FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Thursday, November 3, 2016

1:01 p.m. to 3:49 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Hong, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Michael A. Carome, MD, FASHP

(Consumer Representative)

Director of Health Research Group

Public Citizen

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Allen J. Vaida, BSc, PharmD, FASHP

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Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

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PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

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The Compounding Pharmacy

Hickory, North Carolina

TEMPORARY MEMBERS (Voting)

Antonio Fojo, MD, PhD

(Participation in diindolylmethane discussion via telephone)

Professor of Medicine

Director, Neuroendocrine Centers

Columbia University Medical Center

Co-Director, James J. Peters Veterans Affairs/Columbia University Cancer Center

New York, New York

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

1:01 p.m.

Call to Order

Introduction of Committee

DR. GULUR: Thank you, everyone, for reconvening. Before we begin, I will introduce one voting, regular government employee who will be in a specific portion of this afternoon's topic. He is Dr. Antonio Fojo from James J. Peters Veterans Affairs, Columbia University Cancer Center. He will participate only in the diindolylmethane topic.

We will now proceed with the FDA presentation by Dr. Michael Brave.

FDA Presentation - Michael Brave

DR. BRAVE: Good afternoon. I'm Dr. Brave. I'm a medical officer in the Division of Oncology Products I, the Office of Hematology and Oncology Products. I'd like to thank my colleagues listed here for helping me review this nomination for diindolylmethane.

Diindolylmethane, abbreviated DIM, has

been nominated for the list of substances that can be compounded. The proposed use is "for the treatment of cancer." We are uncertain whether this would mean in combination with other chemotherapeutic agents. The proposed route of administration is by mouth. The references submitted with this nomination include only non-clinical information, not clinical safety or efficacy data.

DIM is an active metabolite of indole-3-carbinol, abbreviated I3C. This I3C is found in cruciferous vegetables. Epidemiological studies suggest that persons who regularly eat cruciferous vegetables have lower risks of some cancers. DIM is marketed as a dietary ingredient in dietary supplements. It is available as capsules and tablets in strengths ranging from 100 milligrams to 300 milligrams and is also sold as powder.

DIM is a small organic molecule. I3C is a precursor form of DIM. In the acidic environment of the stomach, I3C dimerizes to

the biologically active and stable DIM and its associated oligomers, collectively referred to as acid condensation products. On average, 100 grams of cruciferous vegetables containing I3C is estimated to convert to approximately 2 milligrams of DIM.

DIM can be synthesized from the condensation of indole with formaldehyde and is easily characterized using standard analytical spectroscopy. Potential impurities of synthetic DIM include residual starting materials such as indole and formaldehyde. The latter is toxic.

Diindolylmethane is highly insoluble in water but is stable as a solid when kept away from light at 4 degrees centigrade. These conditions are likely to impact the storage requirements for a compounded drug product. Based on available information, there are no major concerns about the physical or chemical characterization of DIM. It is a small organic molecule that is likely to be stable as a solid

under ordinary storage conditions when kept away from light.

In non-clinical studies, DIM has been reported to modulate cell-cycle progression. Several potential cancer-preventive properties have been associated with DIM, including cell-cycle arrest, induction of apoptosis, and modulation of estrogen metabolism. However, one group of investigators reported that concentrations of DIM achievable through diet exerted an unexpected proliferative effect on breast cancer cells.

The FDA review team found little animal toxicology data and no published information on repeat-dose toxicology studies conducted under good laboratory practices. In a non-GLP study in rats, DIM induced hepatic metabolizing enzymes, which signals a potential for effects on drug metabolism.

In neonatal mice, administration of 20 milligrams per kilogram of DIM once daily for 3 days resulted in atrophy of white pulp in

the spleen. In adult mice, DIM increased serum cytokines, suggesting a potential for an effect on the immune system. No information was found regarding mutagenicity development or reproductive toxicity, carcinogenicity, or toxicokinetics.

In summary, based on available data in public databases, the toxicology data that we reviewed indicate a potential safety concern. Both the potential safety concerns and the overall limited amount of available data raise concerns about use of DIM in compounding under Section 503A of the Food, Drug, and Cosmetic Act.

Most of the side effects of DIM reported to date have been limited to minor gastrointestinal symptoms, however, one group reported that concentrations of DIM achievable through diet exerted an unexpected proliferative effect on breast cancer cells. In addition, a case of central serious retinopathy was reported in an otherwise

healthy female who presented with headaches and blurry vision after 2 months of, quote, "excessive dietary consumption of DIM."

Visual improvement began 2 weeks after discontinuation of DIM and resolved to baseline after 8 weeks. Safety issues that have arisen in clinical trials will be discussed in subsequent slides, together with the efficacy outcomes for these trials.

The FDA Office of Surveillance and Epidemiology conducted a search of the FDA adverse events reporting system database for reports of adverse events. This search yielded two cases of altered mental status with DIM use. The Office of Surveillance and Epidemiology concluded that it could not assess a drug event causal relationship because the number of FAERS cases was limited, had insufficient data quality, and the presence of confounding medications were also noted.

The FDA Center for Food Safety and Applied Nutrition conducted a search of its

database for adverse events associated with DIM and found 18 reports related to its use as a dietary supplement. Five reports were received of hepatotoxicity. These were hepatitis hepatocellular injury and liver function test abnormality. There were 3 reports of abdominal pain and 2 reports of loss of consciousness.

Then next four slides summarize published reports of clinical experience with I3C or DIM in humans. We found reports of one or both of these compounds having been studied in healthy volunteers in women with abnormal cervical cytology, in women at risk for breast cancer, and in men with prostate disease.

To achieve clinically relevant exposures of DIM, it has been suggested that intake would need to be upwards of 600 grams per day sustained for several years. Therefore, most published clinical trials have used the bioresponse formulation of DIM, a dietary supplement containing microencapsulated DIM, which compared with crystalline DIM is

purported to have higher bioavailability.

This slide summarizes two small clinical trials of I3C and bioresponse's formulation of DIM in healthy human volunteers. Following administration of I3C to humans, only DIM, and not the I3C, was detectable in the blood stream. Following single oral doses of the bioresponse formulation of DIM, DIM was detectable in plasma. GI distress was dose limiting in both studies.

Three groups have conducted clinical trials designed to evaluate whether I3C and/or DIM improved abnormal cervical cytology in women. The small trial by Bell reported that none of 10 patients in the placebo group had complete remission of CIN. However, 4 of 8 patients receiving I3C at 200 milligrams daily and 4 of 9 patients receiving I3C at 400 milligrams daily had complete regression on their 12-week biopsy. While this appears to suggest a potential benefit from I3C, we note that CIN regression is common in untreated

patients.

The number of patients included in this trial was small, and long-term follow-up was not provided. In larger trials by Del Priore and Castanon using the bioresponse formulation of DIM, no effect on cervical cytology was demonstrated.

Three pilot studies have evaluated the bioresponse formulation of DIM in women at increased risk of breast cancer. No safety concerns were identified in these trials, although it is not clear whether adverse events were systematically collected.

The efficacy endpoints of these pilot studies were genetic or metabolic biomarkers thought to be associated with increased risk of breast cancer such as urinary excretion of estrogen metabolites and transcription of genes implicated in the development of breast cancer. No clinical study has reported an effect of DIM on reducing breast cancer events.

Four pilot studies have evaluated DIM in

men with prostate interstitial neoplasia or early stage prostate cancer. Each reported an effect of DIM on biomarkers thought to be associated with an increased risk of prostate cancer. We found no clinical study that reported an effect of DIM on reducing prostate cancer. The safety of DIM has not been rigorously studied. Non-clinical findings suggest a potential for adverse events on the immune system and on hepatic enzymes of drug metabolism. No serious toxicity has been reported clinically.

Non-clinical data suggest that DIM has biological effects which could support a rationale for its development as a chemo-preventive agent or as an adjunct to chemotherapy. Results of some exploratory published clinical trials report that DIM has effects on biomarkers thought to potentially correlate with a reduced incidence of cancer. However, we found no published clinical trial that has reported objective tumor responses or

an effect on long-term clinical outcomes. Many approved therapies are available for the treatment of cancer and have well-characterized safety and efficacy profiles.

We found insufficient information to determine how long DIM has been used in pharmacy compounding. Currently, oral compounded formulations of DIM are promoted on the internet as, quote, "natural health supplements." A search of the British pharmacopeia, the European Pharmacopeia, and the Japanese pharmacopeia did not show any listings for DIM.

In summary, DIM is chemically well characterized and expected to be stable as a solid if kept at temperatures below 4 degrees centigrade. The safety of DIM has not been rigorously studied.

Non-clinical findings suggest the potential for adverse events on the immune system and on hepatic enzymes of drug metabolism, however, no serious toxicity has

been reported clinically.

Although non-clinical data suggests that DIM has biological effects which could support a rationale for its development as a chemo-preventive agent or as an adjunct to chemotherapy, no clinical trial has to our knowledge ever been conducted with an objective to determine clinical anti-cancer activity. And overall, there is insufficient information to evaluate the historical use of DIM in pharmacy compounding. DIM appears to be compounded currently and is promoted as a, quote, "natural health supplement." Thank you.

DR. GULUR: We will take any clarifying questions for our presenter from the committee.

(No response.)

DR. GULUR: I guess not. Thank you very much.

DR. BRAVE: Thank you.

DR. GULUR: We will now proceed with the nominator presentations. We have one presentation by Dr. Day.

Nominator Presentation - A.J. Day.

DR. DAY: Good afternoon. My name is A.J. Day. I'm with PCCA. I'm also a member of IACP. As a conflict of interest, PCCA does provide diindolylmethane powder for use in compounding. I wanted to start off with just a brief review of some of the comments from Dr. Brave as laid out in the FDA briefing information.

Physical and chemical characterization, it's well characterized, stability is not a concern, and human safety data does not seem to be a primary concern either. The primary concern had to do with efficacy for the use of various types of cancer. I agree there are very limited -- to be kind -- clinical trials on the use of diindolylmethane for the treatment of cancer.

Practically speaking, we're not using in the compounding world diindolylmethane for the treatment of cancer. I understand the reason why that was included in the nomination,

period, and that is, the nomination asks for potential uses. And as you go through clinical review of literature through PubMed, clinicaltrials.gov, and other resources, all of the clinical trials focus on the treatments of various types of cancer.

There is quite a bit of in vitro data. There's a lot of material that indicates potential benefits, but in terms of human clinical trials for different types of cancers, that's really not where the compounded community is utilizing DIM historically. Really, the purpose of utilizing DIM in compounding has been for modulation of estrogen metabolism. There's not good clinical evidence for this in the literature, and that's why that was not included because you need supporting data with that nomination, and it just didn't exist in a reputable format.

So when estrogen, whether it's estradiol or another form of estrogen, is ingested or it's absorbed into the human body, it's

metabolized to estrone. And then estrone is further metabolized through a hydroxylation process. The primary metabolites are 2, 4, or 6 hydroxy estrones. The two hydroxy estrones are considered to be the, quote, "safer" metabolites. They tend to be less carcinogenic, based on in vitro studies, that the 4 or 16 hydroxy metabolites.

As was mentioned, the source of diindolylmethane, it is a bioconverted form of I3C, which is found in cruciferous vegetables. So there are a number of different dietary sources for indole-3-carbinol, which does get bioconverted to DIM, such as flax, lignans, kudzu, a little bit from soy, as well as from other cruciferous vegetables such as broccoli.

I wanted to make sure that the committee and FDA is aware that in the compounding community, I've never come across -- and I've consulted with our colleagues -- any indication that diindolylmethane was being prescribed or dispensed for the treatment of specific types

of cancers. It may be used to shift metabolites of estrogens away from the supposedly more carcinogenic metabolites in patients who have a family history or personal history of different types of cancer, and they are receiving hormone therapy.

Typically, the dosing that has been used is 200 milligrams once a day. That's the most common dose that's prescribed. That is a dose that is available in dietary supplements throughout the country. Sometimes that's 100 milligrams, sometimes as low as 25 milligrams. But those are the ways that I've typically seen it utilized in compounding.

So then the question is why is it being compounded if it's available as a dietary supplement? A lot of that comes to some of the conversations that we had with the dermatologic requests from this morning, which has to do with knowing what's in the preparation, what's your patient really getting.

This is an example of our certificate of

analysis. You can see the chromatographic purity on that, 99.7 percent. You can see the analysis for loss on drying for a variety of other components that we screen our materials for so that we can have a degree of certainty of what the patient is actually receiving as opposed to buying a dietary supplement that has various fillers, dyes, or other ingredients that the patient or physician may not be aware of. So this is really where the utility of having diindolylmethane compounded comes into play. Thank you very much.

Clarifying Questions from the Committee

DR. GULUR: Questions for our presenter from the committee?

(No response.)

DR. GULUR: Thank you, Dr. Day. Oh, you do? Ms. Davidson?

MS. DAVIDSON: A.J., are there any other alternatives that will push the metabolism of estrogen to the non-toxic or less toxic metabolites that you're aware of?

DR. DAY: I'm not an expert in the metabolic by-products and pathways for the estrogens. The ones that I'm most familiar with I3C and DIM.

DR. GULUR: Dr. Brave, did you want to comment on that? All right.

Dr. Wall?

DR. WALL: A.J., do you receive most of the requests for this from patients walking in, and who have read about it and want a dietary supplement, or are these prescriptions from who?

DR. DAY: Typically, the prescriptions come from endocrinologists or general practitioners who tend to focus a little bit in hormone replacement therapy, perimenopausal therapy for women, and it is as a prescription.

DR. GULUR: Please?

DR. DAY: How do they know it's effective?

DR. DAY: I don't have the data on that. I think we would have to ask the physicians'

perspective.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Thank you, Dr. Day.

DR. DAY: Thank you.

Committee Discussion and Vote

DR. GULUR: Since the agency did not receive registrants for the fourth open public hearing session, we will move on to the committee discussion and voting. We will now begin the panel discussion. Any comments from the committee?

(No response.)

DR. GULUR: In that case -- Ms. Davidson?

MS. DAVIDSON: Just a comment to answer the question that was just asked of A.J. It does look like in at least four of the studies that were presented by FDA, that there is increased urinary excretion of the 2-hydroxy metabolite -- 16-hydroxy metabolite. So there does appear to be some evidence that it does

increase the elimination of these metabolites of estrogen. There was one where there were no observed effect on either of these metabolites, but I just wanted to make that comment.

DR. GULUR: Any other comments?

(No response.)

DR. GULUR: All right. We'll proceed to the vote. FDA's proposing that diindolylmethane not be included on the 503A bulk list. Should diindolylmethane be placed on the list? And again to reiterate, if you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list.

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

If there is no further discussion, we will now begin the voting process. Please press the button firmly on your microphone that

corresponds to your vote. You will have approximately 15 seconds to vote. After you have made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again.

Dr. Fojo apparently might actually be on the phone. If you are on the phone, would you please introduce yourself?

(No audible response.)

DR. GULUR: Apparently we're not able to get the connection. So we will continue with the vote. I'll read the question one more time.

FDA is proposing that diindolylmethane not be included on the 503A bulk list. Should diindolylmethane be placed on the list?

Do any of the committee members require me to repeat the instructions on the vote again?

(No response.)

DR. GULUR: In that case, please

proceed.

(Pause.)

DR. GULUR: We're waiting for Dr. Fojo's vote.

DR. FOJO: Yes. This is Tito Fojo. This is Dr. Fojo. And now I can hear myself. I'm sorry. I couldn't get through, but I've been listening to the whole presentation online, and I've submitted my vote.

Do you want me to say --

DR. GULUR: Did you have any comments, Dr. Fojo?

DR. FOJO: I sent in also a comment, and it had to do with the fact that there was clearly no evidence of -- no credible evidence it had had activity as an anti-cancer agent. I understood that there was a -- shall we say pull-back from that as it was being discussed. It was stated that that was not its purpose, although it was concerning that there was some promotion of it for that purpose, and that should obviously not be the case.

DR. GULUR: Thank you, Dr. Fojo.

DR. FOJO: That's all that I have to say.

DR. GULUR: Because the third time is a charm, I'm going to repeat this question.

(Laughter.)

DR. GULUR: FDA is proposing that diindolylmethane not be included on the 503A bulk list. Should diindolylmethane be placed on the list? Please vote now.

(Vote taken.)

DR. HONG: We have 1 yes, 8 nos, and zero abstain.

DR. GULUR: Thank you. We're going to start with the comments. Is Dr. Fojo still on the phone, and would he like to comment on his vote?

(No response.)

DR. GULUR: No. So we will start with Dr. Vaida in that case.

DR. VAIDA: Allen Vaida. I voted no for the reasons that FDA gave in their

recommendations.

DR. PHAM: Katherine Pham. I also voted no. I didn't see a clear benefit in efficacy to offset the potential risk of drug-drug interactions.

DR. WALL: Donna Wall. I voted no for the reasons previously said.

DR. CAROME: Mike Carome. I voted no for the same reasons as stated.

DR. HOAG: Steve Hoag. I voted no for the reasons said. And perhaps in the future, if more evidence becomes available, maybe we would reconsider this, but for now it's not there.

DR. DiGIOVANNA: John DiGiovanna. I voted no for the reasons mentioned.

MS. DAVIDSON: Gigi Davidson. I voted yes, although I was again prepared to come in and vote no on this. I was not aware of the indication that Dr. Day brought to our attention for women at risk for estrogen-receptive cancers metabolites. So

this was a struggle for me, but I didn't hear that there are any alternatives. I didn't see a safety signal. The substance seems to be well characterized.

The bioresponse dietary supplement is not a regulated product, and so I feel like the compounding arena would be a more reliable place for patients to obtain this substance.

DR. GULUR: Thank you. I voted no for reasons already stated, and we will conclude the vote with this.

We're going to wait for Dr. Fojo to call in and record his vote.

(Pause.)

DR. FOJO: Can you hear me now? I can hear myself now. So my vote is no. [Inaudible] -- comment as I did before, that there was no evidence of any cancer activity. As regard to the compound as a whole, I didn't see that the evidence was very persuasive to much of [inaudible] -- advocate for. I think that at [inaudible] -- but I would have to say

that the data is available --

I don't have a printout, so it will not be the same thing. But I said that I voted no, and that the reason was -- I said I voted no, and that the reason was, initially, for the comments that I had made before. And that was that there was no evidence that this had any anti-cancer activity or I should say no credible evidence.

As for the other properties that were advocated, I [indiscernible] those as well. There was insufficient data or evidence. And given that, I couldn't see that this was a compound to which a yes vote should be submitted. So I voted no.

DR. GULUR: We have met the requirements for this vote, and we will now proceed with the FDA presentation for vasoactive intestinal peptide. Dr. Johnson?

FDA Presentation - Susan Johnson

DR. JOHNSON: Our apology for the technical glitches this afternoon. My name is

Susan Johnson, and I'm an associate director in CDER's Office of Drug Evaluation IV. I'll be discussing FDA's review of vasoactive intestinal peptide. I'd like to recognize and thank the members of the review team representing the various review disciplines. And I'd also like to thank Pawanprit Singh and Sharon Thomas, the regulatory project managers who have done a tremendous job in keeping this compounding review process and planning for this meeting on track.

Vasoactive intestinal peptide, or VIP, was nominated for use as a nasal spray in the treatment of a condition described as chronic inflammatory response syndrome, or CIRS. Regarding physical and chemical characteristics, VIP is an endogenous peptide comprising a 28-amino acid chain. The peptide has also been shown to have a 3-dimensional conformation that is critical to its functionality.

VIP can be prepared using solid-phase

peptide synthesis and HPLC purification. A bioassay can be used to confirm its secondary structure. Stability of VIP in a nasal solution will be related to its concentration, pH, and storage temperature. VIP is prone to degradation in a dilute solution.

Potential impurities from the manufacturing process include modifications in the peptide sequence such as extra amino acids called insertions or dropped amino acids called deletions. Potential manufacturing impurities also include the presence of residual solvents.

There are potential impurities from degradation of VIP, including aggregates of the peptide, changes to the secondary structure, and peptide fragments. The presence of peptide impurities and degradants in a compounded product raises concerns about potential immunologic responses, a safety concern that I will discuss in later slides.

The physical and chemical characteristics of VIP can cause the safety and

efficacy of VIP to be affected by nasal delivery from a nasal spray. There are physiologic factors that can affect intranasal delivery of a peptide. In addition, accurate and consistent administration via nasal spray depends on factors like droplet size distribution, plume geometry, and priming requirements.

In summary for this evaluation factor, VIP is a peptide whose activity is dependent on its synthesis as a 28-amino acid sequence peptide with a proper secondary structure. Concentration, pH, and temperature affect stability of VIP and formation of its degradants, and reliable dose delivery from a nasal spray involves consideration of numerous device and physiologic factors.

Moving now to safety considerations, VIP is an endogenous neuropeptide with diverse physiologic roles in mammals. The peptide was identified in the 1970s, and its physiologic research continues to investigate VIP's

potential activity and potential therapeutic uses. The half-life of VIP is short in both humans and in animals. In animals, VIP has been shown to have rapid hepatic clearance and cross the blood-brain barrier.

There are no animal data regarding acute toxicity, genotoxicity, developmental, and reproductive toxicity, or toxicokinetics. VIP was shown in a 45-day study in rats to be a tumor promoter for colon cancer, but no standard two-year carcinogenicity study has been conducted. Overall, the available non-clinical data are inadequate to establish and characterize the safety of VIP therapy for human use.

In humans, the potential for immunologic reactions exists in association with the administration of a peptide or protein. VIP itself may trigger such a response as could any of the possible impurities or degradants that I identified earlier. It's important that VIP be characterized in association with its synthesis

process and that the stability of VIP be considered for the life of the compounded product.

Looking at adverse events that have occurred in clinical trials, most were found to be mild and related to VIP's vasoactive effects. However, in a study of VIP in the treatment of pulmonary arterial hypertension, a group of patients were reported to have had an increase in VIP auto-antibodies. In two cases, the immunologic response was reported to have been severe. Searches of the FAERS and CAERS reporting systems did not return reports of any adverse effects.

To summarize our review of VIP safety, we find that there are insufficient, non-clinical data particularly to determine the safety of VIP for human use in a chronic condition. The majority of adverse events are reported to be mild, however, potential immunologic reactions are an important consideration with the administration of a

peptide, and severe reactions of this type have been reported. Therefore, characterization and control of the peptide impurities and degradants is important for the safe use of VIP.

We note that there are no approved treatments in the U.S. for the nominated use of CIRS. Our review considered the evidence of VIP effectiveness to treat a condition called chronic inflammatory response syndrome, CIRS. This condition is not found in standard disease indexes such as ICD-10 or MedDRA. We have identified one publication in which VIP was studied in the treatment of CIRS specifically for a condition in which CIRS is proposed to be attributable to exposure to water-damaged buildings.

Twenty patients were enrolled in this open-label study. No placebo or active treatment comparator was included in the study design. Each patient was reported to have had previous treatments for CIRS provided by the

investigator. The published report does not specify enrollment criteria such as the identity or severity of symptoms or the plasma levels of the 12 endogenous substances monitored in the study.

VIP plasma levels are theorized to be abnormally low in association with CIRS. VIP treatment was intended to be used 4 times a day for a period of 18 months, but only 8 of the 20 patients reported using the substance as much as 3 or 4 times a day during that period. Five patients reported stopping the treatment intermittently.

Evaluations were conducted at baseline 12 and 18 months. Among the evaluations of plasma levels for the 12 substances and physician assessment of symptoms, no primary endpoints were identified and no efficacy thresholds were specified. Looking specifically at VIP plasma levels, there was no information provided about the timing of plasma sampling relative to dosing. At 18 months, the

mean VIP level of a treatment group was found to be statistically lower than the mean VIP of the comparator group.

To summarize, there is inadequate clinical information regarding VIP's use in the nominated CIRS condition. The single trial of CIRS water-damaged buildings does not provide a basis on which we conclude that VIP is associated with clinical improvement. In addition, the study does not provide evidence that the intranasal administration of VIP used in the study resulted in systemic exposure.

Regarding historical use of compounding, we did not find adequate information to determine how long VIP has been used in pharmacy compounding. We did find that VIP is currently advertised on the internet as being available in nasal and injectable compounded formulations. Another name for VIP is Aviptadil, and outside the U.S., Aviptadil is approved in combination with the drug phentolamine for intracavernosal injection use

in the treatment of erectile dysfunction.

In summary, VIP is a 28-amino acid peptide with a specific secondary structure. Both impurities from synthesis and degradation of the peptide can be associated with immunologic reactions. We find there are inadequate non-clinical data to establish the safety of VIP use in humans, particularly for chronic use. Clinical safety data that are available to us primarily show mild adverse effects associated with VIP's vasodilatory activity, but severe immunologic reactions have been documented. We do not have adequate clinical information about the condition called CIRS.

The single trial assessing the effectiveness of VIP to treat CIRS water-damaged buildings did not establish that VIP is associated with clinical improvement or that VIP is systemically available from intranasal delivery. We do not have adequate information to establish the historical use of

VIP in pharmacy compounding.

Therefore, we find the physical and chemical characterization, safety, efficacy, and historical use in compounding of VIP weigh against its inclusion on the list of bulk drug substances that can be used to compound products in accordance with 503A of the FD&C Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you. Any clarifying questions? Dr. Carome?

DR. CAROME: Mike Carome. Did the Shoemaker study, the clinical trial involving the 20 patients, would that have required an investigation or new drug application to the FDA? And if so, was one submitted to the FDA? And did the FDA under that, if it got one, review the study that was conducted?

DR. JOHNSON: I'm going to refer that to Ms. Gebbia.

MS. GEBBIA: We generally don't disclose the existence of INDs unless they've been

publicly disclosed by the party that has submitted it.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Thank you, Dr. Johnson.

We will now proceed with the nominator presentations. We have one presentation on vasoactive intestinal peptide from Dr. Ritchie Shoemaker from Hopkinton Drug, Incorporated.

Nominator Presentation – Ritchie Shoemaker

DR. SHOEMAKER: Good afternoon. My name is Rich Shoemaker. For clarification, I'm a retired physician. I am not affiliated with Hopkinton Drug. I'm medical director of a private, non-profit research organization called the Center for Research and Biotoxin Associated Illnesses. I hope my response will clarify some of the comments made by Dr. Johnson.

What I will attempt to work with you today is that, reality, for the people who have a multi-system illness acquired following

exposure to the interior environment of water-damaged buildings, as well as other illnesses, given names like fibromyalgia and chronic fatigue syndrome, we have been able to show through physician use that intranasal VIP safely corrects proteomic and transcriptomic abnormalities. And that paper was accepted for publication last week. It would have been impossible for the FDA to review ahead of time but was supplied in the packet to Dr. Hong.

We also have a manuscript in preparation showing effectiveness of VIP in correcting grey matter nuclear atrophy, and a total of 10 structures in the brain using an FDA-cleared software program called NeuroQuant. There is no data anywhere showing that any drug can safely correct proteomics, transcriptomics, and grey matter nuclear atrophy.

What we showed in the paper referred to by Dr. Johnson was statistically significant improvement that was durable without adverse effects over 18 months in a group of patients

who had followed a 10-step protocol that's been peer reviewed and published previously, and has been subjected to two placebo-controlled, double-blinded trials.

There is no other variable that was changed in this study to show systemic benefit other than use of VIP. The reason that some patients did not complete all 18 months of the trial is that many felt better to the point of not needing any medication well before the 18-month duration. They did not continue the drug beyond that time.

The 2016 paper was accepted for publication in Medical Research Archives and has been supplied to you. It is absolutely dramatic, showing that resolution in ribosomal and nuclear-encoded mitochondrial gene expression, these changes approximate to the factor of 10 to the 43rd power. No study has ever shown this benefit in any medication. The study on 39 patients that also was included in the packet sent to Dr. Hong showed remarkable

correction, along with longer use of VIP, of grey matter nuclear atrophy.

VIP is not compounded in a dilute solution. It's a concentrated solution of 500 mics per mL. One percent glycerin is added to a sterile saline solution to help preserve secondary structure and prevent protein aggregation. All glassware is used in preparation. It's disinfected with 70 percent isopropyl alcohol.

Included in the packet we sent to you were multiple HPLC stability studies confirming VIP nasal spray is highly stable with API maintaining correct amino acid sequence. Subsequent to the expiration of the due date for materials, we received two analyses from Alliance Protein Laboratories confirming circular dichroism analysis of vasoactive intestinal peptide in aqueous methanol maintains its alpha helix and the beta folds.

The product itself is highly stable with a pH of 6.1 to 6.2. It has been shown to be

stable in refrigeration for up to 90 days. Each of the bottles used is labeled for use for 30 days. There are USP monographs regarding the packaging of the nasal sprayer in residual solvent levels, showing acceptability well below limits in the packet provided to you.

The history of this drug is it was first used in November 2008. The prescribers see great benefits in the survey sent to you. This is just a small group of the docs that are using this. It is known by physicians that use it that the quality of life restoration is remarkable, and the drug itself has been life-saving in more than a few cases. The manufacturer has shown 98.8 percent purity of the drug. And specifically in regard to immunologic responses, there's no evidence in any of the uses that we have seen of any cytokine release syndrome, and there's nothing to support anti-drug antibody issues.

The two patients reported as having those issues were listed in a letter in

response to Dr. Sayeed [ph] writing about pulmonary hypertension. They never were published. We have not seen any documentation anywhere of who those patients were, what they had wrong with them, and what alternative approach to diagnosis was made. I do suggest that that information not be given as much weight as Dr. Johnson provided.

Currently in the U.S., there are 1700 patients taking VIP; 314 physicians are writing prescriptions to a single drug, Hopkinton Drug in Hopkinton, Massachusetts. The drug has been refilled over a thousand times with total refills approaching 8,000. We have known five patients who had to stop VIP due to adverse effects, usually due to their low-grade rise of lipase in association with biliary sludge formation in a positive HIDA scan.

Regarding immunogenicity, using the guidance for industry and from the FDA published in August of 2014, acute use of VIP reduces dypsnea, shortness of breath, and joint

pain in less than 10 minutes. There is no [indiscernible] seen, observed cytokine release syndrome.

In terms of looking at some of the genetics and the HLA haplotypes, some of the patients with CIRS, as mentioned, HLA-DRB1-4 and DQ3-DRB4-53. These people are associated with the worse rheumatoid arthritis, the worse problems of autoimmune hepatitis, the worse malaria, and the worse CIRS. Defective antigen presentation is suspected and has been published by Dr. Steer [ph] regarding lung patients.

What we have not seen is any evidence of undesirable antibody responses or anything suggesting that. We see no augmented responses in these illnesses, which are activated immune system illnesses. The theoretical delivery risk of intranasal VIP might improve or increase immunogenicity, but actually less is seen. And what we see in a significant number of our patients with anticardiolipin antibodies

and ANCA is those auto-antibodies often convert to normal.

Chronic use of over 6 months is rare. There's a downwards titration over time. It's not increasing. There's no evidence of tolerance. Pulmonary hypertension is the element most and highly associated with improvement with VIP, beginning within 1 month lowering pulmonary artery pressure below 8 millimeters of mercury. Exercise tolerance is better. Executive cognitive function is better. I'm going to come to that in just a sec.

The transcriptomics are done with next-generation DNA sequencing. They are now accepted for publication, have not come out. The compound is anti-inflammatory. It corrects massive mitochondrial gene activation that are nuclear encoded and corrects the sarcin-ricin loop of the 28-S subunit of the ribosome. This is found in all of these chronic fatigue illnesses, and we actually think we've found

the magic bullet but have not published enough patients, as you already know. It corrects abnormalities in layered levels of granzymes and defenses and activates Ikaros to substantial benefit.

When we look at changes in grey matter, nuclear atrophy, use for longer periods of time show remarkable correction of nuclear atrophy; with less than 12 weeks, only 11 percent of these atrophic nuclei improving. But over 24 weeks -- granted, it is a small study -- 33 percent improved. By dose, we see the same sort of dose-response relationship where higher levels of doses show improvement in 20 regions; 35 percent are improved and 21 percent resolved their abnormalities of nuclear atrophy to equal controls. If we look, out of these 10 structures, 3.5, 3.4, and 3.6 before use of VIP, and 0.9, which is equal to controls, afterwards is just stunning.

The VIP is stable in solution. There's nothing to suggest anti-drug antibodies. So

called severe immune adverse effects are not supported in the literature other than reported in one letter, and is not supported by 8 years and 1700 patients' experience in using the drug.

There are now three studies. Granted, two are very recent. And I apologize. We've been working as hard as we can. Three studies on VIP show efficacy and safety without significant adverse effects. Given that we know -- and there's no argument that VIP accumulates in the brain, and the positive effects of Ikaros as well, the resolution of grey matter in nuclear atrophy has never been seen before.

Historical use continues to grow as the same safety and efficacy seen beginning in 2008. And based on the four criteria listed above, we feel that these criteria weigh heavily to add VIP. What we're looking at is a drug that has restored life to some of the most disabled people I've seen in treating 300,000

patients in my primary care career. Thank you for your attention.

Clarifying Questions from the Committee

DR. GULUR: Do we have clarification questions from the committee for the presenter? Dr. Carome? I'm sorry. Dr. Vaida, would you like to go first?

DR. VAIDA: Is Hopkinton Drug the only place that compounds this for you?

DR. SHOEMAKER: To my knowledge, it is the only one at this time. Other pharmacies are considering using this drug. There's a pharmacy in Los Angeles, one in Montana, and one in Texas that would like to use it.

DR. GULUR: Dr. Carome?

DR. CAROME: Mike Carome. Two questions. Can you tell us whether an IND, an investigation new drug application was submitted to the FDA for the research that was conducted?

DR. SHOEMAKER: No IND was submitted. It's my understanding that because this was on

a list that said it could be -- sorry. It was not on a list that said you couldn't compound it, that an IND was not required. If I'm incorrect, please correct me.

DR. GULUR: We'll allow the FDA to comment on that.

MS. GEBBIA: I'll say that our clinical investigations generally require an IND. That's really all I can say about the case at this point. We have regulations about INDs that have been published, and I would refer folks to those at this point.

DR. CAROME: And could you clarify whether any of the clinical trials that you've referenced were randomized, placebo-controlled trials?

DR. SHOEMAKER: Not at this state. The grey matter nuclear atrophy study was just recently presented at a conference on October 15th. There were a number of Alzheimer's researchers that were certainly very interested. That was a proof of concept

trial. To tell someone we can fix grey matter nuclear atrophy would be laughed at before our data were presented. We're not laughing about that anymore.

DR. GULUR: Dr. Braunstein?

DR. BRAUNSTEIN: I see all this research being done, and obviously all these claims of efficacy, and I'm curious. Why are you seeking approval on this list as opposed to seeking a new drug application approval? I mean, to me this is a backdoor. This is not really the mechanism for registration of new drugs.

DR. SHOEMAKER: The drug is not new in the United States. Biogen Idec Canada has phase 2 trials under the name Aviptadil. It's been noted in research papers in 1970 to have diverse multi-pluripotent beneficial effects. It's not an attempt to get around the FDA. It was continuing the process of using a drug that has been used since 2008 with a prescription for compounding.

DR. GULUR: Dr. Wall?

DR. WALL: I believe you said this drug, you put it through a peer review process. Could you describe that process for us?

DR. SHOEMAKER: The Journal of Health provided a peer review for the paper published in 2013. Medical Research Archives did a peer review for the transcriptomics. The third paper that we are writing up now is a draft to the manuscript and has not been submitted for peer review at this time.

DR. GULUR: Could you describe the IRB process you underwent to conduct these studies?

DR. SHOEMAKER: Yes. I used Copernicus Group IRB and Research Triangle North Carolina. I submitted in 2009 informed consent documents and a protocol that was back in forth in the public. The approval of the drug came -- of the IRB came in 2010. For the genomics, we asked the same IRB for a waiver of informed consent on retrospective use of people already in our data set. We use the next-generation sequence here at NC State for our samples.

The same review process, a retrospective review, was granted a waiver on a separate application through IRB for the NeuroQuant. In the packet we submitted to you, there are two papers on NeuroQuant. One was peer reviewed and published by Neurotoxicology and Teratology, and then there was a second paper that was published in an online journal.

DR. GULUR: Thank you, Dr. Shoemaker. And during this IRB process, it was never brought to your attention, or it was never raised that this should perhaps go through the IND process?

DR. SHOEMAKER: Because we didn't know that it was required to be an IND since it was not on a list that said you couldn't compound it. The question of IND never came up.

DR. GULUR: Thank you.

Yes, Dr. Wall?

DR. WALL: Another question. You said that the side effect profile was minimal, but could you elaborate on what side effects you

have seen, and were there any unexpected ones?

DR. SHOEMAKER: The side effects are looked at hyper-acutely when the drug is first given in a physician's office. There will be one spray given on one side of the nostril after someone's blown their nose. The patient is monitored. We look for changes in joint discomfort at 5 minutes, 10 minutes, and 15 minutes. We also look for ability to take a deeper breath, a more full breath.

I fully admit that our attempt to show cognitive improvement in 15 minutes is somewhat subjective at best. People are followed every time they refill a prescription, are you having any problems that are new since you've used the drug. We do not have a formal reporting system for adverse effects thought to be due to the drug.

In the first two years of experience, we did see elevated levels of lipase, never more than twice normal, then resolved with removal of the drug. But when we saw that lipase

elevation, and given the pancreatic secretion profile, it shouldn't have been too surprising, we stopped the drug.

At the same time, because that was a little unusual -- why would one person have lipase problems and another person didn't, same age, same gender, same race -- we then looked for -- with a centigram for biliary abnormalities. They were normal. They were in all cases.

Then we looked with HIDA scan, and we saw a marked reduction in excretion of tracer, suggesting that a problem with biliary sludge was contributing to the rise in lipase. Rather than give you a definitive answer and exactly the market biology-wide, because it was so rare, we stopped the drug and went on. Those people did not get benefit from VIP and duration.

Now that we know about the transcriptomic changes, now that we know the mechanisms that this drug is actually doing at

the fundamental basis of illness, we are looking at a breakthrough in this chronic fatigue illness. I'm sure you've heard arguments about chronic fatigue syndrome over the years. We're looking at the first time we can show the genomic and transcriptomic abnormalities that a safe drug let's people enjoy, and giving back life, and you fix pulmonary hypertension. I'm telling you, you have to see some of these folks to believe them.

DR. GULUR: Go ahead, Dr. Pham.

DR. PHAM: So clearly the focus has been on the intranasal delivery of VIP, however, in the FDA materials, in historical use and compounding, they mentioned that the nasal and injectable compounded formulations have been advertised. Are you aware of its injectable use?

DR. SHOEMAKER: I'm sorry. This is such a big room, and I've got bad hearing. Could you --

DR. PHAM: Just that apparently the FDA materials also talk about this drug, including nasal and injectable compounded formulations. Are you aware of its injectable use?

DR. SHOEMAKER: I have never seen injectable use of VIP. That was new. I'd never seen anybody use VIP for intracavernosal injection until the FDA found that paper. But specifically, it's nasal spray only, no -- and then the other issue is that the systemic kinetics of the drug are such that it will be lysed by endopeptidase in hepatic metabolism so fast, I can't see how an injection that would contribute to possible introduction in the blood supply would make sense.

DR. GULUR: Ms. Davidson?

MS. DAVIDSON: Considering that you believe that this will reverse grey matter nucleus atrophy, that has many more implications than the diseases you mentioned. And if you've got 1700 patients that are receiving it now very successfully in one

provider pharmacy, that sounds very much like an IND situation to me. Would you consider filing an IND with future submission for such a miracle drug?

DR. SHOEMAKER: Absolutely. This drug has been a magnificent addition to care of some of the most desperately ill people you ever want to see. I'd be happy to submit INDs if that were demanded, but I do speak for the people that are on the drug now that cannot give up the quality of life that they have now.

MS. DAVIDSON: And maybe this is further discussion later, but if he were to file an IND and the drug was not added to the list, would he still be able to continue to use this drug in those patients?

DR. GULUR: So we'll defer that for our discussion portion. Any other clarifying questions?

(No response.)

DR. GULUR: Thank you, Dr. Shoemaker. We appreciate your presentation.

DR. SHOEMAKER: Thank you for your attention.

MR. MIXON: Were his slides provided to the committee?

DR. GULUR: I'm sorry?

MR. MIXON: Were his slides provided to the committee?

DR. HONG: Slides that were presented?

MR. MIXON: Yes.

DR. HONG: No. The nominator's slides are not presented to the committee [inaudible - off mic].

Committee Discussion and Vote

DR. GULUR: Since the agency did not receive registrants for the fifth open hearing session, we will move on to the committee discussion and voting. We will now begin the panel discussion of vasoactive intestinal peptide, and we can start with Ms. Davidson's question, which was referred.

Would you like to repeat that?

MS. DAVIDSON: Do you need me to repeat

it?

MS. GEBBIA: No. I don't think so. My memory is a little -- should be able to handle that one. And please jump in if I'm incorrect. But my understanding is if an IND was submitted and it wasn't placed on clinical hold, and it met requirements and then consistent with what was in there, that patients could be treated pursuant to it.

DR. GULUR: Any other questions? Dr. Braunstein?

DR. BRAUNSTEIN: Could you just repeat that? I missed the point about a hold. Is there a hold on --

MS. GEBBIA: No, no, no. I said if an IND were submitted and it weren't placed on clinical hold. Sort of the IND, we don't approve them the way we do other things. It's just that we put a hold on it. So if a hold weren't placed on it, then it could proceed.

DR. BRAUNSTEIN: I see.

DR. GULUR: Any further discussion,

clarification points? Yes?

DR. VAIDA: I had one question on the adverse reactions. So since this isn't like the study, these studies are being done under an IND, but they're approved by an IRB, none of those reactions have to go to FDA, right? They just go to the IRB? Because it looked like the FDA scoured their database and found nothing, and then we just heard that there were some reactions.

MS. GEBBIA: Right --

DR. VAIDA: I'm just curious --

MS. GEBBIA: It wasn't reported the way you would report adverse events through an IND. That's correct. I would have to defer to others about the basis of getting that, where they got that.

DR. JOHNSON: We have requirements, regulations that pertain to the submission of adverse events for compounds that are being studied under an IND. The requirements do not spread to information that is not being

generated under an IND.

DR. GULUR: If there are no other questions from the committee members, I have one question. And perhaps the FDA can help me understand this. Institutional review boards, would it be reasonable to consider that they would be familiar with the requirements of an IND?

DR. JOHNSON: Absolutely.

DR. GULUR: Does the FDA have any purview in educating IRBs on this should they find that they are unaware?

MS. GEBBIA: Yes. I think that's an issue that we are -- there are regulations that pertain to human subject protections that are under the FDA's purview and also HHS's.

DR. GULUR: Thank you very much.

Any further discussion points? Dr. Braunstein?

DR. BRAUNSTEIN: Sure. And I think -- and maybe the FDA will need to deal with this. But under the Code of Federal

Regulations, 312.2A, applicability for requirements for an IND -- I'm sorry, B, exemptions, "The clinical investigation of a drug product that is lawfully marketed in the U.S. is exempt from the requirements of this part if all of the following apply."

I'm just wondering if the definition of lawfully marketed is perhaps unclear because I do believe that if a product can be compounded, it is lawfully marketed in a sense. And that is sort of a conundrum here, looking at the way the Code of Federal Regulations is worded, and you may want to take a look at that.

MS. GEBBIA: Yes, thank you. We're considering our policies in this area. We're aware of that.

DR. GULUR: Thank you. Any further discussion from the panel?

(No response.)

DR. GULUR: We will now end our discussions and start the vote. The question before us is, FDA is proposing that vasoactive

intestinal peptide not be included on the 503A bulk list. Should vasoactive intestinal peptide be placed on the list?

Please press the button firmly on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote.

(Vote taken.)

DR. HONG: For question 2, we have zero yeses, 8 nos, and zero abstain.

DR. GULUR: Thank you. We'll begin with Dr. Vaida for comments on his response.

DR. VAIDA: Allen Vaida. I voted no, and it just seems like -- I agree with one of the members here that it just seems like a backdoor effort, and that an IND should be put forward for this.

DR. GULUR: Dr. Pham?

DR. PHAM: Katherine Pham. I voted no as well for similar reasons about the IND, though hope that if there are patients that need to continue therapy or on the current protocol, that that access does not get

disrupted.

DR. WALL: Donna Wall. I voted no for the same reasons. It sounds in Dr. Shoemaker's presentation that there is something that is really working and needs to be explored more on a national basis, which is why it really needs an IND so that the entire profession, or all of these patients across the country, if effective can take advantage of it.

DR. CAROME: Mike Carome. I voted no for the same reasons just stated.

DR. HOAG: Steve Hoag. I voted no for the same reasons. It sounds more in the research stage. And from the discussion today, it sounds like this is something that needs to be more investigated.

DR. DiGIOVANNA: John DiGiovanna. I voted no for the reasons that have been mentioned. I'm not quite sure about the IND issue. I think my perspective is I'm not clear that I understand what this condition is. It's not a well-recognized, established disorder

where it is clear that it's easy to identify who has it and who doesn't have it. And that makes it quite difficult to determine if treatment is effective or isn't effective, or in whom it might exhibit certain toxicities versus others. And that's the reason I think it's important to study it in a rigorous fashion.

MS. DAVIDSON: Gigi Davidson. I voted no for many of the reasons stated. For a drug that will potentially reverse grey matter nucleus atrophy, which could be useful in Parkinson's disease, multiple sclerosis, Alzheimer's, dementia, I think Dr. Shoemaker has the key element in place, and that's an IRB, which this group has discussed often as the major obstacle to filing an IND for compounded preparations.

He's already got that, so I think to protect the potential for this drug and certainly for the 1700 patients that are currently on it, that an IND is the way to go

in this case. And I would not want to deny those 1700 patients access.

DR. GULUR: I voted no for all the reasons that have previously been stated. With that, we will conclude this vote.

Thank you, everyone, for your participation. We will now have our afternoon break. Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. Please return to your seats at 3:25 p.m. Sorry, 2:35. We are very ahead of schedule. Thank you.

(Whereupon, at 2:20 p.m., a recess was taken.)

DR. GULUR: Thank you, everyone. We'll reconvene for the afternoon session. We will now continue with the FDA presentation on demonstrably difficult to compound drug products that employ topical delivery systems. Before we begin, we will have Dr. Cindy Hong read the Conflict of Interest Statement

Conflict of Interest Statement

DR. HONG: The Food and Drug Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of Boards of Pharmacy, the United States Pharmacopeia, 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 USC 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 USC 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 his or her 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness

testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

During this meeting, the committee will discuss drug products that employ transdermal and topical delivery systems, which were nominated for the Difficult to Compound List. The nominators will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. For the record, Dr. Michael Carome has been recused from participating in the discussions and voting for this topic. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the

topic at issue.

We would like to note that Dr. Donna Wall is a representative member from the National Association of Boards of Pharmacy and that Ms. Gigi Davidson is a representative member from the United States Pharmacopeia.

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 USP. Their role is to provide the committee with the points of view of the NABP and 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. Ned Braunstein and Mr. William Mixon are participating in this meeting as nonvoting 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. Braunstein is employed by Regeneron Pharmaceutical, and Mr. Mixon is employed by The Compounding Pharmacy.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. GULUR: Thank you. The FDA would like to pass along some samples currently to the committee members. Dr. Caroline Strasinger will present on topical delivery systems.

FDA Presentation - Caroline Strasinger

DR. STRASINGER: Thank you. I would like to discuss with you the transdermal or topical delivery system today. I am Caroline Strasinger from the Office of New Drug Product in the Office of Pharmaceutical Quality within CDER. I do want to stress that transdermal or topical delivery systems for this discussion does not include any liquids or semi-solids such as gels, creams, lotions, foams, ointments, or sprays.

I will briefly introduce you to the transdermal or topical delivery in general, as well as the topical or transdermal delivery system, and then we'll go through the evaluation criteria for the Difficult to Compound List, including complex formulation, drug delivery mechanism, dosage form, complex

characterization, and control of drug bioavailability, complex compounding process, as well as complex physicochemical or analytical testings, and provide you with the recommendation of the FDA.

First, transdermal systems are designed to deliver active ingredient across the skin and into systemic circulation. Their target is the blood stream. Their target is to get the drug into systemic circulation. Conversely, topical delivery systems are designed to deliver the active ingredient into local tissue. So their target is not the blood stream itself, rather the lower layers of the epidermis, the dermis, or the subcutaneous tissue below. Again, there is a difference between the two transdermal delivery systems. The blood stream topical delivery systems are designed to deliver the active ingredient to local tissue.

Despite those broad differences, we group these two together in this conversation

because these products employ similar manufacturing and quality control concerns that would present similar risk, patient safety risk in the end.

Again, it is important to stress that we are not considering liquids and semi-solids such as gels, creams, lotions, foams, ointments, and spray in this review. I think we recognize that there are transdermal and topical delivery gels, creams, and lotions out there, but for this purpose, we are only looking at the transdermal or topical delivery system.

Briefly, we can broadly divide these products into two major categories: matrix type transdermal or topical delivery systems, or reservoir type systems. You're probably most familiar with matrix type systems. They do dominate the market. Some examples would be nicotine transdermal system such as NicoDerm CQ. The lidocaine topical patch would be an example of a topical delivery system that

would represent a matrix type system.

Reservoir systems are less common. Some that are currently present on the market would be the testosterone transdermal system. On this particular board, this is the only board with reservoirs. I will pass this around. But the reservoirs look like this, and the matrix are on all your boards that you receive right now, and look like this at the bottom.

In general, they do all contain some major components that are quite similar to each other. All transdermal or topical delivery systems include a release liner, which is that part that you would peel away from the product and throw away in the end. They all contain a backing membrane, which is that outer surface, so once applied, that's what you would see on the surface of your skin. And they all contain an adhesive in order to maintain contact with the skin.

The difference between the two are actually where the drug API itself resides. In

a matrix type system, the drug would reside in the matrix itself, so it would be dissolved in or contained in a matrix layer. That is the pink layer on the top design there. In a reservoir type system, there is a liquid or gel component to it, however, it is entrapped between two membranes. So it's a fully-sealed contained unit, but there is a gel reservoir inside the product itself.

Despite they might appear quite simple, they look very simple with films, they do contain very specialized characteristics in order to elicit a quality product. Some of those characteristics that we will explore in the next 20 or so minutes will be specialized raw material control selection, distinctive manufacturing processes, and unique in-process and final control measures.

What is meant by eliciting a quality product would be, A, that it has to deliver a specified amount of API. It has to have control impurities. Many of the excipients

used in these are adhesives used in other industries, so they may have interesting impurity profiles, but a quality product would be able to control these impurities.

They need to maintain adhesion. Transdermal and topical delivery systems vary greatly across the market. Some are designed to deliver a drug for just a few hours, while some are designed to deliver a drug for up to 7 or a week-day -- a couple days to 7 days. And they must limit irritation. As I mentioned, some of the excipients can be quite irritating. They are not necessarily medical grade adhesives, so they do elicit irritation. So a proper quality product is one that controls irritation as well.

The first criteria is complex formulation. This is going to be a common theme throughout the next 20 minutes. API delivery through the skin is influenced by a set of complex characteristics of the active ingredient and the other excipients. We're

going to hear that theme over and over about how the excipients and the complexity of the choices available interact with the active ingredient, as well as the batch-to-bath variability of the active ingredient in the excipient itself. Not only do they affect delivery of the API, these factors can make it difficult to maintain adequate functional properties such as adhesion and limiting irritation.

So delving a little deeper, looking at the properties of the API that impact product performance, one would be the polymorphic form. Transdermal and topical delivery systems often require a specific polymorphic form, or the drug is supposed to remain in an amorphous form.

Inadequate control of your polymorphic form or your state of your drug would lead to excessive crystallization in the vehicle, whether that be a reservoir gel or the adhesive matrix. Now, the problems that can arise from

that is, A, you don't have drug for delivery, but, B, you can also lose adhesion because the system becomes more rigid because of the crystals.

Solubility is critical for transdermal and topical delivery systems. For the API to pass the skin, it needs to be in a dissolved state. Sink conditions are necessary to deliver the drug across the skin. Now, sink conditions refers to the driving force. You have a high concentration at the surface or in the transdermal or topical product. It has to slowly decrease as you move into the lower levels of the skin and the systemic uptake. So if you don't maintain that sink, that concentration gradient, you won't have consistent delivery.

Compatibility is critically important. The physical, chemical, or physiological interactions of the API and the excipients, they interact with each other. And the way that they interact can often result in product

stability, manufacturability, efficacy, performance, therapeutic activity, and they can lead to varying side effect profiles.

Then finally, purity is an important property of the API that needs to be evaluated and maintained. While we understand a lot of the permeabilities of the API itself, a lot of time the impurities associated with that API are not well understood. Therefore, if your API is not pure, you may delivering impurities at a rate that you don't understand -- or don't evaluate.

Moving forward with the excipients in the complex formulation, characterization and control of those key functional excipients are critical to the safety, efficacy, and quality of the transdermal or topical delivery system. Excipients used in transdermal systems include various and multiple adhesives, permeation enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers, tackifiers, and the list goes on

and on.

When you looked at the boards that went by, you could see they were quite varied across the board. Many of these products, even though they do appear like simple films, they do contain multiple adhesives in order to maintain their adhesion, so it's not simply just one adhesive with a drug dissolved in it. All excipients and their varying combinations can influence active delivery or product adhesion, and therefore their safety profiles.

Looking specifically at the adhesive, because most often in transdermal and topical delivery systems, adhesive itself is the largest component, the performance of the finished product can vary widely based on the selected adhesive system. And I refer to it as an adhesive system because, as mentioned, they often contain multiple adhesives in them.

There are primarily three types of adhesives. There are few others out there, but generally they can be divided into basically

three categories: acrylate, polyisobutylene/polybutene, or PIB adhesive, and a silicone adhesive. Now, on the ingredients list, they would appear as those, however, there are actually hundreds of different grades of each of those three categories. Each grade of the categorized adhesive contains its own individualized raw material characteristics such as viscosity profiles, impurity profiles, solvent systems, molecular weight ratios.

Those polyisobutylene and polybutene, the PIBs, the different grades will have different high molecular weight polymers than low molecular weight polymers. You start playing with those ratios in the different grades, and you're going to get a different viscosity profile and a different adhesion profile.

Selected cross linkers, functional end groups, these are all parts of polymerization. Again, selecting one of these three main

categories of adhesives does not necessarily mean that you're always going to have the same adhesive because there are so many different grades.

Adhesives are qualified in the manufacturing world through extensive testing as a raw material. So as the raw material's received, manufacturers then test it as a laminate. So they cast it and dry it and test the properties of tack adhesion, all of the properties of just the adhesive in a dried state, and then they'll test it in the final product. So this just illustrates how much testing goes into just picking the correct raw material.

In summary, transdermal and topical delivery systems are created from ingredients with highly variable chemical and physical properties, and you must have predictable and controllable composition and stability, and exhibit consistent functionality, all of which can be influenced by the raw material that's

actually selected in how they are controlled. So as such, we feel that transdermal or topical delivery systems presents demonstrable difficulties for compounding.

Looking at the complex delivery system mechanism itself, factors influencing the delivery of an API through the skin can include obviously the quantitative and qualitative composition. We just explored that a little bit, so proper excipient selection is important.

Excipients again will individually and collectively influence the rate of delivery as well as product performance, meaning adhesion, or it can be a factor that influences API through the skin. Obviously, as mentioned, some of these products are designed for just a couple of hours wear; some are designed for multi-day wear. If the product does not stay adhered to the skin, you will not have API delivery.

Finally, one other area we want to touch

on is physical design, which would include surface area backing membrane and thickness of the matrix. API delivery is directly proportional to the surface area of the transdermal or topical delivery system that is in contact with the skin. The thickness of the adhesive matrix itself, so that layer that is cast, can influence delivery and API delivery, as well as adhesion, and the type of backing membrane itself can actually influence delivery and adhesion.

Just as there are many, many different grades of adhesives, there are many, many different backing membranes as demonstrated by the boards that went around. There were cloth type ones, metallized ones. There were lots of different ones on all those boards.

An example of how it would impact API delivery is some of these membranes have what is considered low moisture vapor transmission ratio. That means the liquid cannot permeate your sweat; for instance, cannot permeate

through the backing membrane, and it provides occlusion. When you have occlusion, your stratum corneum hydration goes up, and therefore your skin permeability goes up.

Some products are designed to have that occlusive backing membrane. Conversely, some products are designed to not have that occlusive backing membrane. So if a compounder were to choose the wrong backing membrane, you could dramatically change the delivery profile of the product.

Stiffness of backing membrane, thickness of the adhesive layer, and the surface area can all influence skin adhesion. Very thick membranes are very rigid structures. They may not conform to your movements as you turn and twist. Conversely, very thin membranes may make it very difficult to adhere to the product. It will wrinkle as you pull that release liner off and make it difficult to adhere to the skin.

In summary, the mechanism by which

active ingredient is delivered through the skin is complex because it involves designing and manufacturing a product that can deliver a specific amount of API per unit area, per unit time, maintain adhesion for the duration of intended wear, and have minimal irritation of the skin throughout wear and upon removal.

Again, the dose delivered is affected by several factors which may adversely affect safety and efficacy, including lack of precise control of raw materials, as well as the manufacturing process. Therefore, we feel this complexity creates a demonstrably difficult product to compound.

Transdermal and topical delivery systems are considered complex dosage forms. As we've already explained, they have complex formulations and complex drug delivery mechanisms. Transdermal and topical delivery systems necessitate extensive product development, and characterization, and precise control over the raw materials and

manufacturing processes. As such, they present a demonstrable difficulty for compounding.

Now, looking at bioavailability, as we mentioned, they're very complex, and even small changes in performance characteristics can have a significant impact on local and systemic bioavailability and efficacy of the product. Thinking about locally-acting products -- so again we're going back to the topical delivery systems -- they often have little to no systemic uptake. Remember, their target is local tissue, not the blood stream. As such, bioavailability is often assessed using pharmacodynamic studies or clinical endpoint studies, chemical endpoint approaches such as is your pain relieved, yes or no, or a scale.

Systemically-acting products, so transdermal delivery systems, their PK profiles can be impacted by several physiological factors, including something known as a skin depot effect. And that's where actually the layers of the skin themselves serve as a

reservoir, and the reservoir is influenced by the chosen excipients that are in the product.

So if you apply a product here, the drug is absorbed into the local tissue. It may remain there. When you remove the product, you now have a depot You go to apply your next product you're delivering from your depot as well as your new product. Absorption differences at different application sites are quite well known and studied in literature as well.

To assess bioavailability as part of the approval process -- so for NDAs and ANDAs -- applicants typically have to perform a multitude of in vitro pharmacokinetic and other in vivo assessments such as irritation/sensitization studies as well as adhesion studies. Currently, there is no single easily reproducible reliable method of measurement that can quantitate the dose delivered by the product and received by the patient.

These measurements would be necessary to consistently make a product with a delivered dose that uniformally falls within an acceptable range. Because there are no methods to characterize bioavailability, compounded transdermal or topical delivery systems may not possess the appropriate bioavailability profile, and thus they can pose significant safety/efficacy risks to the patient.

In summary, in vitro assessments such as in vitro release testing and in vitro adhesion testing, which we'll explore shortly, alone are not sufficient to accurately predict permeation, bioavailability, and overall clinical effect. Even the small changes in performance characteristics can significantly impact the local and systemic bioavailability and efficacy of a product. Therefore, transdermal and topical delivery systems are considered complex systems for which bioavailability is difficult to assess and may not be achieved, and therefore present a

demonstrable difficulty for compounding.

So let's look at a potential compounding process so we can understand how complex it would be. Transdermal and topical delivery systems require specialized processing to reproducibly yield products with predictable drug delivery. Thinking about the reservoir, so even though there's not a lot of those on the market, let's take a look at those.

Transdermal and topical delivery systems that would employ a reservoir type delivery system requires specialized heat sealing equipment to fully entrap the gel between the membrane layers of the product to prevent leaks. Leaks can be very dangerous for others as well as the person that is wearing the product itself. Therefore, manufacturers have to have very specialized heat sealing equipment that will fully entrap the gel, and then they have to monitor that those seals remain tight throughout the stability of the product.

Looking more at the more common process

now, even the simplest of matrix products -- I mentioned how complex many of these are, but if we broke it down to the very simplest of products, they're going to contain at least three major steps, including mixing, casting, drying, and laminating.

In the mixing stage, that's where you're going to dissolve your API. You're going to mix up your permeation enhancers, your adhesives, and you're going to create a uniform mix. That mix will then be transferred to a caster or a coder. In the casting and coding stage, these casters and coders themselves are quite varied. There are many, many different designs out there, but in general, you want a uniform casted thickness and coat.

Most people do not realize that where we actually cast and coat is on the release liner. So that piece that we end up throwing away is where the product is actually made. So the release liner passes underneath the caster or coder. It picks up its uniform thickness, and

then it passes into an oven where the solvents are driven off. Once it exits the oven, that is when the backing membrane -- so that piece that's on the out exterior of the product -- is then laminated.

Breaking the three processes down just a little more, mixing is critical to achieving a uniform mixture of API and excipients. Exceeding the solubility limits, incomplete mixing, or dissolution of the API can result in decreased API available for delivery. Overmixing -- so you can't just mix it up until you think you have a uniform mix -- or excessive propeller speeds can actually introduce air bubbles into the mix. When you cast that out, you have an uniform matrix, and therefore it could lead to adhesions problems, or even delivery problems.

Additionally, formulations often contain immiscible adhesives or penetration enhancers. As mentioned, many products have multiple adhesives. That is because when you dissolve

your API in one adhesive, the tack of that adhesive will drop, so you have to boost your adhesion with another adhesive. Those adhesives often are immiscible, and therefore you end up with kind of an emulsion mix. It's very important that you then have a uniform mix when you cast out this laminate.

Variable mixing times, holds, so how long it takes you to get that mix to the caster, and on to the laminate, and into the dryer can actually influence adhesion properties or delivery, as well as the transfer can lead to unintended phase separation. So if you get the oil/water mixture, that would lead to not a uniform product.

Casting is critical to achieving a uniform thickness or coat weight. This is typically performed on automated equipment with precise gap thickness and speed controls to produce uniform thickness and coat weight. Varying this thickness in coat weight directly affects the API content. Just as there are

numerous adhesives in backing membranes, there are many, many release liners commercially available.

Selecting a release liner that is incompatible with the mix or casting on a non-coated side of a release liner can result in permanent bonding of the release liner. I've actually demonstrated this here. Once you remove that release liner that I did at the very beginning -- I flipped it over and applied it to the product, and now it is permanently bound to the product or it's causing cohesive failure. So that just illustrates that if you coat on the wrong side of the release liner, which is just a clear membrane, you can actually result in a poor quality product.

Appropriate drying is critical for driving off solvents. It's not as simple as putting a transdermal laminate into an oven and turning it on. Conventionally this is performed in multi-chamber ovens with very precise control of temperature, drying time,

and air flow.

If you drive off solvents too quickly with too high of temperatures at the very beginning, you can lead to bubbles forming in your matrix. Too low or shorter of drying times may not entirely drive off all the solvents, and therefore you believe behind this soft, tacky, transdermal system or topical delivery system which would impact stability, delivery, and adhesion properties.

It's critical for controlling residual solvents and volatile adhesive impurities. As mentioned, many of these adhesives are used for other industries, the automotive industry and industry that uses some kind of tacky adhesive. Often these are similar adhesives, and as such, they have many impurities in them that we would not want to apply to the skin. The drying process is critical to driving off most of those impurities.

If the critical process parameters of drying temperature, dryer air flow, and line

speed are not adequately optimized and controlled, efficacy, product performance, and safety may be negatively impacted. So as such, it is important to note that transdermal and topical delivery systems are complex, and they use specialized equipment, allowing for automated processing and precise control for both reservoir and matrix type delivery systems. Any errors in the major steps of mixing, casting, or drying of the transdermal system or topical delivery system are reasonably likely to result in variability in the delivered dose and product performance.

The final consideration we have is complex testing. Extensive characterization and development studies on specific formulations, the functional properties, and the manufacturing process is necessary to help assure satisfactory performance. A large number of complex tests are needed to help ensure satisfactory performance of the transdermal system or topical delivery system,

including raw material testing, release testing, and stability testing.

We've spoken a lot about raw material testing, rigorous qualification of key excipients as required. Raw material properties like viscosity and impurity content way up stream often have a dramatic impact way down stream on the finished product. Suppliers' adhesive specifications are often very wide, so manufacturers often must set internal specifications that are much more narrow so they can assure that the adhesive they are receiving from the manufacturer will fit their product profile.

Release testing includes in vitro adhesion testing. There are actually four tests that we typically would require in an NDA or ANDA that would include peel adhesion, release liner peel, and tack and shear. These are just four different types of tests to test those adhesive properties of every batch that comes off the manufacturing line.

It's important to note the characteristics of these methods, so things like conditioning time, how long the product sat before we put it on our apparatus, how long it sat on the apparatus, the angle of the peel, the peel rate, the substrate, all of these significantly affect the results obtained, and that's compounded by the fact that -- I need to hurry up. The point is that the complexity of testing increases with the number of operators, each of which would have to achieve the same results consistently.

In vitro adhesion, it's very, very important to note that in vitro adhesion testing does not correlate well with in vivo adhesion testing. We use in vitro adhesion testing to ensure batch-to-batch consistency. There is no magic number using these in vitro methods that would say a product would adhere to a human. That is critically important to understand. Once the transdermal or topical delivery system has demonstrated adequate

adhesion through in vivo studies, then we set our specifications for the in vitro adhesion testing to assure batch-to-batch consistency and throughout shelf life.

Due to the impact of interplay of API adhesives and other excipients on adhesion properties, compounded transdermal or topical delivery systems would need to be tested through in vivo and in vitro methods in order to ensure product performance.

I'm not going to go into great detail on other release tests, but some other examples include obviously assay uniformity, impurity, and residual solvent testing. It's important to note that like in vitro testing, sophisticated equipment and specialized methods are needed to be developed.

In essence, you're not just developing an HPLC method to test for assay. You first have to develop a method that can extract the API from the product, and then develop a method for HPLC. The same could be said for all the

impurities. You have to first extract those impurities from a manufactured product and then test their quantity. The lack of quantitation of residual monomers, adhesive impurities, and the residual solvents would adversely affect the safety of the product in each batch manufactured.

For stability testing, there are many quality concerns that can creep up on us on stability. Some of those are cold flow, which is the oozing of adhesive beyond the matrix parameters. This can lead to use and adhesion difficulties. Crystallization we've already talked about.

Leachables, there are residual solvents in these products that can actually extract other impurities from pouching, from the backing membrane, from the release liner, and then you also have those impurities to worry about. The toxicity and skin penetration of those impurities would also be unknown.

Finally, volatile penetration enhancers,

penetration enhancers that are formulated into the product or critical for a certain delivery profile, if those are not manufactured appropriately and not maintained throughout the shelf life, you can have vastly different permeation profiles.

In conclusion, we feel that the complex physicochemical and analytical testing, including raw material release and stability, help assure satisfactory performance. These tests are difficult to develop, validate, and perform routinely. They have to use highly specialized and unique equipment, and analysts often have to receive very complex and considerable training to perform them consistently. So as such, they present demonstrable difficulties for compounding.

The final comment to make is the risk-benefit to patient. There are approximately 25 unique transdermal or topical delivery systems on the market with many available generic formulations approved under

NDAs and ANDAs, including pain management, contraception, Alzheimer's, Parkinson's, smoking cessation; the list is quite extensive.

As discussed, strict quality control on raw materials and the manufacturing process and product are needed. Some ingredients in approved transdermal and topical delivery systems may cause hypersensitivity. However, it's important to note that any attempt to compound them by removing or replacing a specified ingredient is reasonably like to adversely affect the product performance.

The most common components to cause irritation is first and foremost the active ingredient. You can't avoid this in a compounded product, so therefore we'll skip that one.

The adhesive is the next most common component to cause irritation. The adhesive cannot be avoided. If you tried to substitute it or remove it, you would change the delivery and/or performance of the product as we've

discussed.

The third most common component to cause irritation is the penetration enhancer. Substitution or removal can change delivery and/or performance. Penetration enhancers work in a variety of ways. You can't just simply substitute one, or you're going to change how the penetration enhancer works. Any benefit of allowing these products to be compounded is outweighed by the risk discussed.

As such, we recommend that transdermal delivery and topical delivery systems present demonstrable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on the safety or effectiveness of this category of drugs, taking into account the risk and benefit to patients. Accordingly, we believe that transdermal or topical delivery systems should be included in the Difficult to Compound List under the sections of 503A and 503B of the Federal Food, Drug, and Cosmetic Act. Thank

you.

Clarifying Questions from the Committee

DR. GULUR: Thank you very much. Any clarifying questions? Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. You haven't talked about particulate systems like those that incorporate lipid particles and other sorts of materials within a non-solid vehicle. And it strikes me because I was a little confused when I saw the terminology here, that aren't what you're really talking about here are systems incorporating a solid component? Because those are the ones that need to have an adhesive applied? And you're not talking about systems that may have other types of -- for example, lipid particles and other things, spheres, to incorporate.

DR. STRASINGER: We would only be discussing transdermal or topical delivery systems, not gels, creams, lotions, which I believe that would be where your lipid particles would be. Is that what you're

referring to?

DR. DiGIOVANNA: Yes. There are a number of different types of creams and lotions that incorporate the active agent into some sort of particulate matter, lipid particles or that sort of thing. And it kind of gets a little bit confusing when there -- at least it was to me when I was reading this, what you're talking about. But I think you're only talking here about things that include some solid component. Is there anything here that doesn't include a solid component?

DR. STRASINGER: They're all contained transdermal and topical delivery systems. That is the dosage form. Therefore, we're only looking at -- I guess if your understanding is solid as what is going around on those boards, that is the dosage form we're considering, not the gels, creams, lotions, sprays, or ointments, or foams.

DR. DiGIOVANNA: It just sounds like that's a convoluted way when you exclude the

gels, creams, liquids. But then again, aren't we not going to get into a discussion at some point about those creams or lotions or gels that are so complicated to compound because they have other -- these particulate systems?

MS. GEBBIA: I'd have to go and check, but I think the kinds of products that you're talking about may have been or could be separately nominated. I think it's different than what's the subject of this. We can double-check that, but I think what we're talking about is these systems, the reservoir and the matrix type that she showed and displayed.

DR. DiGIOVANNA: I think we had a discussion of this in a prior meeting, and it was by someone from the FDA who had a lot of expertise in engineering and whatnot. And we talked about the different types of complex systems. And there are a number of different types of complex systems that don't involve what you have here, which is a physical, solid

structure, but also have components that are very, very complicated and difficult to compound.

So I was kind of confused as to either why those weren't in here or why this wasn't phrased as something that -- and only to my eye -- it seemed to have a solid component to it, and that's really what these were.

MS. GEBBIA: I think the way that we phrased it is based on what the nomination was, and FDA's nomenclature, and the way that we treat these. Of course, we're just looking at one category here. We've got a lot more nominated substances and categories and products to look at. So it's not to say that we won't be looking at them in the future.

DR. GULUR: Any other questions? Ms. Davidson?

MS. DAVIDSON: That was a very comprehensive presentation, and you convinced me.

DR. STRASINGER: Thank you.

MS. DAVIDSON: I do have one question, though. There are some iontophoretic reservoir patches that don't have active in them. Any vote here to include these dosage forms on the demonstrably difficult would not preclude a compounder from loading those iontophoretic reservoir devices. That would not be considered compounding a transdermal dosage system, would it?

MS. GEBBIA: Those systems are also not part of this category.

MS. DAVIDSON: Okay.

DR. GULUR: Dr. Hoag?

DR. HOAG: In the early days of this kind transdermal patches, often it was the skin that was a rate-limiting step. The early developments of this -- I haven't been in school for a while, so I haven't taken a class lately. But is that still the case? Of all these transdermal patches, how much of that is released from the patch rate limiting versus the stratum corneum being rate limiting?

DR. STRASINGER: So it's varied. The products out there, some have rate-controlling membranes; some do not. It really depends on how they are designed and how they were formulated originally, and then how they were tested to demonstrate proper delivery in the therapeutic window. I can't disclose which ones have them, but there are products out there with rate-controlling membranes, and there are products without rate-controlling membranes in which the skin would be the rate-limiting step.

DR. HOAG: I was just curious, like what percentage of those types of systems -- and you may not know the answer to that.

DR. STRASINGER: I actually don't know off the top of my head. I can just tell you there's both out there.

DR. GULUR: Any other questions?

(No response.)

Open Public Hearing

DR. GULUR: Thank you. We do not have

any nominator presentations for this. We will now proceed to hear the open public hearing speakers. I will read the following OPH statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your oral or written statement to advise the committee of any financial relationship that you may have with the product, and if known, its direct competitors.

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

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Please introduce yourself, sir.

DR. DAY: My name is A.J. Day with PCCA

in Houston, Texas. I'm the director of the pharmacy consulting team, and I do not have any conflict of interest to disclose with this presentation. Dr. Strasinger did a phenomenal presentation on all of the complexities involved with transdermal dosage forms, and I think that she did an excellent job laying out the numerous concerns that happen in the development of essentially a device.

It's an engineering control issue with these matrix- or reservoir-based patch systems for the most part. To make those accurately and consistently in today's environment with today's technology does require an industrial complex of engineering.

For those reasons, there's no evidence of any compounding of this dosage form happening in today's environment. I think that that's something very important to keep in mind. Are we putting items on the list just to say it's difficult to make, or does there need to be evidence that it's actually been an

attempt to compound something before we spend our resources and our time to place it on a list that is regulating and creating policy around compounding?

To go back to the definition that FDA's put into this system, transdermal delivery systems as defined here are drug products that employ a matrix or reservoir type transdermal or topical delivery system. For the purposes of this review, FDA is not considering a TDS to be liquid or semi-solid such as gels, creams, lotions, foams, ointments, or sprays that are intended for use without a matrix or transdermal reservoir system, so something that's applied directly to the skin is not included in this review.

I think that's a very important distinction. It's something that was just the subject of this discussion here. And there are numerous formulations and FDA-approved products that are topically applied gels or lotions or creams for transdermal use. In fact, even

going back to USP 1, we heard the reference to the USP 1 from 1820 earlier this morning. It has numerous formulas listed for topicals with some of those even having transdermal properties.

Here we have a topical gel with transdermal effect utilizing diclofenac sodium as an FDA-approved product, and when you look at the bottom of your screen -- this is straight out of the package insert -- the formulation for this product is fairly simple. In fact, it's a standard carbomer-based gel utilizing a couple of penetration enhancers. So this is the type of directly applied, where you're taking the gel and applying it directly to the skin formulation that would not be subject to the limitations of these transdermal systems as defined by this review.

On the other hand, we have other FDA-approved products that utilize these matrix or reservoir type of systems. Here we have one that utilized the active ingredient fentanyl in

a patch form. And you can see, again, directly from the package insert available from FDA, the data going into providing the approval and the data required for clinicians to understand how to best utilize these drug products.

Something that's important to note is that this list of demonstrably difficult applies to both 503A and 503B outsourcing facilities. And when we're looking at the type of data to develop some of the pharmacokinetic profiles that we utilize in understanding how the drugs work, the data used behind these is from relatively small patient populations. We're talking about populations of 8 or 10 patients.

Now, there's adverse event reporting data that utilized larger cohorts of patients. But the actual pharmacokinetic data is coming from very small patient populations. So to imply that a 503B facility would be unable to develop this sort of data, of at a minimum what was available to get this drug on to the

market, is something to keep in mind, that when we're looking to find out how the specifics of the drug could be utilized, of how a preparation could be compounded under certain processes and developing data to support that, there is history of relatively small groups of patients being utilized to provide that level of evidence.

Again, here's a lidocaine patch, an FDA-approved product where you have the numbers that are used to develop our pharmacokinetic parameters being quite small. Here we have 15 patients involved with these studies to show distribution as well as pharmacokinetics over a period of time.

Now again, they do have multiple-dose studies that looked at larger groups of patients, up to 30-35 patients, when they're looking at some of the clinical parameters, but the pharmacokinetic data, again, is all coming from very small patient populations.

So again, looking at today's

environment, I would absolutely agree that transdermal systems, which are essentially devices as defined here in this meeting, they are beyond the capability of extemporaneous compounding in today's environment. And for that reason, there's no evidence that it's happening today. The policy implication of creating these things on to a list, where we have no evidence of it actually occurring today, is something that I think we need to be aware of.

There was an analogy earlier this morning from the auto industry about changing lanes when you're needing to find a new course of action to get to your destination, so conveniently, I had an auto analogy in these slides. In the 1940s, in 1940 actually, the NHTSA and Department of Transportation developed their regulations in the United States for headlights. Those were not updated for 43 years until 1983. In Europe and Asia, they're utilizing today technologies in their

headlight systems that improve safety for the drivers as well as for pedestrians and other travelers on the roads that also lower costs in manufacturing and for maintenance.

There's a petition from the auto industry in the United States in 2013 to the NHTSA to update their regulations, to update this policy because back in 1940 and 1983, the concept of a computer having some sort of integration with the way your headlights function was unthinkable. And I fear that we're getting into a similar tunnel vision approach here, where we're not having any incidence of these items being compounded, and we're on the cusp of creating a policy that would regulate how technology may be implemented in the future, technologies that we're unaware of today potentially.

So this is further explaining some of that headlight technology, which we don't need to spend a lot of time on, but you can see the drastic impact that it could have on traffic

safety.

Looking at the previous meeting where we discussed metered-dose inhalers and dry powder inhalers for the demonstrably difficult list. Dr. Hoag did ask, "I've never heard of a compounding pharmacist do this. How many prescription per year are in this category?"

Ms. Axelrad from the FDA said, "We don't know of anybody doing it either. We wanted to start with something that's relatively easy and not controversial so that you could essentially understand the process of adding things to the demonstrably difficult list." She went on to say that it was nominated. "Of the 71 things that were nominated, a number of them were metered-dose inhalers. That doesn't mean that people were compounding them. It just meant that somebody didn't want to have them compounded."

We're in a situation where nobody's compounding this. Does it need to be on a list to say you cannot compound what you're not

compounding? So does there need to be evidence of an attempt to compound it before categories of materials are placed on the demonstrably list, and how might that policy that you create today impact or prohibit technological advances for tomorrow, for five years?

In the five-year time period, we've seen a lot of advances, even in the medical field. We've seen FDA approve a 3D-printed medicine. And in another five years, which is completely within the scope of final policy coming out in regards to the 503A and 503B list that this committee is discussing, we don't know what that technology's going to look like.

So my concern is not with anything that was presented in terms of today's limitations and difficulties with creating this type of a dosage form, but the implications of putting something on the list for which there's no evidence that it is actually being compounded today. Thank you.

DR. GULUR: Any questions from our

committee members?

(No response.)

DR. GULUR: Dr. Day, I have a question for you. So are you suggesting then that we should not put this on the list because it would somehow slow down progress, that otherwise if we did not have this on a difficult to compound list, compounders would try to innovate with this?

DR. DAY: I'm not suggesting that compounders in today's environment are attempting this or are looking to develop this technology today. What I am suggesting is that because there's no evidence of it being compounded today, that its placement on the list is irrelevant, and what it means for the future and the progress of technology in the medical field of making some of these types of devices more accessible in the future, that's where we're looking at the potential implications of slowing technological advances and medical care.

Committee Discussion and Vote

DR. GULUR: Thank you.

We will close the open public hearing portion of this meeting and no longer take comments from the audience. We're moving on to the discussion phase, the panel discussion. Do members have comments?

MS. DAVIDSON: I think Dr. Day's question begs the question what happens to this list over time. If we add something to it today and this sort of technology appears tomorrow, what is the process of reviewing this list?

MS. GEBBIA: Sure. Obviously, this is FDA's review -- or the nomination and FDA's review, and bringing substances and categories to the PCAC is step one. The next step is a proposed rule, then we get comments on the proposed rule, and we'll do a final rule. I think we said that until that final rule is published, that we don't intend to take enforcement action with respect to things that

have been nominated for the Difficult to Compound List.

Once something is on the list, we do have a process -- in the final regulation that's codified in our rules, there are processes, citizen petition process, to petition for changes to existing regulations. So nothing -- if there were something in the future, there are ways that we would address it. And that is once we actually get to the final rulemaking stage, which takes some time.

DR. GULUR: Any other questions? Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. So perhaps you can clarify for me. Is the reason that the wording of this is the way it is because that was the way it was proposed? In other words, if there's better wording or different wording, would you have rephrased the question in a different way?

Again, because I'm a little bit confused about the wording to talk about transdermal

delivery systems except, and then the "except" has a long line of exclusions of topicals, when in some of those topicals, there are things that would be considered complex systems that I guess we're not talking about here, varying types of micelles and other complicated to-do things.

However, it appears what we're talking about here would be more perhaps clearly conveyed and not misconstrued in the future if it incorporated perhaps the term that Dr. Day suggested, a device, which this sounds like what we're talking about, or something with complicated structural components rather than system. I mean, system to me, and by the definitions I find, any sort of a topical vehicle is a system.

I guess my concern is that by voting for something that in the future will be considered nebulous may include those other complex systems and not have them addressed individually.

MS. GEBBIA: I think that we've tried to be clear about the scope of what we're talking about here. And with respect to what we ultimately put -- how the entry is framed on the list, I think we'd want to be clear so everybody knew what we were talking about. It's not our intent to put something on there that would capture things that's not intended.

So we're happy to have comments on that. It would be something, of course, that would be also subject to the rulemaking process. I don't have the nominations sitting here in front of me, unfortunately, so I can't tell you exactly what it says. But clearly, we are only talking about what Caroline presented, and if you have suggestions, we can certainly take comments on the best way to frame that so it's clear what our intent is.

DR. GULUR: Dr. Hoag?

DR. HOAG: I thought that you brought up a good point about trying to keep current because I would say it's not that hard to think

about in 5 years, 10 years, someone thinking of a printer. Maybe half the tablets will be printed and stuff. I don't know. That may not be called compounding. Who can predict the future?

The other thing is these outsourcing pharmacies, if they were actually to specialize, I would say that maybe not currently, but in the future they would be able to produce that for small populations. A lot of the things that you brought up were very valid, but a lot of that's toward the generics and are they necessarily trying to match the profile of something.

So in compounding, if you're doing some kind of specialized new thing, I could see that in the future, these outsourcing pharmacies, if they did the appropriate testing, could potentially produce transdermal patches of benefit to the patients.

MS. GEBBIA: Yes. I'll say two things. One is, we would want to know what those are

and be able to assess them in the future. So we don't know what we don't know, and we've presented the information. It's available to us today. As you said, it could even, whatever comes down the future, be considered something totally different [inaudible - mic off].

One thing to consider is whether it would be on a difficult to compound list under Section 503A but not under Section 503B. That is something to consider I think. When we presented our evaluation, we think it applies equally to both, but that's something that can be considered as well.

DR. GULUR: Dr. Pham?

DR. PHAM: I think that part of the purpose of this committee being convened is that we realize that the practice of compounding is as old as the profession of pharmacy, and it has evolved in its scale and complexity quite a bit.

So there are a lot of things that are happening on a more reactionary basis. The

purpose I think of this is to really evaluate, currently with your safeguards and your federal oversight in place, where would you want these products to go. And if it is not in the capacity of the compounding or outsourcing facilities, it is to the FDA.

So you're making these assessments based on if you had to figure out who you wanted to make these products appropriately in a large distribution scale, putting on the list allows for a whole different group to allow that to happen. Right?

So I get that we definitely don't want to impede progress in the future, but we want to also look at the mistakes from the past. We have to really keep safety in mind and the appropriateness of these facilities, whether you're a drug manufacturer who has the ability to make complex device or drug formulations, versus the compounding -- traditional pharmacies versus outsourcing.

I think today people probably know where

they want to see these products made, and I think that's how we should be guiding our votes on this. But I just want to capture that it's not to -- we have seen the practice evolve, so as it evolves, you can make those adjustments later. But we don't want to put -- we have the opportunity to be proactive about it now.

So I think that that's the focus here, whether or not the clarification -- I don't know if this is super limiting, but if you just say matrix or reservoir type delivery systems, and we start with that as a way to vote in the comments. That might be something that kind of helps alleviate the concern about what's being included or not within this specific category.

FDA can probably clarify. Am I missing anything if I were to say, phrase the comment as matrix or reservoir type based on the presentation?

DR. STRASINGER: I want to be clear. Looking at the USP, they define transdermal system as the dosage form -- topical delivery

system as the dosage form. The established name of NicoDerm CQ is nicotine transdermal system. So that's where, from a scientific standpoint, we are coming from saying transdermal system refers to these products just like lidocaine topical patch refers to the lidocaine topical -- that's how it appears in the established name. And USP has defined transdermal systems as those things and topical delivery systems as the local delivery ones.

DR. GULUR: Yes?

MS. DAVIDSON: And I'd like to reinforce what was just said. The nomenclature and labeling expert committee at USP has referred to the compounded transdermal gels, which are not under discussion now, as topical gel systems.

They do not name them transdermal dosage forms regardless of their intended disposition in the patient. They are called topical gels. And so there's a very distinct naming convention that separates these systems from

the gels.

Going back and looking at the nomination from Public Citizen, I don't see any reference to those gels at all. I only see the transdermal delivery systems as defined by USP's naming convention.

DR. GULUR: Dr. Braunstein?

DR. BRAUNSTEIN: Maybe this might clarify things for the committee, and the FDA can help me if I'm wrong. But when you think about the traditional role of compounding -- let's say a product is only available as a tablet, and we need a liquid suspension, or an elixir, or whatever, a liquid formulation. That would be within the typical role of compounding that we understand. That's one example. I'm sure there are many others. Obviously, there are many others.

But I think what the FDA is saying is if there's a product only available for oral route and there was a need or a desire for that product to be available through a transdermal

route, that they don't want that to be done by a compounding alone, that that would have to be something that they want to regulate directly; that is, somebody would need to develop it and apply for a license to sell the product based only after the FDA has reviewed it and determined that it's safe and effective.

Is that basically what you're saying?

MS. GEBBIA: I think -- what I would say -- I agree with what you say compounding is. What we've been tasked with doing is developing under the statute a list of products that we think present demonstrable difficulties for compounding, and we think that things that are these types of transdermal delivery systems meet that.

So we would be concerned about somebody taking something that was available orally, or even a different way of applying it through the skin, but doing it with these transdermal delivery systems.

MS. BORMEL: I think Dr. Strasinger

covered this in her presentation, but I think that these type of -- the specific dosage forms that are covered in her presentation are very difficult and very complicated to make. And so there's no assurance that if they're made by -- in the current state of affairs and the current state of what we know, which is the only thing we really have now to discuss, that if a compounder were to make them, there's no real assurances that the API would be delivered appropriately, that there would be a rate of absorption that would be appropriate, et cetera, et cetera.

But I think that's what Dr. Strasinger -- and you can speak to that, Dr. Strasinger. But that's what she's saying for these particular dosage forms, currently.

DR. GULUR: Dr. Wall?

DR. WALL: Just an FYI. I was just looking through the internet at some compounding pharmacies, and in their repertoires, when they're saying that we can

compound these things, they list patches. I've talked to a couple of folks in the past who have said, oh, yeah, we can make this in patches. And when I think of patches, I think of what they were just talking today. So I think that it is being done.

DR. GULUR: Did any one want to comment on that? Mr. Mixon?

MR. MIXON: Donna, did I understand you correctly to say that you saw where somebody on the internet is advertising a compounded transdermal system, or are you calling it a patch?

DR. WALL: They were talking about compounding products, and we can put it in a patch.

MR. MIXON: In my experience, patch is a very loosely used term, especially among the general lay public. I would submit that no rational compounding pharmacist would try to make a transdermal delivery system such as what we've discussed. I would argue that that

"patch," quote/unquote, is just referring to the cream or gel that's not under discussion, despite what the language on the internet says.

If there's language on there that somebody's trying to make a transdermal delivery system such as we've discussed, I would encourage you to let FDA know so they can do an investigation.

DR. WALL: Well, it says creams, gels, patch. Just FYI.

MR. MIXON: Well, I'm just telling you, in my experience as a compounding pharmacist for a long, long time, we've never considered trying to make these kind of products.

MR. FLAHIVE: And to Mr. Mixon's point, with the thousands of pharmacies out there, it's difficult for FDA to know who's out there, never mind always what they're doing. And this is why we have certain systems we're putting in place, including the Difficult to Compound List, where we want more information before people can make certain products available to

the public.

DR. GULUR: Any further discussion or comments?

(No response.)

DR. GULUR: If not, we will proceed. At this time, we will close the discussion and proceed with the vote.

The question before us is, FDA is proposing that drug products that employ transdermal or topical delivery systems be included on the Difficult to Compound List under Sections 503A and 503B of the FD&C Act. Should drug products that employ transdermal or topical delivery systems be placed on the list? Please vote now.

(Vote taken.)

DR. HONG: Question 3, we have 6 yeses, 1 no, and zero abstain.

DR. GULUR: Thank you. Dr. Vaida, would you like to start the comments?

DR. VAIDA: Yes. I voted wrong.

(Laughter.)

DR. VAIDA: Soon as I let it go.

DR. GULUR: And I was waiting for an interesting discussion on this, Dr. Vaida. I was trying to see what you would have to say.

DR. VAIDA: I let it go. I meant to vote yes. And I just want to clarify that I would make sure that it's for 503A and B because right now, the regs are B, is still voluntary.

DR. GULUR: The question did say 503A and B.

Could we correct Dr. Vaida's vote for the record? Dr. Pham?

DR. PHAM: I also voted yes. I'll just reinforce what you voted. I also voted yes because I think that there was a very comprehensive presentation on the difficulties of compounding for the topical and transdermal. And I also agree that we should include it for both the 503A and 503B.

DR. WALL: I voted yes for the mentioned reasons.

DR. HOAG: I voted yes, and I for the time being, these are very appropriate.

DR. DiGIOVANNA: John DiGiovanna. I voted yes for the reasons that were mentioned. I do think that there's a little bit of lack of clarity about the description. I do think I understand exactly what the FDA intends.

There are transdermal delivery systems, and then there are topical delivery systems. And both of those can deliver a product without a device or with a device. And I think what we're talking about here are the ones that particularly have some sort of device or structure to them. And I also agree that it should apply to 503A and 503B.

MS. DAVIDSON: Gigi Davidson. I voted yes for the reasons that have been stated with the caveat that a petition could be made at a future time should technologies become available to afford this ability to compounding pharmacists, and also with the understanding that this decision will continue to be made

along the lines of USP naming conventions, and that transdermal systems are not confused with topical gels intended for transdermal administration or transdermal disposition.

DR. GULUR: I voted yes as well, to put it on the list, respecting completely the thorough presentation that the FDA provided and all the information with regard to the present day, where it does appear to be a very difficult to compound product.

That said, I also appreciate our public comments, which spoke to the effect that this may have on future innovation. And I am reassured that the FDA has processes in place to review this as required.

Thank you very much, everyone. We will now close this section of this with last words from the FDA officials if they have any comments.

MS. GEBBIA: Thank you very much.

Adjournment

DR. GULUR: No other comments?

(No response.)

DR. GULUR: All right. Well, with that, we are adjourned. Thank you all very much.

(Whereupon, at 3:49 p.m., the afternoon session was adjourned.)