is proposing free base not be included on the bulk list.

DR. REBELLO: Question 1B is, FDA is proposing that CJC-1295 free base not be included. So if you're voting yes, you're recommending FDA --

DR. BURMAN: Not include it.

DR. REBELLO: -- that's correct, yes. So we need to change that.

MS. BORMEL: No, it's correct as written. The question is, should CJC-1295 free base be placed on the list? So if you vote yes, you're recommending it should be placed on the list.

DR. REBELLO: When we read the question here, it says not.

MS. BORMEL: Right. This is Gail Bormel.

We give the recommendation of FDA first. That's just what we are recommending. But because there's a lot of confusion when there are negatives in a question, we then go ahead and ask the question, are you recommending that FDA place CJC-1295 on the bulks list? If yes, that's what you're recommending. If you're saying no, then you're recommending it not be placed on the list. You have to read the question separate from our recommendation.

DR. REBELLO: Got it. Thank you for the clarification.

Are there any further questions regarding the vote?

(No response.)

DR. REBELLO: 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. As a reminder, if you are unsure of your vote or 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 0 yeses, 13 noes, and 0 abstentions. Thank you. I'll hand it back to the chairperson.

DR. REBELLO: Now that the vote is complete, we'll 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. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no. It just seemed like there really wasn't enough evidence to prove it.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted no.

DR. BURMAN: Ken Burman. I voted no.

DR. JENSEN: Kirk Jensen. No.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke. I voted no.

DR. REBELLO: Thank you.

We will proceed with Question 1C. Question 1C, Section 503A Bulk Drug Substances List, CJC-1295-related bulk drug substances. FDA is proposing that CJC-1295 acetate not be included on the 503A Bulk Drugs List. The question is, should CJC-1295 acetate be placed on the list? If voting yes, you're recommending that FDA should place CJC-1295 on the 503A Bulks List. If voting no, you recommend that FDA should not place CJC-1295 acetate 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 a subject of an applicable USP, or National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: 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. As a reminder, if you're unsure of your vote or 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 is 1 yes, 12 noes, and 0 abstentions. Thank you. I'll hand it back to the chairperson.

DR. REBELLO: 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, you can state the reason why you voted as you did into the record.

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted yes.

DR. FENSKY: Tim Fensky. I voted no.

DR. BURMAN: Ken Burman. I voted no.

DR. JENSEN: Kirk Jensen. No.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke. I voted no.

DR. REBELLO: Thank you.

We will proceed with Question 1D. Question 1D, Section 503A Bulk Drug Substances List, CJC-1295-related bulk drug substances. FDA is proposing that CJC-1295 DAC free base not be included on the 503A Bulks List. The question is, should CJC-1295 DAC free base be placed on the list? If voting yes, you're recommending FDA should place CJC-1295 DAC on the 503A Bulks List. If voting no, you're recommending FDA should not place CJC-1295 DAC 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 National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: 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.

(Voting.)

DR. STEVENSON: Takyiah speaking, DFO. For the record, there are 0 yeses, 13 noes, and 0 abstentions. Thank you. I'll hand it back to the chairperson.

DR. REBELLO: Now that the voting is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, I encourage you to state the reason why you voted as you did into the record.

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted no.

DR. BURMAN: Ken Burman. I voted no.

DR. JENSEN: Kirk Jensen. No.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke. I voted no.

DR. REBELLO: Thank you.

We will proceed with Question 1E. Question 1E, Section 503A Bulk Drug Substances List, CJC-1295-related bulk drug substances. FDA is proposing that CJC-1295 DAC acetate not be included on the 503A Bulks List. The question at hand is, should CJC-1295 DAC acetate be placed on the list? If voting yes, you're recommending FDA should place CJC-1295 acetate on the 503A Bulks List. If you're voting no, you're recommending FDA should not place CJC-1295 DAC acetate on the 503A Bulks List.

If the substance is not on the list when the final rules are promulgated, compounders may not

use a drug for compounding under Section 503A unless it becomes a subject of an applicable USP, or National Formulary monograph, or a component of an FDA-approved drug.

Are there any questions or issues from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: 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.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 0 yeses, 13 noes, and 0 abstentions.

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

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: [Inaudible - 3:14:17]

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted no.

DR. BURMAN: Ken Burman. I voted no.

DR. JENSEN: Kirk Jensen. No.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke. I voted no.

DR. REBELLO: Thank you.

We will now proceed with Question 1F. Question 1F, Section 503A Bulk Drug Substances List, CJC-1295-related bulk drug substances. FDA is proposing that CJC-1295 DAC trifluoroacetate not

be included on the 503A Bulks List. The question at hand is, should CJC-1295 DAC trifluoroacetate be placed on the list? If voting yes, you're recommending FDA should place CJC-1295 DAC trifluoroacetate on the 503A Bulks List. If you're voting no, you're recommending FDA should not place CJC-1295 DAC trifluoroacetate on the 503A Bulks List.

If the substance is not on the list when the final rule is promulgated, compounders may not use a drug for compounding under Section 503A unless it becomes the subject of an applicable USP, or National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: 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.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 0 yeses, 13 noes, and 0 abstentions. Thank you.

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

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted no.

DR. BURMAN: Ken Burman. I voted no.

DR. JENSEN: Kirk Jensen. No.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Cooke?

DR. COOKE: David Cooke. I voted no.

Adjournment

DR. REBELLO: Thank you, everyone.

We will now take a quick 10-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will reconvene at 11:00 Eastern Time for the AOD-9604-related bulk drug substances topic. Thank you.

(Whereupon, at 10:49 a.m., the topic 1 session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

AOD-9604-RELATED BULK DRUG SUBSTANCES

(AOD-9604 ACETATE AND AOD-9604 FREE BASE)

Morning Session

Topic 2

Wednesday, December 4, 2024

11:00 a.m. to 12:12 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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(AOD-9604-related BDSs Topic Only)

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OPQAII, OPQ, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(11:00 a.m.)

Call to Order

Introduction of Committee

DR. REBELLO: Good morning, everyone. Thank you for resuming your seats. Before we begin the AOD-964-related bulk drug substance session, panel members who will be in this topic will introduce themselves by stating their names and affiliation. We'll begin with Dr. Billington.

DR. BILLINGTON: Good morning. Charles Billington. I'm Chief of Endocrinology and Metabolism at the Minneapolis VA Health Care System and Director of Obesity Programs at the University of Minnesota and the Minneapolis VA Health Care Systems.

DR. REBELLO: Dr. Yanovski?

DR. YANOVSKI: Susan Yanovski. I am Co-Director of the Office of Obesity Research at the National Institute of Diabetes and Digestive and Kidney Disease.

DR. REBELLO: Thank you.

We will now proceed with the FDA presentation on AOD-9604-related bulk drug substances from Dr. Emily Kneeream and Bini Mathew.

FDA Topic 2 Presentation

Emily Kneeream

DR. KNEEREAM: Good morning. My name is Emily Kneeream. I'm a Clinical Analyst with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting AOD-9604-related bulk drug substances with my colleague, Bini Mathew, from the Office of Pharmaceutical Quality. I would like to recognize the evaluation team, as well as the contributions of many other FDA colleagues. Our special thanks to the Division of Diabetes, Lipid Disorders, and Obesity in OND.

AOD-9604-related bulk drug substances were nominated for inclusion on the 503A Bulks List. The nominations provided inconsistent information regarding the specific BDS proposed: AOD-9604 free base or AOD-9604 acetate. Later in our presentation, these different forms will be

presented in detail. These are being evaluated for the treatment of obesity.

The proposed products were oral capsule, subcutaneous injection, and transdermal topical cream. The nominations were withdrawn; however, due to safety concerns, which will be later explained, FDA is evaluating the substances at its discretion.

We have evaluated publicly available data on the physical and chemical characteristics, historical use, effectiveness, and safety in the compounding of these substances.

I will now turn it over to Bini to discuss physical and chemical characterizations of AOD-9604-related substances.

FDA Topic 2 Presentation

Bini Mathew

DR. MATHEW: Thanks, Emily.

As Emily mentioned, there are two AOD-9604-related BDSs conflated within the two nomination packages. They are AOD-9604 free base and AOD-9604 acetate. This table highlights the

differences between these two forms. UNII code and CAS numbers are only available for AOD-9604 free base. Molecular formula, molecular weight, and chemical structure are unique for each BDS; however, the active moiety is the same for both BDS, which is AOD-9604 free base.

This table highlights the detailed information submitted by the two nominators with the relevant information identified by the FDA. These nominations were later withdrawn. The first nominator nominated AOD-96O4. The UNII code is not provided. The certificate of analysis is provided for AOD-9604. CAS number, molecular formula, molecular weight, and chemical name provided in the nomination package or certificate of analysis matched with the free base form. All this information referred to the same BDS.

On the other hand, we noticed inconsistent information in the second nomination package. AOD-9604 was nominated; however, certificate of analysis accompanied with the nomination package was for AOD-9604 acetate, which is not the same

nominated BDS. UNII code, CAS number, molecular formula, molecular weight, and chemical name provided in the nomination package or certificate of analysis matched with the free base form.

Since AOD-9604 free base and AOD-9604 acetate are two distinct BDSs, we evaluated both forms individually due to the safety concern. I will start with AOD-9604 free base. It is a hexadecapeptide. Tyrosine is linked at the N-terminal end of 15 amino acids fragment of human growth hormone. Two cysteine amino acids are cyclized to form a disulfide bridge, which may lead to peptide degradation.

AOD-9604 free base is reported as a white solid powder, and it is soluble in water up to 2 milligram in 1 mL water. There is no USP drug substance monogram for AOD-9604 free base. It is recommended to store in a dry place to protect against water and moisture. It should be stored in closed containers and stable for three years at minus 18 degrees centigrade, 1 year at 0 to 7°degrees centigrade, and 6 months at

7 to 30°centigrade. In general, peptides are sensitive to product formulation, process, and environment conditions, which may lead to aggregation and degradation.

There is potential for impurities present in AOD-9604 free base, such as peptide-related degradation impurities and peptide synthesis process-related impurities; for example, starting materials, residual solvents, coupling reagents, activators, or catalysts. There is a potential for immunogenicity risk when formulated in an injectable dosage form.

The CoA included tests such as appearance; solubility; identification; peptide purity; water content; and assay. Testing results for the control on impurities, aggregates, bioburden, and bacterial endotoxins were not included. In addition, these nominators proposed other dosage forms such as transdermal cream and oral capsule; however, critical attributes associated with these dosage forms were not included in the submitted CoA.

Here, we conclude that AOD-9604 free base is not well characterized due to lack of certain critical characterization data specific to AOD-9604 free base; potential immunogenicity risk when formulated in an injectable dosage form for subcutaneous administration; and lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream and oral capsule.

AOD-9604 acetate is the acetate salt of AOD-9604. Similar to AOD-96O4 free base, the disulfide bond between the two cystine amino acids of AOD-9604 acetate may also lead to degradation. It is reported as a white solid powder, and its solubility in water is very similar to its free base form. It has no USP drug substance monograph.

The acetate salt form is recommended to store in a sealed container at 2 to 8 degrees centigrade for less than 6 months storage and at minus 20 degrees for more than 6 months storage. As similar to its free base form, AOD-9604 acetate

may lead to aggregation and degradation. Potential impurities can be present, including peptide-related degradation impurities and peptide synthesis process-related impurities.

As similar to its free base form, there is a potential for immunogenicity risk associated with AOD-9604 acetate. The submitted CoA controls several attributes, including related substance. Largest single impurity is controlled at less than or equal to 1 percentage and total impurities at less than or equal to 2 percentage; however, the nature of the individual impurities that can be present at less than or equal to 1 percentage is not provided. All other information is similar to AOD-9604 free base.

In conclusion, AOD-9604 acetate is not well characterized due to the reasons previously discussed for the free base form.

I conclude my presentation here on the first evaluation criteria, which is physical and chemical characterization. Thank you. I will hand over to Emily.

FDA Topic 2 Presentation

Emily Kneeream

DR. KNEEREAM: Thank you, Bini.

The nonclinical and clinical references reviewed do not clearly identify whether the substance discussed is the salt formulation or the free base; therefore, in the next sections, the substance will generally be referred to as AOD-9604.

Here's what we found on historical use in compounding. AOD-9604 was first developed and patented by Metabolic Pharmaceuticals in the late 1990s in Australia for use in obesity. Based on outsourcing facility reports, none reported compounding any product containing AOD-9604. The extent to which it has been used in compounding is unclear; however, it has been widely advertised by medical spas and wellness clinics. One clinic indicated that "peptides are prepared and delivered to your doorstep."

These are marketed online for various uses listed here and in combination with other APIs as

injectables and oral formulations, and have been used in sports as a doping agent. These substances are not recognized in the national medical registries or other foreign pharmacopoeias. In conclusion, there is some evidence of compounded AOD-9604s used. Compounders have prepared injectable and oral formulations for a variety of uses, and they are marketed by medical spas and wellness clinics.

Now, I'll discuss pharmacology and PK information. Based on nonclinical data, AOD-9604 decreases lipogenesis and increases lipolysis in obese rodents. In studies in obese rats and mice, authors noted a decrease in weight gain. It has no effect on plasma glucose or insulin levels or glucose oxidation in rats and mice. The mechanism of action is unknown but unlikely to involve growth hormone receptors.

Based on nonclinical information, in vitro study found AOD-9604 was no longer detected after a 1-hour incubation in human serum. An in vivo study in pigs, IV had a half-life of 3 minutes and oral

had high bioavailability. FDA did not identify clinical studies in humans assessing pharmacokinetics.

I'll now provide a brief overview of obesity. This is a chronic condition that increases the risk for heart disease, diabetes, and cancer. Diagnosis is based on medical history and a high BMI. Treatment may involve the various FDA-approved options as listed on this slide.

I will now present studies on effectiveness for obesity. Wilding described three studies comparing AOD-9604 with placebo. These were part of the drug development by Metabolic Pharma in adults with obesity. One study was via IV route once weekly for 4 weeks in 23 subjects; another was via oral route once weekly for 4 weeks in 16 subjects; and the third study, route and dosing were not specified but administered for 1 week in 36 subjects. In all studies, authors noted AOD-9604 did not show statistically significant weight loss compared to placebo. Study limitations include insufficient details about methodology and

study results, a small sample size, and unclear study parameters.

Herd was an abstract on a study in 300 adults with obesity who received oral AOD-9604 or placebo for 12 weeks. Authors state weight loss over 12 weeks was greater with AOD-9604 than placebo with a non-linear dose response. We note this claim is based on small differences between groups, and interpretation of the study is limited by the minimal data in the abstract, insufficient details about the study methodology, and their results.

Next will be the OPTIONS study. It is important to note this was conducted by Metabolic Pharma during drug development for AOD-9604 for the treatment of obesity. A double-blind, placebo-controlled study in 502 adults with obesity received oral AOD-9604 or placebo once daily for 24 weeks along with a diet and exercise program. Primary efficacy endpoints included weight loss after 12 weeks. Study results reported no significant difference in weight loss between

placebo and AOD-9604. Per the company, weight loss compared to placebo was too low to reach statistical significance.

Continuing with the OPTIONS study, in 2007, the study summary and results were publicly announced by Metabolic Pharma, "The phase 2B trial results for its drug, AOD-9604, do not support the commercial viability of the drug as a treatment for obesity. Development of the drug for this condition is terminated." We did not find details of the study design and preliminary efficacy results in the published medical literature.

In conclusion, in most of the studies we identified, AOD-9604 failed to show benefit for weight reduction when compared to placebo. Drug development was terminated for obesity because of a failed study; therefore, there is a lack of evidence to support effectiveness for the treatment of obesity. There are multiple FDA-approved drug products for use in weight reduction in patients with obesity.

We will now switch gears to discuss safety.

For nonclinical safety, Moré and Kenley summarized three toxicity studies with AOD-9604. A 4-week study in rats via IV showed decreased weight gain, thymus mass, and thymic cortical width. A 6-month study in rats via oral route showed decreased lymphocytic count, decreased osteocalcin levels at week 13, and increased at week 26 in females; and increased creatinine and triglycerides in males. A 9-month study in monkeys showed vacuolation in hepatocytes. Note that the publication does not provide the underlying data; therefore, it is difficult to interpret the author's conclusions.

In conclusion for nonclinical safety, the molecular target and the mechanism of action underlying the pharmacological effects remain unknown, making it difficult to assess the biologic plausibility of the pharmacological effects reported in the different studies. Findings suggest that clinically relevant safety signals may develop with systemic exposures. Nonclinical studies available at the time of the evaluation were too limited to inform safety considerations

for the potential clinical uses of AOD-9604.

The FAERS and CAERS retrieved no adverse events.

For clinical safety, Stier et al. presented a summary of IV and oral AOD-9604 in six placebo-controlled studies. Safety monitoring included interview of subjects for AEs; measurement of vital signs; laboratory parameters, ECG; anti-AOD-9604 antibodies in the blood and serum levels of IGF-1. It is important to note these studies were funded by Metabolic Pharma.

For the IV route, there were two studies in a total of 38 subjects given single doses of AOD-9604 and/or placebo. Reported were 3 AEs severe in intensity, feeling of tightness in chest deemed possibly related to AOD-9604 per authors; and 2 AEs in the placebo group with no additional details provided. AEs most reported included hypoglycemia; headache; euphoria; fatigue; dizziness; nasal pharyngitis; and cough. Authors concluded the safety profile of AOD-9604 was comparable in all treatment groups.

Continuing with Stier, for the oral route, in four studies, patients received AOD-9604 for up to 24 weeks. Serious AEs reported in subjects receiving AOD-9604 include the following: after single doses, diarrhea and pneumonia were reported; diarrhea was deemed possibly related to the substance. In a 12-week study, basal cell carcinoma, moderate lipoma, and other cancers, per authors, not related to the substance In a 24-week study, distribution of SAEs were similar among the groups with no details provided. Other AEs reported are listed here. Authors concluded safety profile of AOD-9604 was comparable in all treatment groups.

Stier noted that for all studies, no statistically significant changes in laboratory parameters, ECG changes, or vital signs in any treatment group; no statistically significant differences in IGF-1 levels among the treatment and placebo groups. Anti-AOD-9604 antibodies were not detected in the selected patients who received oral doses for up to 24 weeks. We note the limitations

of the study include lack of sufficient details such as detailed description and breakdowns of AEs, intervention and outcome, and/or a short-term study duration.

For these substances, an additional safety concern is immunogenicity. The AOD-9604s consist of 16 amino acids. Peptides may elicit an immune response. This response may be enhanced when peptides are given via the subcutaneous route. They pose a risk for immunogenicity, potentially amplified by aggregation, as well as potential peptide-related impurities. The nomination did not include, and FDA did not identify, information about these substances to suggest that they do not present these risks.

To conclude on safety, based on available studies in humans on oral AOD-9604, serious AEs include diarrhea, chest tightening, and various types of cancers. FDA did not find information on the proposed subcutaneous and transdermal use in humans. Obesity is a chronic condition which may need long-term repeated treatments. There is

insufficient information to support the long-term use in these patients. There is limited information to assess immunogenic safety risk for oral administration and no information on subcutaneous and transdermal topical routes. These are peptides containing 16 amino acids, and sequences of this length have the potential to be immunogenic. There are multiple currently available FDA-approved drug products indicated for weight reduction in patients with obesity.

On balance, physiochemical characterizations, information on historical use, lack of evidence of effectiveness, and safety information weigh against both AOD-9604 free base and AOD-9604 acetate being added to the 503A Bulks List. Although available data suggest that these substances have historically been used in compounding, FDA's proposal is based on lack of data related to physical and chemical characterization, concerns related to potential immunogenicity risk, lack of evidence of effectiveness for use in obesity, and insufficient

safety information.

The lack of evidence of effectiveness and limited safety data and the existence of FDA-approved drugs for use in obesity, particularly in light of the fact that obesity increases the risk for many serious diseases and health conditions, weigh against these BDSs being added to the 503A Bulks List.

After considering the information currently available, a balancing of the criteria weighs against AOD-9604 free base and AOD-9604 acetate being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

Clarifying Questions from the Committee

DR. REBELLO: Thank you, Drs. Kneeream and Mathew.

We will now take clarifying questions to the 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.

Are there any clarifying questions for the

presenters?

Dr. Billington?

DR. BILLINGTON: I have a couple. For Dr. Mathew, I think you pointed out that for the acetate form, the drug should be kept frozen and specific criteria for how to be frozen and such. But when the drug is going to be made up for use, it's going to have to not be frozen. So once that happens, how long does it last? Do we have any information at all?

You provided some evidence that said, in serum, it's gone right away, and in the bloodstream, we have nothing, no pharmacology, nothing. So we don't know if this drug exists at all in the body once we give it. Am I right?

DR. MATHEW: Actually, we know the storage condition, that for 6 months of storage, actually it is 2 to 8 degrees centigrade, and for more than 6 months storage, it is minus 20 degrees centigrade, so we don't have much information on that.

DR. BILLINGTON: Right. So once we bring it

out of storage and make it up into a --

DR. MATHEW: No, we don't have --

DR. BILLINGTON: -- form to be given to a person, we don't know what happens to it.

DR. MATHEW: No, we don't have much information on that.

DR. BILLINGTON: And it might well all be gone, based on what we know, which is interesting.

Now, for Dr. Kneeream, my question was about the mechanism of action. In the briefing document, it mentions, first of all, that this material, AOD, was intended to be looking like the active part of growth hormone, but if I read the document correctly, the evidence is that it doesn't bind to growth hormone receptor, and it doesn't increase IGF-1, which would suggest that it's not doing anything in the growth hormone line, which you properly concluded in your slide.

So here we have a drug, a peptide, that was created, thinking it was going to work like growth hormone, but it doesn't do what growth hormone normally does, except that it has these effects on

lipolysis, which now seem to happen for a drug that we don't know how long it lasts, for no reason that we know of. Am I characterizing this fairly accurately?

DR. KNEEREAM: Everything you said was correct, yes, to our understanding.

DR. BILLINGTON: Alright. Well, I guess I have nothing further to say.

DR. REBELLO: Thank you.

We have a question from Dr. Yanovski.

DR. YANOVSKI: Yes. Thank you. Thank you for very clear presentations. I think the data on efficacy, or lack of efficacy, are very clear. I did notice that in the rodent model, the weight loss was thought to be, at least in part, due to beta adrenergic signaling. But am I correct that even though they measured vital signs in patients in the clinical trial, they didn't provide any data about changes in pulse or blood blood pressure? This would be something we'd be particularly concerned about in patients with obesity.

DR. KNEEREAM: This is Dr. Kneeream. If I

understand your question, you're asking if we saw any measures of blood pressure in any of our clinical studies? We did not.

DR. YANOVSKI: They said no changes in vital signs, but they didn't report the actual data.

DR. KNEEREAM: Correct. We don't have the raw data from any of the studies.

DR. YANOVSKI: That would be a concern. Thank you.

DR. KNEEREAM: Thank you.

DR. REBELLO: Are there any further clarifying questions for the presenters?

(No response.)

Open Public Hearing

DR. REBELLO: Being none, we will now begin with 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, financial information may be the payment by the 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 the 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.

We have six speakers, and I invite speaker number 1 to the podium. Please state your name and any organization that you are representing for the record. You have three minutes.

MR. D. DeNEUI: Good morning. My name is Dan DeNeui. I'm the Chief Executive Officer of Evexias Health Solutions, which is a national network of over 10,000 medical providers, all representing many different disciplines of

medicine. In reviewing the recording from the last PCAC session, I was a bit taken aback by the lack of understanding of what compounding is and what it does, and how it is so vitally beneficial to our patients, and an intricate part of our healthcare system. During our last PCAC session, we continued to bring up this evidence; real-world evidence continued to be mentioned in the last session. Allow me to read just one real-world testimonial submitted by one of our patients.

"In September 2022, our world stopped with a single devastating phone call from my daughter's school. Just shy of her 11th birthday, she had endured a harrowing 4 and a half minute seizure in class, leaving us in a storm of fear and uncertainty. We stood on the precipice of a new reality, grappling with the unknowns of her health and the long-term implications of that terrifying moment.

"After months of tests, she was finally diagnosed with Rolandic epilepsy and was told that that was the good kind of epilepsy; however, in

that moment, I found myself in a familiar but terrifying place, sitting across from a physician who lacked the insight and education to provide a comprehensive understanding of all options that were available. Instead, we were handed a choice of prescriptions, two medications, accompanied by a daunting list of potential side effects we did not want for our daughter; yet, as I had fought for my own health a decade ago, I was determined to advocate fiercely for my daughter.

"We forged a new path, rejecting the conventional treatment in favor of a functional medical protocol tailored to her unique needs. Central to her healing journey were two pivotal peptides. Then came the fall of 2023, a time when those two peptides were overnight reclassified, making it impossible for our family to continue to receive the medication from accredited and certified pharmacies. We could have used research only, or not for human use peptides, but we chose not to risk our child's health and were forced to go without.

"My husband and I were engulfed by anger and felt a profound sense of betrayal. It became painfully clear that the very institution meant to safeguard patients were instead prioritizing their own interest over the well-being of children like mine. In that moment, I understood the cruel reality. This was not about protecting my daughter; this is about preserving a broken system.

"While we remain grateful for her remarkable progress, my heart aches for the countless parents who wander through misinformation, lack of options, and who are lost and desperate for answers. The constraints on our medical freedoms and the barriers preventing access to life-saving therapies is nothing short of criminal. This journey is not just ours. It is a call to arms for all who believe in the rights to choose the best path for their loved ones.

"Together, we must rise up and demand the freedom to pursue healing, and to reclaim our power, and to protect the future of our children. We've accumulated thousands of other testimonials

like these stories that truly are life-changing because of the power of peptides." Thank you for your time.

DR. REBELLO: Thank you.

Speaker number 2, please state your name and any organization that you're representing for the record. You have three minutes.

MR. LaVALLE: Jim LaValle, Chair of International Peptides Society, Co-Chair of American Academy of Anti-Aging Medicine. The main point being brought out about AOD is accurate. It's simply for lipolysis and does not have any effect on growth hormone. We've seen 159,000 prescriptions written in the last year that we categorized, through the nine pharmacies that we contacted, from providers who thought that it must have been doing something because patients don't buy things that cost money if it's not having some benefit for them.

I would also add that it's typically used as an adjunct, so it's never just given alone, and instructed, at least with the International Peptide

Society, it's given in construction with diet, exercise, and maybe other medication, so that makes the water a little bit murky.

Four preclinical animal and two human clinical trials were very well done on the assessment of the trials. There were some shortings on all those, but it is reported to be GRAS status as a dietary supplement. I know that doesn't apply exactly for 503A, but it is noted as being safe as a dietary supplement.

I do want to note that in the studies, they saw no immunogenicity changes. Of course, there was no effect on serum IGF-1 because it's a fragment of growth hormone. The fragment is specific to the lipolytic activity of growth hormone; it's not specific to either the release of growth hormone or mimicking growth hormone. One of the big complaints, or at least that we heard at the last PCAC committee, is there's nothing on immunogenicity. In this particular case, no anti-AOD-9604 antibodies were detected in any of the patients selected for the antibody assay.

The summary of this from the authors, at least in terms of safety and tolerability, is that it was indistinguishable from placebo and had none of the adverse effects associated with the use of growth hormone. Of course, one of our biggest concerns is obesity, as was mentioned earlier. Everything we can do to try to keep people at a better body composition weight and less visceral fat is important.

Once again, what we do at International Peptide Society is look at level of evidence. Obviously, it's limited with AOD-9604. It's limited. At the same time, 159,000 prescriptions have been written by providers who have the right to write for a prescription, and instead of people going and getting --

DR. REBELLO: Thank you. We're at time. Appreciate it.

I invite speaker number 3. Please state your name and any organization that you're representing for the record. You have three minutes.

MR. WYNN: My name is Tom Wynn. I'm a pharmacist with FarmaKeio Pharmacy, and I'm here today just representing pharmacists. I'm going to blow through these first ones. We already went through this already when I talked about bulk powder. I want to stop here, and I have AOD acetate up there only because that's the one I'm most familiar with, but it can apply to all.

One of the things that was in the briefing was the FDA, again, was talking about aggregates, immunogenicity. The study that they used was one that was done in Europe, and it was ten of the most frequently encountered falsified peptide drugs in the Belgian market. They investigated the peptides and acquired three different suspect illegal internet pharmacies.

They took product from that and tested it, and using that product, that's where they came up with different aggregates and things that were there and they found within those peptides. AOD and CJC were both in there. So, of course, if we're talking about a counterfeit pharmacy, we're

probably going to find a lot of different solvents in that that we're not only going to see. They found arsenic. They found lead.

So the significance is that we don't know what the starting part was for those counterfeit pharmacies. Did they start with a crude peptide or was it something like more what you'd use for a reagent; or is it one that we use in pharmacies? It's about 98 percent. As you saw in most of the C of As, they were popping up earlier. Again, Biopeptek and Darmerica are FDA registered and FDA inspected, and the purity is documented. Peptides with a higher purity are less likely to vary from batch to batch and are less likely to aggregate than less pure peptides.

What I'm getting at is, if you're taking that information from a counterfeit pharmacy and you're applying that to all peptides, you can't do that. We don't know the purity and what that starting point was. The other question I had -- I think it was slide 26 of the immunogenicity talk -- there was a comparison of a commercially

available peptide to a compounded peptide. It was not stated what peptide that was. It can't be CJC or AOD because there's not a commercially available product. Which one did they use? It wasn't stated.

We also don't know how they got it. Did they get it from a counterfeit pharmacy? Did they have a pharmacy submit it? We just kind of brushed over that and went on, and everybody took it for granted. But that information, we need more information about it. If I was presenting information, I would have to probably also say what lab was it at, did they do a method validation, and all these other aspects that were not commented in that particular slide on immunogenicity.

We keep thinking about that that can occur, and it's constantly going to be can occur. There's no talk of prevalence. How prevalent is it? We don't know. I haven't seen it in any of the studies that they actually presented, both in the briefing and the ones that they're talking about in the original talk; so I don't really know how much

that's actually going to occur, is what I'm getting at. And usually, it can be something to where it's going to be some type of --

DR. REBELLO: We're at time. Thank you very much.

MR. WYNN: Thank you.

DR. REBELLO: I invite speaker number 4. Please state your name and any organization that you're representing for the record. You have three minutes.

DR. E. LEE: Hello. My name is Dr. Edwin Lee. I have no financial relationship. I'm a board certified endocrinologist in Orlando. I'm going to start with a brief history of AOD-9604, and I'm going to basically just say AOD instead of saying AOD-9604. It's a tongue twister.

AOD is a 16 amino acid peptide. It comes from the very end of human growth hormone. It does not have any growth hormone effect. We've heard before, it does not raise IGF-1. It does not react to the growth hormone receptor. In the late 1990s, Dr. Frank Ng and his colleague developed AOD. They

were excited, Dr. Frank Ng, that AOD had an effect on lipolytic effect with weight loss in rats and mice.

In human studies, there was over $50 million investigated and poured into to see if this actually works in humans. You've heard that it basically was ineffective, but it was very well tolerated in close to 1,000 patients. One positive spin is that there's no negative effect on carbohydrate metabolism. We also heard that there's no anti-AOD antibodies detected in any of the patients.

This is something you can find on the internet. I typed in AOD and GRAS status, and this was in June of 2012. It says, "AOD-9604 receives GRAS status. AOD receives pivotal GRAS status recognition to enter U.S. market, conditional on publication of our existing safety data." I'm trying to basically get a copy of this because I cannot find it on the FDA website, this GRAS status that was issued. So I'm trying to reach out to the companies out there to see if I can get a copy of

that letter.

I want you to focus on this picture here. You have two different men. They're the exact same weight, exact same body mass index, same height; it's just that they have different body composition. One's leaner and one's heavier. Think of AOD stimulating lipolysis and reducing lipogenesis, and that's what it's been shown to do. Unfortunately, we can't find that data with the six randomized-controlled studies that were done in Australia and the UK because they never published it.

DR. REBELLO: We're at time. Thank you very much.

DR. E. LEE: Thank you.

DR. REBELLO: I'd like to invite speaker number 5 to please come to the podium. Please state your name and any organization that you are representing for the record. You have three minutes.

DR. ROSEBUSH: Sure. My name is Lee Rosebush. I'm a PharmD, a pharmacist, Doctor of

Pharmacy, and a lawyer, and represent some of the pharmacies associated with this lawsuit. I wanted to bring up three things very quickly as those slides are being brought up. We went through this earlier. There were four specific criteria that are supposed to be reviewed. Notice, based on some of the questions that were just asked, one of those criteria did not include mechanism of action and, in fact, if we had mechanism of action as one of the requirements, you could take off both OTC- and FDA-approved drugs. For example, I'd ask you what's the mechanism of action of Tylenol, acetaminophen, or what's the mechanism of action of lithium? The mechanism of action of a drug does not necessarily apply to the efficacy associated with that drug.

Two, from this perspective, we've also tried to get USP monographs that were mentioned. We've met with Brian and the USP team to ask to develop a USP monograph for all three of these peptides and were denied. The reason we were denied is because they're not FDA approved. If they were FDA

approved, we wouldn't be here. Accordingly, you can't get a USP monograph, nor can you get FDA approval, to compound a product. It's a solution that you could never be able to meet.

Third, from this perspective, as we've mentioned before, there are multiple criteria. If you look at FDA's own briefing documents, they say there's a long history associated with compounding this product. Accordingly, that is met.

We've gone through the criteria. I would point out, number 3, in the history, in this perspective, it's been used 158,000 times. Here's the CoA from that perspective and the immunogenicity aspects associated with this. It can also be used orally. That's been skipped over, so you'd also have that as taken care of. I would then ask the question, why is this necessarily being taken off now?

If you could jump ahead a few slides, down to where we say real-world evidence, you will see, in this perspective, that FDA has approved products previously using real-world evidence. In fact, as

we talked about this last time with Charlie, as little as 14 patients has been used before, previously, by the FDA to approve a product using real-world evidence. In this situation, we have 158,000 prescriptions. We have provided the data, again, that Charlie has mentioned in his readout from last time associated with that data. In addition, as was pointed out here, in this case, a phase 2B clinical trial that has 536 trials. Here's the material with the footnote showing that FDA has actually approved using real-world evidence in as short as 13 patients, and it's done 13 times in the last 5 years.

Now, again, appearing here, you'll see very little adverse events associated with 158,000 prescriptions. We talked about efficacy. That was the last question from this association here. I would point to that second bullet point. Notice in this case that, yes, there have been questions associated with the overall statistical significance, but there was weight loss. In fact, females responded better. As I mentioned last time

at the PCAC hearing, my understanding from this administration is no federal regulator should ever stand between a healthcare provider and a female when she's making her healthcare decisions.

DR. REBELLO: Thank you. We're at time.

DR. ROSEBUSH: Thank you.

DR. REBELLO: I'd like to invite our last speaker who will be participating virtually. Speaker number 6, please state your name and any organization that you're representing for the record. You have three minutes.

DR. JORDAN: Thank you. Good morning. My name is Dr. Brad Jordan, and I'm the Associate Vice President of Regulatory Policy for Eli Lilly and Company. I'm happy to deliver remarks today on behalf of Lilly in opposition of the addition of AOD-9604 to the FDA bulk substances list.

AOD-9604 is a synthetic fragment of the C-terminal region on human growth hormone designed in the early 1990s; however, clinical development of this molecule for the treatment of obesity was terminated in 2007 because the molecule failed to

show a significant therapeutic effect in clinical trials. In fact, the CEO of Metabolic, the company that initially tried to develop the drug, noted that their clinical program had been successful and that it clearly demonstrated that the molecule was not affected. Other attempts at studying this molecule for tissue repair and pain have similarly failed to demonstrate efficacy.

AOD-9604 is a complex peptide, and the nomination of this molecule to the bulk list is essentially an effort to circumvent the FDA drug approval process. At the same time, false and misleading advertising by compounding pharmacies touting the effectiveness of this molecule for weight management and tissue repair is being used to deceive patients. Lilly urges the PCAC to vote against the replacement of this molecule, AOD-9604, on the bulks list.

The nomination of AOD-9604 is part of a trend that is especially concerning to Lilly. Over the past several years, some compounded pharmacies have created unproven, untested, and unregulated

protein- and peptide-based therapies, including many at very large scale. Notably, we are now seeing entities marketing compounded versions of complex investigational drugs. We also continue to see entities mass marketing compounded versions of complex macromolecules in completely untested formulations, including sublingual versions of medicines that have only been approved and studied as injectables and versions such as combination products created seemingly at random. These practices obviously circumvent the FDA approval process, are not grounded in science, and potentially present dangerous practices that could harm patients and threaten public health.

We are also concerned that some compounding pharmacies are routinely making unsupported claims for their products and circulating them widely online. False and misleading advertising for compounding drugs has led to a massive black market alternative to authentic FDA-approved medicines. These marketing practices pose a significant threat to the integrity of the FDA approval system and put

patients at risk.

Lilly urges FDA and the committee to halt all mass compounding of protein- and peptide-based therapies, and to consider placing all such complex macromolecules on the Difficult to Compound List in order to gain control of the current situation and prevent further risks to patients. Thank you.

Clarifying Questions from the Committee (con't)

DR. REBELLO: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. We will now take additional comments or questions from committee members.

Do members of the committee have questions or comments regarding anything that was presented in this segment of the session?

Dr. Serumaga?

DR. SERUMAGA: Yes. Brian Serumaga from the USP. I would like to make a comment for the committee because USP was mentioned in one of the submissions from the general public. USP does

create monographs, as you all know, for bulk drug substances, and also monographs for FDA-approved products that are conventionally manufactured, and also monographs for compounded preparations. The guidelines for submitting materials for creation of monographs at USP are clearly elucidated in the USP website, so I am reading the information that's in the public domain.

USP encourages all entities to submit information, either for the creation of a new monograph or the revision of an existing official monograph; however, it's important for the committee to also remember that USP is not a drug regulator. So it is USP policy not to create monographs for materials or products that are not FDA approved or that are, indeed, not legally marketed. That might be one of the reasons why sometimes when we get nominations for monographs at USP, we decline. USP is not a drug regulator. The monograph creation process at USP cannot be used to circumvent the new drug approval process that is legally required in the Food, Drug, and Cosmetic

Act. Thank you.

DR. REBELLO: Are there any further == go ahead.

DR. SHETTY: FDA would like to make two comments. This is Daiva Shetty. I want to comment on the real-world data. The information on the use alone is not the same thing as real-world evidence. Real-world evidence is the clinical evidence about the usage and potential benefits or risks of medical products derived from analysis of real-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 by the presenters are simply numbers of prescriptions filled by unidentified pharmacies that do not identify the use, dose, route of administration, and duration of exposure. And most importantly, it does not provide any data related to the safety and effectiveness of the drug; therefore, we consider this information as describing historical use in

compounding. Thank you.

Emily?

DR. KNEEREAM: Hi. This is Emily Kneeream. I just wanted to make a comment on the GRAS status that we heard. AOD-9604 is not currently listed on FDA's GRAS list and has not been through FDA's GRAS determination, based on our search. In the Metabolic Pharma company document that we saw projected on GRAS status, it appears if you read the whole document, that this is a self-determination. Thank you.

DR. REBELLO: Gabrielle Cosel?

DR. COSEL: Thank you very much. I just wanted to add an additional comment. Some access concerns were raised earlier, and I wanted to remind the committee of our presentation earlier today about the availability of the IND process for access.

As was shared earlier, individuals may be able to receive investigational products containing AOD-9604-related substances under an IND, provided applicable requirements are met. Individuals can

receive investigational products containing this substance either through a clinical trial or through FDA's expanded access program. Expanded access is a potential pathway for a patient with a serious disease or condition to get access to an investigational product for treatment outside of clinical trials. I just wanted to remind the committee of that as well.

DR. REBELLO: Any further questions or comments?

MR. WESDYK: Hi. Russ Wesdyk, OPQ, FDA. I should also comment on some of the impurities, CoAs, and Daniela's slide regarding immunogenicity, as that was raised. We do acknowledge the receipt of additional C of As, and in some cases, they provided additional information that was incremental to our own, and helpful; however, in some cases, it also included additional information that raised additional concerns. We need to continue our evaluations of that.

It was mentioned that Daniela's slide highlighted a peptide, and that's true. I

mentioned that, too, with her next-to-last slide. I can't name that peptide because it continues to be an active investigation, but it's not one of the three. I would have thought that was immediately obvious because we were including marketed product. If it was marketed product, we wouldn't be sitting here talking about it; they could compound it.

What we found in that case was marketed product had a very clean impurity profile and lower immunogenicity potential, and in the case of compounded samples, which we pulled, we found a much higher impurity profile and potential for immunogenicity. I can't name it, but it's a peptide that is similar to what you see here, a large molecule peptide.

That's as much as I can say there. Thank you.

DR. REBELLO: Additional questions or comments?

(No response.)

DR. REBELLO: Anyone online?

(No response.)

Committee Discussion and Vote

DR. REBELLO: 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 a question to the committee and panel discussions. I'd 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'll proceed with our second question, which is a voting question. We'll 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've entered your vote. Please press the button firmly that corresponds to your vote. If you're 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's voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you wish to. We'll continue in the same manner until all questions have been answered or discussed.

Question 2. Section 503A Bulk Drug Substances List, AOD-9604-related bulk drug substances. FDA's evaluation addressed two AOD-9604-related bulk drug substances, which include one active moiety and two different BDSs. FDA proposes using a single voting question to address them as a group.

Do committee members agree to vote on AOD-9604-related bulk drug substances discussed today and AOD-9604 as a group; yes or no? If any member of the committee votes no, FDA will take separate votes on each of these substances. In

voting yes, committee members will vote on the substance as a group and will proceed to answer voting question. If voting no, committee members will vote on each of the substances separately and will proceed to answer additional voting questions.

Are there any questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: If there are no further questions or comments concerning the wording of the voting question, we will now begin the voting process. Please press the button on your microphones that correspond to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or which to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Hello. This is Takyiah Stevenson, DFO speaking.

Dr. Yanovski, a reminder for our voting members online to please submit their vote via email. Thank you.

DR. YANOVSKI: I've done so. I can do it again.

(Pause.)

DR. STEVENSON: Takyiah Stevenson, DFO speaking. For the record, there are 12 yeses, 0 noes, and 0 abstentions. Thank you. I'll hand it back to the chairperson.

DR. REBELLO: Thank you.

Now, that the vote is complete, we'll go around the table and have everyone who voted state their name and vote.

DR. DURHAM: Todd Durham. I voted yes.

DR. VAIDA: Allen Vaida. I voted yes.

DR. BOGNER: Robin Bogner. I voted yes.

DR. SERUMAGA: Brian Serumaga. I voted yes.

DR. REBELLO: Elizabeth Rebello. I voted yes.

DR. GURA: Kathleen Gura. I voted yes.

DR. McELHINEY: Linda McElhiney. I voted

yes.

DR. FENSKY: Tim Fensky. I voted yes.

DR. BILLINGTON: Charles Billington. I voted yes.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted yes.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Anita Gupta. I voted yes.

DR. REBELLO: Dr. Yanovski?

DR. YANOVSKI: Susan Yanovski. I voted yes.

DR. REBELLO: Since everyone voted yes, we will proceed with Question 2A.

Question 2A, Section 503A Bulk Drug Substances List, AOD-9604-related bulk drug substances. FDA is proposing that AOD-9604 and AOD-9604 acetate not be included on the 503A Bulks List. The question at hand is, should AOD-9604 and AOD-9604 free base and acetate be placed on the list? If voting yes, you're recommending FDA should add 9604-related bulk drug substances on the 503A Bulks List. If voting no, you're recommending FDA should not place AOD-9604-related bulk drug

substances on the 503A Bulks List.

If the substances are not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes subject of an applicable USP, or National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: 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'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or 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 is 1 yes, 11 noes, and 0 abstentions. Thank you.

DR. REBELLO: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote --

DR. YANOVSKI: I believe there was an error because I voted no on my email, for 2A.

DR. STEVENSON: Hold on, Dr. Yanovski. This is Takyiah speaking. One moment, please.

DR. YANOVSKI: Sure.

(Pause.)

DR. STEVENSON: Apologies for the delay. This is Takyiah speaking. Just one moment. We'll continue in a moment.

(Pause.)

DR. STEVENSON: Apologies for the delay. Takyiah speaking. Correction for the total. For the record, there were 0 yeses, and 12 noes, and 0 abstentions. We'll go around the table for everyone to state their name and vote into the record. Thank you.

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathleen Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted no.

DR. FENSKY: Tim Fensky. I voted no.

DR. BILLINGTON: Charles Billington. I voted no.

DR. REBELLO: Dr. Padma Gulur?

DR. GULUR: Padma Gulur. I voted no.

DR. REBELLO: Dr. Anita Gupta?

DR. GUPTA: Anita Gupta. I voted no.

DR. REBELLO: Dr. Susan Yanovski?

DR. YANOVSKI: Susan Yanovski. I voted no.

Adjournment

DR. REBELLO: Thank you.

We'll now break for lunch, and we'll reconvene at 1:00 Eastern Time. Please take any

personal belongings with you. Remember that there should be no discussion of the meeting topic during the lunch break amongst yourselves or any member of the audience. Additionally, those panel members participating in the remaining topic discussions, plan to rejoin at 12:45 Eastern Time. Those that are joining us virtually are also included in that to ensure you are seated before we reconvene at 1:00. Thank you. Enjoy lunch.

(Whereupon, at 12:12 p.m., the topic 2 session was adjourned.)