FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Thursday, November 3, 2016

8:31 a.m. to 12:05 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

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PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

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Senior Vice President and Head of Regulatory Affairs

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William Mixon, RPh, MS, FIACP

(Industry Representative)

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The Compounding Pharmacy

Hickory, North Carolina

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

8:31 a.m.

Call to Order

Introduction of Committee

DR. GULUR: Good morning, everyone. I would first like to remind everyone present to please silence your cell phones, Blackberrys, and other devices if you have not already done so. I would also like to identify the FDA press contact for this open session meeting, Ms. Lyndsay Meyer. If you are present, please stand.

Good morning. My name is Padma Gulur. I am the acting chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee to order. We will now ask that those at the table, including FDA staff and committee members, to introduce themselves, starting with the FDA to my far left and moving along to the right side, ending with one of the industry representatives, Dr. Braunstein.

DR. GANLEY: Charlie Ganley. I'm the director of Office of Drug Evaluation IV in the

Office of New Drugs at CDER.

MS. GEBBIA: Emily Gebbia. I'm a senior advisor in CDER's Office of Compliance and the acting agency lead on compounding.

MS. BORMEL: I'm Gail Bormel. I'm in CDER's Office of Compliance, the Office of Unapproved Drugs and Labeling Compliance.

MR. FLAHIVE: I'm Jim Flahive. I'm a regulatory counsel in CDER Compliance Office of Unapproved Drugs and Labeling Compliance.

DR. LAWSON: I'm Rosilend Lawson. I'm a regulatory counsel in CDER's Office of Compliance as well.

DR. KO: I am Hon-Sum Ko, medical officer in dermatology and dental drugs products division in the Office of New Drugs.

DR. EPPS: Good morning. I'm Dr. Roselyn E. Epps. I'm a clinical reviewer in the Division of Dermatology and Dental Products.

DR. LIEDTKA: I'm Jane Liedtka, medical officer here at the FDA.

DR. HONG: I'm Cindy Hong, designated

federal officer for PCAC.

MS. DAVIDSON: I'm Gigi Davidson, and I represent the United States Pharmacopeia.

DR. DiGIOVANNA: I'm John DiGiovanna. I'm a dermatologist at the National Cancer Institute, NIH.

DR. HOAG: I'm Steve Hoag. I'm a professor at the University of Maryland School of Pharmacy.

DR. CAROME: I'm Mike Carome, director of Public Citizen's Health Research Group.

DR. WALL: I'm Donna Wall, clinical pharmacist at University Hospital in Indianapolis and represent NABP.

DR. VAIDA: Allen Vaida, and I'm a pharmacist and executive vice president at the Institute for Safe Medication Practices.

MR. MIXON: Good morning. Bill Mixon, former owner of The Compounding Pharmacy, Hickory, North Carolina; and also member of the North Carolina Board of Pharmacy; member of the USP Expert Committee for Compounding; and surveyor for ACHC.

DR. BRAUNSTEIN: Ned Braunstein. I'm the head of regulatory affairs at Regeneron Pharmaceuticals, and I'm the pharmaceutical and biotechnology industry representative.

DR. GULUR: Thank you, everyone

For topics such as those being discussed today, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a reminder, individuals will only be allowed to speak on the record if recognized by the chair. We look forward to a productive meeting.

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

discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during break or lunch.

Today, we will cover five bulk drug substances nominated for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act: glycolic acid, trichloroacetic acid and kojic acid, diindolylmethane, and vasoactive intestinal peptide.

For each of the five substances, we will hear presentations from the FDA, ask clarifying questions, hear nominators' presentations, ask clarifying questions of them, hold an open public hearing, and have committee discussion and voting.

This afternoon, we will also discuss drug products that were nominated as drug products that present demonstrable difficulties for compounding and that cannot be compounded under Sections 503A and 503B of the FD&C Act, which are transdermal and

topical delivery systems.

Let us begin. We will now 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, speaking, teaching, writing, patents and royalties, and primary employment.

During this meeting, the committee will discuss five bulk drug substances nominated for inclusion under Section 503A bulk's list. FDA will discuss the following nominated bulk drug substances and the uses FDA reviewed: glycolic acid for hyperpigmentation, including melasma and photodamaged skin; trichloroacetic acid for common warts and genital warts; kojic acid for hyperpigmentation and as a chelating agent to promote wound healing; diindolylmethane for cancer; and vasoactive intestinal peptide for chronic inflammatory response system. The nominators of these substances will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which specific matters related to the five bulk drug substances 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. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the bulk drug substances.

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 stakes 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 bulk drug substances not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants are 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 at issue that could be affected by the committee's discussions. Thank you.

DR. GULUR: Thank you. We've just been joined by one other member. Would you mind introducing yourself?

DR. PHAM: Katherine Pham, public health advocacy for The Pew Charitable Trusts.

DR. GULUR: Thank you. We will now proceed with FDA introductory remarks from Ms. Emily Gebbia.

FDA Introductory Remarks - Emily Gebbia

MS. GEBBIA: Good morning, everybody. My name is Emily Gebbia. I am a senior advisor in CDER's Office of Compliance and the acting agency lead on compounding while Julie Dohm, who you met at the last meeting and who is the agency's lead on compounding, is on leave. I want to welcome everybody to the sixth meeting of the Pharmacy Compounding Advisory Committee meeting.

Dr. Gulur and Cindy just went through all of the topics that we're going to discuss today, so I won't repeat them again now. But I will note that

as in the June meeting, we have scheduled time for nominators to speak and to have an open public hearing after each of the different topics that will be discussed.

I also wanted to take this opportunity to provide you with an update on policy documents that have been issued by the agency since the committee last met in June. In July, FDA issued two draft guidances concerning the agency's proposed policies regarding compounding of drugs that are essentially copies of commercially available or approved drugs under Sections 503A and 503B of the FD&C Act. Each draft guidance document was available for comment for 90 days, and the comment period closed on October 11th.

In August, FDA issued a draft guidance concerning insanitary conditions at compounding facilities and provides examples of conditions that FDA considers to be insanitary under Section 501(a)(2)(A) of the FD&C Act. The public comment period for this draft guidance closed in October as well.

On October 7th, FDA published a final rule amending the list of drug products that may not be compounded under Sections 503A and 503B of the FD&C Act because they or their components have been withdrawn or removed from the market for safety or effectiveness reasons, which is known as the Withdrawn and Removed List. The final rule added 24 entries to the list and modified the description of one drug entry on the list. These substances were discussed during the first meeting of the Pharmacy Compounding Advisory Committee in February 2015.

Finally, on October 18th, we published a proposed rule to amend that very same list, which would add three new entries that were discussed at a prior PCAC meeting and proposed rules available for public comment, and the comment period closes January 3, 2017. All of the FDA's policy documents, including the draft guidances, final rule, and proposed rule, are available on our compounding website under the section titled Regulatory Policy.

With that, I'd like to thank you for participating in today's advisory committee meeting. We look forward to having a productive meeting and continuing to work together.

DR. GULUR: Thank you.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the committee. We will now proceed with an FDA presentation on glycolic acid from Dr. Jane Liedtka.

FDA Presentation - Jane Liedtka

DR. LIEDTKA: Good morning, everyone. I'm Jane Liedtka. I'm a dermatologist and a medical officer here at the FDA. And once we get the slides going, I'm going to talk to you about glycolic acid.

(Pause.)

DR. LIEDTKA: First, I'd like to introduce my team. Ben Zhang is the chemistry reviewer for this product. Jianyong Wang is the pharmacology/toxicology reviewer. Doanh Tran is

the clinical pharmacology reviewer.

Glycolic acid at a strength of 0.08 percent to 70 percent has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for topical use in the treatment of hyperpigmentation disorders and photodamaged skin.

Glycolic acid is also known as hydroxyacetic acid. It was also nominated for subcutaneous injection and topical use as an anesthetic and in the treatment of keratosis and warts. This review, however, will focus on the topical use and hyperpigmentation and photodamaged skin because adequate support was not provided for the other nominated uses.

Glycolic acid is currently available in cosmetic formulations such as creams, pads, and lotions, and is present as an excipient in some topical drug products.

First, I'm going to go over a few regulatory definitions to set the scene. Whether a product is

a cosmetic or a drug under the law is determined by the product's intended use. There are different laws and regulations that will apply to each type of product. A drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or an article other than a food that is intended to affect the structure or function of the body.

A cosmetic is an article, other than a soap, that is intended to be rubbed, poured, sprinkled, sprayed, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering appearance. Cosmetics are regulated by CFSAN. They do not undergo premarket approval of products or ingredients except for color additives.

Topical acids cause exfoliation or shedding of the skin surface. The extent of the exfoliation depends on the type and concentration of topical acid on its pH and on the other ingredients in the product. Examples of topical acids include glycolic, lactic, citric, kojic, and

trichloroacetic acid. Examples of intended use of acids in cosmetics would include smoothing fine lines or improving skin texture and tone. Examples of intended use of acids in drugs would include hyperpigmentation, including melasma, or warts, or genital warts.

With regard to the physical and chemical characterization of glycolic acid, it is a small organic molecule, which is pictured here. It's highly soluble in water, it's easily characterized with various analytical techniques, and there are no stability issues reported in the literature. Glycolic acid is likely to be stable under ordinary storage conditions in the proposed dosage forms, such as lotions and gels.

There are various synthetic routes that can be followed to prepare glycolic acid. Likely impurities can include formaldehyde and monochloroacetic acid, which are starting materials. Impurities can also include residual reagents or sodium chloride, formic acid, and methoxyacetic acid, which are byproducts from the

synthetic process. When potential impurities such as those listed above are controlled, the physical/chemical characteristics do not raise significant safety concerns.

In summary, for physical and chemical characterization, based on the available information, there are no concerns about the physical and chemical characterization when potential impurities such as formaldehyde are controlled at acceptable levels. Glycolic acid is a well-characterized small molecule that is likely to be stable under ordinary storage conditions.

Next, we're going to move on to pharmacology and toxicology. One theory for the mechanism of action of alpha-hydroxy acids, also known as AHAs, in exfoliation is that they reduce the calcium ion concentration in the epidermis and remove calcium ions from the cell adhesions by chelation. This causes disruption in the cell adhesions and results in desquamation. Glycolic acid can also suppress melanin formation by inhibition of tyrosinase activity.

With regard to safety pharmacology, an intraperitoneal dose of 1,000 milligrams per kilogram of glycolic acid was a potent inhibitor of oxygen consumption and glucose metabolism in rat liver and myocardium in vivo, but it did not affect brain oxygen consumption. With regard to acute toxicity, glycolic acid in high concentrations, such as a 70 percent solution, causes local effects that are typical of a strong acid such as dermal and eye irritation.

With regard to repeat dose toxicity, in a 3-week dermal toxicity study in hairless guinea pigs, erythema and/or flaking of the skin were noted at 5 and 10 percent concentrations of glycolic acid. Glycolic acid was a potent calculi inducer in 4- to 12-week repeat dose oral toxicity studies in rats, with an increase in renal oxalate and nephrotoxic effects. In a 2-week inhalation toxicity study in rats, respiratory tract irritation, hepatocellular degeneration, and thymus atrophy were noted.

With regard to genotoxicity, glycolic acid

was negative for mutagenicity in the Ames test and the mouse lymphoma assay. Glycolic acid was negative for clastogenicity in an in vitro chromosome aberration assay and an in vivo micronucleus assay in mice. With regard to carcinogenicity, glycolic acid did not show photocarcinogenic potential in SKH-1 hairless mice.

With regard to reproductive and developmental toxicity, oral, that is gavage, doses of glycolic acid up to 600 milligrams per kilogram per day were administered to female rats during gestation days 7 to 21. Maternal toxicity was seen at doses greater than or equal to 300 milligrams per kilogram per day. Developmental toxicity was also noted at these doses, including fetal weight reduction and increases in skeletal malformation.

In summary for pharmacology and toxicology, there is a lack of non-clinical data for the evaluation of chronic dermal toxicity and dermal carcinogenic potential of glycolic acid. The available non-clinical data do not raise serious safety concerns about glycolic acid when used

topically at low concentrations.

Next, we're going to move on to a discussion of human safety. The topical application of glycolic acid enhances photo-irritation by ultraviolet light. Because of the potential to enhance sensitivity to sunburn, CFSAN guidance for industry recommends that labeling for cosmetics containing AHAs include a sunburn alert. That alert reads as follows.

"This product contains an alpha hydroxy acid that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards."

With regard to pharmacokinetic data, there were no reports of human pharmacokinetic studies following topical application of glycolic acid. In vitro studies indicate pH and time dependence for glycolic acid penetration of the skin with a decrease in pH or an increase in the time of application, resulting in enhanced penetration.

There are both FAERS and CAERS adverse event reporting for glycolic acid. FAERS is the FDA adverse event reporting system, and CAERS is the cosmetic adverse event reporting system. Forty-five cases were retrieved regarding glycolic acid from FAERS, and 19 cases were retrieved from CAERS.

Clinical trials with the indication of melasma revealed mainly local irritancy manifestations such as burning, erythema, swelling, and vesiculation. Rarely post-inflammatory hyperpigmentation and scarring were seen. During clinical trials for photodamaged skin, erythema and dryness were predominantly seen.

These reported adverse reactions appear to be readily manageable and temporary in duration, but there is no information on long-term outcomes.

With regard to alternative therapies, for melasma, the approved drug product Tri-Luma is indicated for the short-term treatment of moderate to severe melasma of the face in the presence of measures for sun avoidance, including the use of sunscreens.

With regard to photoaging, there were numerous topical retinoids that were approved, examples being tretinoin and the tazarotene products, the indication being as "an adjunctive agent for use in the mitigation, or palliation, of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs."

There are also numerous injectable botulinum toxin type A products that are indicated for the temporary improvement in the appearance of moderate to severe glabellar lines. Also, Botox cosmetic is indicated for lateral canthal lines. And then there were procedural or non-drug therapies such as laser, microdermabrasion, intense pulsed light, that are also available for the treatment of both melasma and for improving the manifestations of photodamaged skin.

In summary for human safety, the available information does not raise major safety concerns associated with the topical use of glycolic acid.

Next, we'll move on to effectiveness.

Clinical trials for hyperpigmentation were performed, and a literature search revealed that there were multiple reports of studies involving the use of glycolic acid for the treatment of melasma and for other hyperpigmentation disorders. Most of these were active controlled trials. There was one trial which included vehicle as control.

With regard to clinical trials for photoaging, some of the trials on the hyperpigmentation disorders also included endpoints that are traditionally associated with photoaging studies. In addition, there were two clinical trials that specifically addressed the effective glycolic acid on manifestations of changes associated with photoaging.

With regard to the effectiveness, a summary of the clinical trial data reveals that glycolic acid peels in strengths of 20 to 70 percent result in improvement that is comparable to that of other peels such as tretinoin, trichloroacetic acid, lactic acid, Jessner solution, or capryloyl salicylic acid.

With regard to a summary of the clinical trial data for manifestations of changes associated with photoaging, glycolic acid as a component in the Vivite Skin Care System had a similar effect on wrinkles when compared to Cetaphil. As an 8 percent cream, it was superior to vehicle for sallowness and overall severity of photodamage.

With regard to the seriousness of the conditions that are proposed indications for glycolic acid, hyperpigmentation disorders and photodamaged skin are not serious conditions per se. The pathological changes predisposing to skin cancer may be associated with photodamage.

In summary for effectiveness, there are numerous active controlled trials that show consistently positive results in the treatment of melasma with glycolic acid either as a peel or as a topical agent. Overall, the evidence suggests a role for second-line treatment of melasma that has failed standard therapy or as an adjunctive treatment to commonly used topical medications. There is some evidence from a vehicle-controlled

trial that may support the effectiveness of glycolic acid for the mitigation of manifestations of photodamaged skin.

With regard to the historical use in compounding, glycolic acid has been used in pharmacy compounding in the U.S. since at least the mid 1990s. The uses of glycolic acid have included ameliorating the appearance of skin aging, melasma, other pigmentation disorders, calluses, keratoses, acne, and psoriasis.

The extent of use cannot be exactly determined, however, countries with reported use include Brazil, Mexico, France, Singapore, Thailand, Korea, India, and Turkey, in addition to the United States. Glycolic acid is listed on foreign pharmacopeias, including the British and the European pharmacopeia.

Finally, as a recommendation, balancing the four evaluation criteria, which include the physical and chemical characterization, the safety, the effectiveness, and the historical use in compounding, a balancing weighs in favor of

glycolic acid, up to 70 percent for topical use, to be added to the list of bulk drug substances that can be used in compounding under the 503A of the FD&C Act. Standard of care for use at strengths of 20 to 70 percent is in-office application by a licensed healthcare professional.

Does anybody have any questions?

(No response.)

DR. LIEDTKA: Great. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Actually, at this time, we will accept clarifying questions from the committee. We ask that you limit your questions to clarifications only. Members will have further opportunity for discussion at the end.

MS. DAVIDSON: I'm curious about the characterization that the standard of practice is in-office application of the 20 to 70 percent solutions. Considering that 503A compounders are not allowed to prepare compounds for office use, have you thought about the logistics of how this is going to happen?

MS. GEBBIA: I can help with that question. You're correct that under Section 503A, you have to have a patient's prescription. But there would be no reason that a dermatologist couldn't write a prescription for a patient, the patient gets the drug, and it's provided in the office.

We also, as you know, in our entries don't limit the setting in which the drug is provided. We can do some with route of administration and that sort of thing. But we wanted to provide that information about the standard of care as part of the presentation just for the committees and public awareness.

MS. DAVIDSON: Thank you. That's exactly what I was getting at, is would that be a limitation if added to the list as the site of -- or the environment --

MS. GEBBIA: Right. It wouldn't. It was just more information that we thought would be useful for people to have about how this is used.

MS. DAVIDSON: Great. Thank you.

DR. GULUR: Mr. Carome?

DR. CAROME: Mike Carome. I wanted to question you about the level of evidence on effectiveness. One of the things in FDA's review packet was a Cochrane review looking at the treatment of melasma with glycolic acid, among other things.

They noted in their summary of conclusions that the quality of studies evaluating melasma treatments were generally poor and available treatments are inadequate, and high-quality, randomized controlled trials on well-defined participants with long-term outcomes to determine duration response are needed.

When I looked at many of the trials that generally are small, and most of them have an active control without a vehicle control, they mix -- often the glycolic acid was used along with multiple other agents, so it's hard to isolate, really, what was the effect of the glycolic acid versus vehicle or the other active ingredient.

Do you agree with the Cochrane review, that really the level of evidence here is poor in terms

of effectiveness data, that these trials really were not well designed, and in many ways, they're small?

DR. LIEDTKA: I certainly agree that the trials overall were small, and that from a point of view of the standards that we use when we're designing trials for drug approval, are different from the standards that are used in other clinical trials. Glycolic acid has been used by dermatologists for at least 30 years on a routine basis without there being either significant concerns from an adverse event point of view or any issues with its effectiveness.

Clearly, it's effective for some patients, and it is generally used in combination with multiple other products. There is no single product that works for melasma in particular, but even less so for the other types of hyperpigmentation. So you're generally throwing everything you've got at that condition, at those conditions.

DR. GULUR: Dr. Pham?

DR. PHAM: A question about the approved product, Tri-Luma for melasma, being that the condition appears to be a chronic condition, and then the Tri-Luma is indicated for short-term treatment, did you find in the historic use of glycolic acid -- I know that you mentioned in the animal, the non-clinical data, there was not any non-clinical data about the chronic safety -- or sorry, safety of chronic use of glycolic acid.

Did you see anything in the historic use about the duration of treatment with glycolic acid?

DR. LIEDTKA: Again, it's more of a clinical experience than anything else. There aren't good placebo-controlled, long-term chronic-use trials. Melasma always comes back. Most forms of hyperpigmentation come back when you stop treatment, so you do serially treat. And that is the standard of care both with the approved products and with multiple non-approved products.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. I have a question, but maybe just a clarification. I

think just for the group, there's a difference in the way the different products are used. I think usually the Tri-Luma or those products that are prescription products are applied by the patients at lower dose for long periods of time. Usually, I think this is use of glycolic acid would mostly be an in-office application that would rarely be done. It's sort of like a booster treatment.

So that's done under controlled settings. So these concentrations, in my experience, would not be something that really would be chronically used on a daily basis. Perhaps done every few years, or that sort of thing, would be more likely. So this is really kind of a little different, and that's where it may be a little confusing to just look at it on the surface.

Am I correct?

DR. LIEDTKA: Absolutely. Thank you.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Yes. On the commercially available, or one of the commercially available products, you mentioned Proactive. Looking at the

adverse events that were reported -- and this is an OTC product, so I wouldn't expect many, but it seemed like 90 percent were from that product. But I couldn't find what the concentration was in that product. They also have a plus.

Do you know what it was?

DR. LIEDTKA: There are multiple, multiple Proactive preparations. Proactive has about 20 different products that combine. Some of them have glycolic acid; some of them don't. Some of them have multiple other agents. They're usually all used in combinations. I don't know off the top of my head what the concentrations are of the various Proactive products, but Proactive is not a single product. It's multiple, multiple products.

DR. VAIDA: No. I was just curious. Thanks.

DR. LIEDTKA: We can certainly look that up and get back to you on it.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: We will now proceed with the

nominator presentations. Thank you. We have one presentation, Mr. John Voliva from the International Academy of Compounding Pharmacists.

Nominator Presentation - John Voliva

MR. VOLIVA: Good morning. My name is John Voliva, and I'm the executive vice president of the International Academy of Compounding Pharmacists, and I have no conflict of interest to declare in regards to this drug.

IACP represents over 3600 compounding pharmacists, technicians, and pharmacy students across the United States, Canada, Australia, and Europe. As a fourth generation pharmacist, the practice of pharmacy is not only my chosen profession but is something I am proud to say runs in my family. As a compounding pharmacist, I know firsthand the power of our niche a pharmacy has to positively affect patients' lives.

For this particular bulk drug substance, IACP appreciates the FDA's recommendation to add glycolic acid to the bulks list. I would also like to provide a note of appreciation to this committee

who volunteers their time to serve. In the end, the work put forth by the nominators of these substances, the FDA, and the committee will affect the provision of health care now and in the future. And I hope the committee can constantly keep the ultimate end user, the patient, in the front of their minds while making their decisions.

Thank you for your time today, again, for your service, and we look forward to working with this committee and the agency at future meetings. Thank you.

DR. GULUR: Thank you. We will now entertain any -clarifying questions for the nominator from the committee.

(No response.)

Open Public Hearing

DR. GULUR: Thank you very much.

We will now proceed to hear 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 written or oral statement to advise the committee of any financial relationship that you may have with the product, and if known, its direct competitors.

For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals 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.

DR. DESAI: Good morning. My name is Seemal Desai. I'm a board certified dermatologist from the American Board of Dermatology, and I'm here representing the American Academy of Dermatology Association, as well as the American Society of Dermatologic Surgery Association. Of note, I practice in Dallas, Texas. I have two private

practices where most of my clinical experience is focused on pigmentary disorders in patients with skin of color, and I'm also a clinical assistant professor at the UT Southwestern Medical Center in Dallas.

I'd also like to point out that I'm the secretary-treasurer of the Skin of Color Society, as well as the president-elect of that group, as well as the international advisor to the International Pigmentary Disorders Society.

So it's a pleasure to be here this morning to speak about glycolic acid, and I'd like to thank the committee for that excellent presentation, particularly Dr. Liedtka on the science behind that drug. And I'd like to mention that we are very much in support of the FDA's proposal to include this on the bulk substances list.

We do use glycolic acid very, very frequently, especially in my patient population, which includes patients of color, as well as those suffering from chronic pigmentary disorders, particularly melasma. And it has been mentioned by

some of the committee members in a very eloquent way, melasma is a chronic skin condition. In fact, when patients come into my office who come in with melasma, many of them are frustrated having seen multiple other doctors before, having been treated even by other dermatologists who potentially don't have an interest in pigmentary disorders.

I equate melasma to a chronic skin condition just like psoriasis, just like chronic inflammatory other skin conditions because though there are ways for us to lighten the hyperpigmentation and reduce the burden of the cosmetic outcome of the skin condition, oftentimes it does come back. And it's with the use of in-office treatments, particularly with glycolic acid chemical peel treatments, which was, as mentioned, we use in a controlled setting very regularly, that we can actually manage these chronic conditions for these patients.

I'll give you an example. Melasma tends to be a condition that oftentimes affects women in their post-partum period or oftentimes affects women who are on oral contraceptives. In fact,

it's been linked scientifically to be hormonally induced and that hyperpigmentation that happens typically happens due to some estrogen-like phenomenon that is causing a basal layer of melanin production.

So you can imagine that you have a post-partum female who's in the joys of the after part of giving birth of their newborn, but comes in 6 to 8 weeks later with dark brown patches all over their face. You can imagine that that's somewhat of a dichotomy between the joys of early motherhood and then experiencing this sort of change in their skin.

So this is an important condition. And though it may not be medically serious in terms of other systemic implications, I think we as dermatologists really have a heighten sense of awareness that these patients do need our help, and glycolic acid happens to be one ingredient, which has been shown in many studies, especially here in the U.S. and in Asia, to be very effective in the controlled setting, especially in the 20 to

70 percent concentrations.

So I'd like to thank you all for proposing to include this on the list, and I'm happy to take any questions.

Clarifying Questions from the Committee

DR. GULUR: Any questions? Dr. Vaida?

DR. VAIDA: Do you use the product alone or in combination with other ingredients?

DR. DESAI: Great question. So I actually use this in combination with other therapeutic steps in the armamentarium of treating the disease. The easiest way to explain it, and the way I explain it to my patients, is that this is not going to be the type of condition where I can just write you one prescription and send you on your way, and hope you're better and everything's good.

This tends to be the type of condition where I may write a topical bleaching agent such as the commercially available product, which was mentioned in the presentation, but that's only for a short course. That is not a prescription that I would provide many refills for, would have the patient go

unmonitored for a long period of time because that in turn has its own side effects.

What I'd then have to do is have the patient come back 6 to 8 weeks later after starting the topical, and then incorporate glycolic acid, particularly in-office chemical peels. And in the 20 to 70 percent concentration, I actually do use it, monotherapy, where you can actually apply it simply as a chemical peel agent in the office, and do that every 2 to 3 weeks. On average, 4 to 5 sittings has a nice effect on helping reduce the epidermal melanin content.

You can combine that also with other topical products, especially retinals because, as we know, retinals also help with turning over the epidermal cell layers. And by doing that, we're hoping to get rid of some of that pigment at the same time. So I actually do use it in the in-office setting as monotherapy but combine it with adjunctive at-home treatments of which photo protection and retinols are really one of the mainstays.

DR. GULUR: Mr. Mixon?

MR. MIXON: Thank you for being here and speaking. Since 503A, conditional compounding pharmacies must have a prescription for products used in the practice, are you able to obtain this from a 503B outsourcer, or do you write a prescription for your patients and send them to the pharmacy, which they return with for treatment? How do you handle that?

DR. DESAI: I've done it in both ways actually. You can get proprietary blends of glycolic acid when applying them just as chemical peels, and there are commercially available brands that actually dispense those for in-office use. But oftentimes, and in many of my patients who potentially can't afford those in-office treatments, this is a great ingredient for me to add into a compounded mixture to allow the patient to still have that effect of the epidermal cell turnover without incurring the cost of coming to see me every 2 weeks.

It's nice to have that flexibility to offer that to my patients, especially those who come to

see me knowing that they have this chronic skin condition and have already exhausted lots of money on over-the-counter cosmeceuticals, over-the-counter products, and potentially other prescriptions to no avail.

MR. MIXON: Thank you.

DR. DESAI: Thank you.

Committee Discussion and Vote

DR. GULUR: Since there are no further questions, the open public hearing portion of this meeting has now concluded -- thank you -- and we will no longer take comments from the audience. We will now begin the panel discussion of glycolic acid. Do the committee members have any comments? Dr. Vaida?

DR. VAIDA: Two of the three groups that actually proposed this drug, one had the subcutaneous in there, and then the other one had their usual whatever route is prescribed. So once again, there isn't any restriction. And once the drug gets on the list, it could be topical only. I mean, this has come up at prior meetings, but I

don't know if it was ever definitively answered.

MS. GEBBIA: My understanding is we can put it on the list for topical use. The subcutaneous use you mentioned, there wasn't any support provided for that use, and so we've only considered it as topical, and we can limit it by the route of administration when we put it on the list. We can't do it by indication, what they use it for, but we could do it for topical.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: We will now end our discussions and start the vote. The panel will be using an electronic voting system for this meeting. Each voting member has three buttons on your microphone: yes, no, and abstain. Please vote by pressing your selection firmly three times. After everyone has voted, the vote will be complete.

Voting will be on the drug product just presented. This vote question relates to whether this product should be included on the 503A bulk list. After the completion of the vote, we will

read the vote from the screen into the record, and then hear individual comments from each member.

FDA is proposing that glycolic acid, up to 70 percent for topical use, be included on the 503A bulk list. Should glycolic acid be placed on this list? If you vote no, you are recommending FDA not to place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

If there is no further discussion, we will now begin the voting process. Please press the button three times on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. 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. We'll begin.

(Vote taken.)

DR. HONG: Question 1, we have 8 yeses, zero

nos, and zero abstains.

DR. GULUR: We will now entertain comments from the voting members. We will start with Dr. Vaida.

DR. VAIDA: I just want to verify or at least say that it would be topical only; yes with topical only.

DR. PHAM: Katherine Pham. I voted yes in favor of adding to the bulk substance list based on the historic use over decades in the U.S., other countries, the seemingly temporary and readily manageable adverse effect profile, though I did seem to pick up on that serious reactions were present but potentially confounded with other agents.

DR. WALL: Donna Wall. I voted yes for the reasons that have previously been stated, and it seems to have a very appropriate use in therapy.

DR. CAROME: Mike Carome. I voted yes. In part, I was initially concerned about the effect as stated, but I'm reassured that with expertise in treating this condition, that it can be used safety

and effectively.

DR. HOAG: Steve Hoag. I voted yes for all the reasons mentioned. It seemed like it was little downside risk, and it had a valuable treatment option. One thing I would -- because there's no USP monograph, I would worry about like industrial sources of chemicals getting into the supply chain, so that's something I think people should consider.

DR. DiGIOVANNA: John DiGiovanna. I voted yes. I want to thank the FDA for a very clear presentation supporting the long-term use of a drug where there is, longstanding, a number of controlled studies showing efficacy and little toxicity, and for the public comments that helped the advisory committee members understand that this is a useful product that should be available.

MS. DAVIDSON: I'm Gigi Davidson. I voted yes based on FDA's review of the product, and I also appreciate the contributions by the clinical practitioners that reinforced that decision. And I will take it back to USP for consideration of

development of a substance monograph for quality attributes.

DR. GULUR: Padma Gulur. I voted yes for reasons already stated, and again would like to thank everyone for their contributions, which made it very easy for us to come to this decision today, and again to reinforce Dr. Vaida's comment that this is being placed for topical use.

We will now have Dr. Roselyn Epps present on trichloroacetic acid.

FDA Presentation – Roselyn Epps

DR. EPPS: Good morning. I'm Dr. Roselyn E. Epps. I'm a clinical reviewer in the Division of Dermatology and Dental Products, and I'll present trichloroacetic acid. As I begin, I wish to acknowledge the review team, Ben Zhang, chemistry reviewer; Jill Merrill, pharmacology/toxicology reviewer; Doanh Tran, clinical pharmacology team leader; and Elizabeth Marek, historical use reviewer.

Trichloroacetic acid, or TCA, has been nominated for inclusion on the list of bulk drug

substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for topical use in the treatment of common warts and for genital warts. TCA was also nominated as a chemical peel, which refers to a procedure rather than a recognized medical condition. However, we have considered information about the use of TCA as a chemical peeling agent where relevant, including a discussion of reported adverse reactions and efficacy information.

TCA is currently available in undiluted neat also known as 100 percent form and at various diluted strengths. TCA is available in cosmetic formulations and skin peel kits and widely available from distributors and on the internet.

TCA is a colorless, crystalline solid that is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability has been found in the literature. TCA is stable under refrigeration and in acidic and neutral solutions. TCA decomposes when heated and in basic aqueous solutions. Decarboxylation also

occurs under basic conditions.

TCA is synthesized by chlorination of acetic acid to yield a mixture of monochloroacetic acid, or MCA, dichloroacetic acid, DCA, and trichloroacetic acid, TCA. Impurities produced during synthesis include MCA and DCA, residual starting materials, and degradation products, including chloroform.

Chloroform has high toxicity, and DCA and MCA can have toxicities depending upon the exposure level. Although DCA and MCA are progressively more toxic than TCA, these unreacted impurities are unlikely to be present at levels of concern in medical grade TCA. Other impurities are unlikely to be significantly toxic.

To summarize, TCA is a small organic molecule stable under refrigeration as well as acidic in neutral conditions. It is easily characterized using various analytical techniques.

When regarding the pharmacology and toxicology of TCA, the pharmacologic action is denaturation and precipitation of proteins in the

laboratory and in the clinical setting. When studied in rats, the acute oral lethal dose, or LD50, was 5000 milligrams per kilogram. No repeat dose dermal toxicity studies were located.

When regarding mutagenicity, TCA was non-mutagenic in many strains of salmonella typhimurium, however, positive mutagenicity results are reported in two strains. Positive mutagenicity results may have been due to high TCA concentrations, which caused protein precipitation.

When regarding the developmental and reproductive toxicity, embryofetal studies in rats were conducted with oral TCA administration. Maternal and embryonic toxicity was shown at greater than or equal to 330 milligrams per kilogram per day, and embryolethality was reported at greater than or equal to 800 milligrams per kilogram per day. High oral doses in rat studies leading to embryotoxicity may not be relevant to topical clinical use in humans.

When regarding carcinogenicity, no carcinogenicity studies with a dermal exposure to

TCA were located. Long-term oral exposure to TCA induced liver tumors in mice but not in rats. TCA-induced liver tumors in mice are considered a species-specific effect and may not have clinical relevance in humans. No toxicokinetic studies with dermal exposure to TCA were located.

In summary, the toxicity of TCA after topical administration has not been fully evaluated in non-clinical studies, and the available animal data do not raise serious safety issues for topical use in humans.

While no clinical trial specifically designed to address the safety of TCA were located, safety assessments were among the study procedures reported in several clinical trials. There were few published reports in FAERS, as stated, the FDA adverse event reporting system. No published reports of human pharmacokinetic studies following topical application of TCA were located. Overall, the safety profile of TCA in these trials was consistent with that provided in clinical reports.

Typical adverse reactions have been reported

with TCA application, and they include mild to prolonged erythema, pigmentation changes, hyperpigmentation, and/or hypopigmentation, as well as burning, pain, tenderness, and pruritis. Site-specific reactions have been reported with TCA application in the genital and the eye area, including ulcerations and severe vestibulitis in the genital area and corneal punctate keratitis and conjunctival infection with eye area application.

Safety assessments were among the study procedures in several clinical trials. The safety profile of TCA in these trials was consistent with that provided in reports. In addition to more serious reactions in the eye area and ulcerations reported in most studies with TCA application in the genital areas, adverse events were reported more frequently at higher concentrations. With localized wart treatments, scars and hypopigmentation were reported most frequently.

Alternative therapies for warts are available. FDA-approved and over-the-counter therapies to treat common warts and genital warts

include salicylic acid, imiquimod, and Podofilox. Clinical trials directly comparing the safety of TCA to that of FDA-approved treatments for warts are not available.

In summary, clinical trials involving genital and common wart treatment reported erythema, pigmentation changes, pain, burning, and erythema. More serious adverse reactions, including ulcerations, were reported in the genital and eye areas and at higher concentrations. FDA-approved therapies are available to treat warts.

When regarding effectiveness, the concentration of TCA in clinical studies ranged from 10 percent to 100 percent. Five studies were conducted for external genital warts; four studies had an active control; and one study was open label with no comparator. The clearance rates varied widely from 31 percent to 100 percent. For common warts, two dose-ranging studies were identified with one study comparing TCA to cryotherapy. Again, there was a large variation in response

rates, from 12 percent to 93 percent.

One of the nominations included two references for TCA potentially related to its use as a chemical peel agent. The two references cited, one was for atrophic acne scars and one for melasma. We considered these studies to the extent that they are relevant for consideration of the chemical peel nomination.

In the study of atrophic acne scars, a 100 percent TCA was compared to a percutaneous procedure. In the melasma dose-ranging study, TCA was compared to glycolic acid and tretinoin treatment. The comparators in these studies are not approved drug therapies for these conditions, and no conclusions can be drawn regarding the efficacy of TCA.

Generally, common and genital warts are not serious or life-threatening conditions, but less commonly, warts may develop into extensive recalcitrant infections as well as pre-malignant and cancerous conditions.

In summary, we did not identify adequate and

well-controlled clinical trials evaluating TCA efficacy in the treatment of genital or common warts. The available information suggests that TCA may be efficacious in the treatment of these conditions, however, the limited data are from small, open-label, active-controlled trials or case reports.

Historically, TCA has documented use in pharmacy compounding in the United States for at least 20 years. Uses of TCA have included warts, melasma, actinic keratoses, solar lentigines, acne with secondary scarring, as well as xanthelasma. While TCA has been used to treat warts and as a chemical peel for more than 40 years worldwide, the extent of use is unclear. Foreign recognition includes European and British pharmacopeias.

We considered four evaluational criteria, which are physical and chemical characterization, safety, effectiveness, and historical use in compounding. A balancing of the four evaluational criteria weighs in favor of the addition of trichloroacetic acid for topical use to the list of

bulk drug substances that can be used in compounding under 503A of the Food, Drug, and Cosmetic Act. The standard of care for use of TCA in wart treatment is an office application by a licensed healthcare professional.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Epps.

We will now accept clarifying questions from the committee. Dr. Vaida?

DR. VAIDA: So in your recommendation, it's that this is only for in-office use. That's what you're --

MS. GEBBIA: We can't make that limitation on the setting in which it's used. As was the case with glycolic acid, we provided the information on what the standard of care is so that that information was available to the committee and public. We can limit it to topical versus another route of administration, but we can't prescribe the use only in an office setting.

DR. VAIDA: I didn't think that you could, but I just wanted to verify that that's -- because

the concentrations are from, what, 0.1 to 90 percent. And I just want to verify that that was the recommendation on standard of care.

MS. GEBBIA: Yes.

DR. VAIDA: All right. Thank you.

DR. GULUR: Okay. Thank you very much, Dr. Epps.

We will now proceed with the nominator presentations. We have one presentation by Dr. A.J. Day from the Professional Compounding Centers of America.

Nominator Presentation – A.J. Day

DR. DAY: Good morning, everybody. My name is A.J. Day from PCCA in Houston, Texas, and we do have a conflict of interest to state. PCCA does provide trichloroacetic acid for use in the compounding community.

I wanted to take this opportunity to just show a quick image of what compounding looks like in a community setting. I don't know how many of you have actually gotten to see a compounding pharmacy lab. So we do have all of your personal

protective equipment, working within a powder-enclosed container facility.

Your scale is integrated with the computer software. You also have on the right side of the screen -- I don't know if you can see it, but there's a bar code scanner, so we are identifying the correct item that we're utilizing in the compounding process, the specific lot number.

All of this is integrated into our software to make sure that the right item is utilized for the right process, the right amount is being weighed out, and all of this is done in an enclosed setting.

In addition to some of the data that the FDA presented on TCA -- and we thank FDA for the recommendation of adding it for use in compounding on the bulk's list -- there is a very comprehensive review article that was published in 2012 in the Journal of Clinical Aesthetic Dermatology, and this was specific to the application in genital warts.

As you can see from the recommendation for under destructive and surgical options, TCA is

listed as an option as administered by the physician. In my 10 years in compounding, this has always been an office-use, office-administration compound. And under the regulations of 503A, that means that the physician would write a prescription for TCA that would then be applied to the patient in an office setting by the licensed healthcare professional.

It does note that the level of evidence is a B and that the clearance and recurrence rates are as stated. High clearance rates with relatively low morbidity is the conclusion there. And I also included for your reference some of the specific discussion points that this article utilizes, as well as the literature citations utilizing that review article.

In addition to that, the IUSTI 2011 guidelines talks about how they currently use and recommend TCA in Europe. This is the European Guideline for the Management of Anogenital Warts, and it's on behalf of the European branch of the International Union Against Sexually Transmitted

Infections, European Dermatology Federation, and the Union of European Medical Specialists.

As you can see, they've got home therapy options within clinic therapy. It's in the same line as cryotherapy. This is always done in an office setting. It is also in the current CDC recommended regimen for external anogenital warts. And you can see the specific outline for how the CDC recommends it being utilized as provider-administered therapy options.

As mentioned, it does appear on the European Pharmacopeia. This is an image of the monographs specifically there, and it was in the United States Pharmacopeia 21. And something that's important to note is that the USP 21 requirements for TCA were actually a little bit more strict on the purity components of it than the European pharmacopeia current recommendation. And the material that PCCA does carry -- and you have a copy of that certificate of analysis with the nomination material -- complies with the USP 21 standard, which is a higher degree of purity.

Again, I thank the committee for your time and the FDA for the recommendation, and I'm here for any questions you may have.

Clarifying Questions from the Committee

DR. GULUR: Thank you. Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. So I'm a little unclear. So TCA was in the USP and no longer is? Can someone explain to me what that means and how that happens?

DR. GULUR: Ms. Davidson?

MS. DAVIDSON: Thank you. Typically, monographs are omitted from the USP if they are no longer commonly used or if they don't meet more contemporary requirements in USP. And I don't know the story behind this particular monograph, but I do know that the standards for impurities have gotten even more stringent since USP 21, so I suspect it has something to do with impurities, but I can find out.

DR. DiGIOVANNA: So perhaps then for the FDA, it was my understanding that if there was a USP monograph, that it was a compound that was

evaluated separately than if there was not. So what about something like this where there was then and there is not now for nebulous --

MS. GEBBIA: It's not -- I think -- and I'd have to pull up my statute. But we've been looking for what's currently in the USP NF. There's currently a monograph in there -- there's currently no monograph for this product.

MS. BORMEL: Official monographs are those that are in the current USP NF, the official compendia. So this is not an official monograph because it's not in the current issue of the USP NF.

DR. DiGIOVANNA: So the reason that it's not in the current monograph really doesn't relate to it. It just is an accident of nature that it's not, and then it falls into the regulation or out of the regulation, I guess.

MS. BORMEL: Well, USP revises -- I mean, I think Gigi Davidson gave a good explanation. But USP every year issues the official USP NF, the official compendia, and they may take certain

monographs out and put other monographs in. So it's constantly being revised.

The statute is pretty clear that what is official is the current USP NF and its supplements. So every year, we have a new USP NF. I think we're in USP 36. So this is 21. The USP goes back to 1820, so we are looking for the current one, and that's what the USP, which is a non-governmental organization, which issues -- what they put out every year in the official compendium.

DR. DiGIOVANNA: I guess what I'm trying to get at is for the same reason they decided to not include it then, can they decide to include it in the next one?

MS. BORMEL: Yes, they could.

DR. DiGIOVANNA: And then it would no longer fall within this regulation.

MS. BORMEL: Well, it would already be -- we wouldn't need to put it on a list if it were in the official USP NF, correct. But right now it is not.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Is the bichloroacetic acid, is

that a USP monograph, do you know? You said the CDC recommended to TCA, and bichloro is -- does the bichloro have a USP monograph?

DR. DAY: I have not looked into that specifically.

DR. VAIDA: I'm just curious because that's --

DR. GULUR: Ms. Davidson's going to check for us it appears, so we'll hold on that question for a few minutes.

Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. I'm not sure. Perhaps the FDA has a take on this, Dr. Epps. But it was my understanding that -- and I may not be correct, that TCA may be a safer option than the bichloroacetic acid. I've actually never seen the bichloroacetic acid used, but I have used the trichloroacetic acid.

DR. GULUR: Dr. Epps?

DR. EPPS: Well, the concentrations of the dichloroacetic acid are so low in the TCA that it's not -- in the medical grade TCA, it's not

considered to be toxic, in the TCA that would be used medically. Does that answer your question? Sorry.

DR. DiGIOVANNA: No. Bichloroacetic acid versus trichloroacetic acid is my question, maybe for one of the toxicology people.

DR. EPPS: Maybe I'll defer.

DR. DiGIOVANNA: It was my understanding that TCA, as its used as a product or compound, is a safer one that bichloroacetic acid, but I'm not certain of that. That was my question.

MS. GEBBIA: I'm not sure that was part of the scope of the review. Since trichloroacetic acid was nominated, that's what we've looked at.

DR. GULUR: So while we're waiting for Ms. Davidson to look things up, Dr. Day, I have a question for you with regard to -- thank you very much for showing us what a compounding pharmacy looks like on the inside. Is that would you say standard, that all compounding pharmacies follow those standards: bar code scanners, computer-connected weighing scales, compounding

under the hood so to speak?

DR. DAY: I can't speak to all compounding pharmacies. I can say that the best practices are generally regarded as having that degree of integration, and all of that is for the sole purpose of enhancing accuracy and safety of the preparation and of the compounding personnel.

So is it something that is available to all compounding pharmacies? It is. I can't speak on behalf of all the compounding pharmacies to say that they have that in there.

MS. GEBBIA: I would just say you can go on to our website and see the list of regulatory actions, which would suggest that there is still a great amount of variability in compounding practices. And we continue to see observations of poor-quality practices at a number of compounding pharmacies. So I think it is helpful to illustrate, but the range of what practice actually looks like is quite variable.

DR. GULUR: Mr. Mixon?

MR. MIXON: As a surveyor for the

pharmacists to be accredited, I would say that this bar coding technology, integrating the balance with the computer software is commonly used.

DR. GULUR: Mr. Mixon, would you take a few minutes to explain to the committee what the process is for accreditation and how many pharmacies actually are accredited?

MR. MIXON: Pharmacy compounding accreditation started back in -- Gigi, what would you say -- 2008-2007.

MS. DAVIDSON: I think the first pharmacies were accredited in 2008, I believe, by PCAB.

MR. MIXON: It's a voluntary accreditation process. It's a very rigorous process. Currently, there are under 500 accredited pharmacies I believe. I was not prepared to fully answer this question, but PCAB accreditation is, to my knowledge, the only -- to use the analogy of the good housekeeping seal of approval that there is for -- and Donna Wall's shaking her head, that there are others, or is another.

DR. GULUR: What is the denominator,

Mr. Mixon? You said 500 are accredited. How many pharmacies are we looking at, compounding pharmacies?

MR. MIXON: That's a very good question and a highly debated number. I've seen as high as 7500, but you must realize that every pharmacist that goes through pharmacy school is trained to do some compounding. I would say the majority of community pharmacists do a smidgen of compounding, but very few compound as a full-time job relative to the overall.

I've heard there is -- the number of compounders is as high as 7500, but there's a very broad range of compounding activities that are included in that number. Sorry. I can't give you better numbers.

DR. GULUR: That's okay. Thank you.

Dr. Pham?

DR. PHAM: Just as a reminder, traditional and community pharmacies will fall under 503A unless they register as an outsourcing facility under 503B. So federal oversight by the FDA is

only, as of now, over 503B. And at the 503A, pharmacies are going to still be regulated by state. So if we're talking about accreditation and quality and consistency, it's still going to vary from state to state, hopefully in legislation, but more likely probably regulation. But that's just -- I'm not going to opine on that.

But the main thing also -- to go back to the FDA announcement earlier about the unsanitary conditions, which is also going to be a driving standard. And that's still in draft guidance form, so I don't know that we can really make baseline standardizations on the quality of compounding pharmacies.

MS. GEBBIA: I just want to add one clarification. FDA 503A is federal statute. Pharmacies that are compounding and subject to Section 503A, and are seeking to qualify for the exemptions in 503A, don't have to register with FDA, so we don't know of all of them. There's obviously far more of them than we could ever possibly go out and inspect.

We do inspect pharmacies that are seeking to qualify for those. A number of them that we have inspected have been PCAB accredited and still have had conditions which have caused us to issue a warning letter. So I wanted to make that clarification as well.

MS. BORMEL: I also wanted to clarify that although the state boards of pharmacy generally have day-to-day jurisdiction over the boards of pharmacy, the agency does have jurisdiction of where drugs are made, and we do get involved when we have -- especially when there are poor standards at state-licensed pharmacies when we're aware of it.

I also wanted to clarify that the current USP NF is 39. Also, we took a look at the database that we have. We have an online version of the USP NF, and we could not find bichloroacetic acid or chloroacetic acid. I mean, I defer to Gigi Davidson, but that was our findings.

DR. GULUR: Thank you very much. Mr. Mixon?

MR. MIXON: Thank you. I just want to

remind the committee that when FDA does inspect compounding pharmacies under 503A, they are still inspections, or have been until very recently, to see CGMP standards, not USP standards.

MS. GEBBIA: If a pharmacy is compounding and doesn't meet the conditions in Section 503A for the exemptions from certain provisions of the Food, Drug, and Cosmetic Act, then they are required to comply with current good manufacturing practices. I'm happy to spend some more time talking about this if it's helpful to the committee, or we can circle back to the substance at hand. I don't know how relevant this --

DR. GULUR: I think we can circle back to the substance at hand. But it would be worthwhile, perhaps -- considering that we're being shown pictures of what standards are, it would be good for the committee to know if that's standard or what else is going on.

MS. GEBBIA: Yes, absolutely. I think we could certainly take under advisement adding a presentation in the future regarding that.

DR. GULUR: Thank you. And we'll give Ms. Davidson a chance after all the work.

MS. DAVIDSON: The conspicuously absent standard that is not being discussed here is USP compounding standards, which were culled out in the DQSA, and so they are in place. They are adopted by the majority of states now, and the compounding standards are in the process of being significantly revised to improve the processes that we saw on the screen.

There are very good checks and balances that are very granular in their description of all the steps that now must be taken to ensure that even though you don't have a bar coding device, you will not miss an important step in the compounding preparation process.

We've just addressed personnel protection, processes, equipment, monitoring of both employees and environment. So I'll let Dr. Wall speak to why some of the states have decided not to follow USP standards when it's culled out in federal statutory requirements, but there are standards in place that

do greatly ensure the safety of compounding as compared to previous times.

DR. GULUR: Dr. Wall?

DR. WALL: What I was going to comment on when you were talking about inspections, there is actually now a national inspection that you can request as that pharmacist. It's called the VPP. It comes out of NABP where they come in, and it's an intense inspection of looking at all of the standards. Where it's being used is quite often if you want to ship into other states and the other state wants to have that kind of an inspection, that is then applicable to all the various states and to meet that process.

So that process is being done -- I don't have the numbers -- I asked for it -- because I know that they've got more backed up. They're working their way through it. Everything that's coming along, it's getting better and better and more accurate as we go along. And I'm not going to answer Gigi's question right now.

DR. GULUR: All right. Well, thank you.

Any further questions for Dr. Day? Dr. Hoag?

DR. HOAG: I have one comment. I have the USP on line. I could only find glycolic acid as a reagent, which kind of goes back to my concern about industrial chemicals, making sure that it's a proper grade.

I'm just curious. How is this -- going back to the trichloroacetic acid, how is that administered? As a solution, a suspension, aqueous? What's a typical way of applying that?

DR. DAY: Typically, it's formulated in glycerin. That's the most common way that I've seen it utilized, sometimes in flexible collodion. But our goal is to put it into something that has a degree of viscosity so that it stays at the site of application.

Sometimes the dermatologist will protect the surrounding tissue using vaseline or other methodologies. But you want something that has a little bit of viscosity to it to help keep this at the site of application, at that wart.

DR. GULUR: Dr. Pham?

DR. PHAM: There is some information about serious reactions occurring at higher concentrations. What's the highest concentration that you normally would see it compounded in, or what's the frequency of that higher concentration?

DR. DAY: Common concentration that I've seen is 10 percent, 10 to 20, 25 percent, is the ballpark that we typically see 10 being the most common. The highest that I've seen has been about 80 percent. That's my personal experience.

DR. GULUR: Dr. Vaida?

DR. VAIDA: That just raised the question -- looking at the studies that were presented, 6 out of 7 were in concentrations of greater than 35 percent. So that's what you're saying, it's usually 10?

DR. DAY: In my experience of the requests from pharmacies and dermatologists looking to formulate trichloroacetic acid, the range is typically between 10 and 25 percent, and the dominant concentration that I've seen is

10 percent.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: I think it really depends on the use. I mean, TCA is really used as a controlled destructive agent the same way you might use a cryotherapy, which is destructive, or an electrocautery, or even a laser in this modern day and age.

So I think that from that perspective, it's often used in concentrations of 25, or 50, or 75 percent, but it depends on what it's particularly being targeted to. So that would be for a very small lesion or that's very large, where you wanted to create more destruction. So I think that's where the leeway comes from.

DR. GULUR: If there are no further questions, we'll -- did you have a comment?

MS. DAVIDSON: I just put in a request to USP to find out why the monograph was omitted.

DR. GULUR: Thank you, Ms. Davidson. Thank you, Dr. Day.

DR. DAY: Thank you.

Open Public Hearing

DR. GULUR: Appreciate your presentation.

We will now proceed to hear open public hearing speakers. If you could introduce yourself again.

DR. DESAI: Thank you, Madam Chair. Seemal Desai, board certified dermatologist practicing in Dallas, on faculty at UT Southwestern, and speaking on behalf of the American Academy of Dermatology Association, as well as the American Society for Dermatologic Surgery Association.

I'd like to thank the FDA for an excellent presentation, and Dr. Epps for putting together that great science behind trichloroacetic acid, and for all the comments, especially of the committee today, and for having the permission to speak here.

I think the key for TCA is that it's actually a very versatile ingredient. In fact, it's one of those ingredients that I find to be very effective in a wide range of skin conditions, and that I think is the beauty of this ingredient. It's quite inexpensive, so when it comes to drug

costs and all of the things we're dealing with in society now with healthcare cost, TC is actually quite inexpensive to use.

But the beauty of it is that depending on what concentration I use it in, I can actually treat lots of different skin conditions in the office. And I'll give you an example. In the lower strength, which I use quite frequently, around 15 to 20 percent is my go-to. I actually consider this to be a superficial peeling agent. And it's great to use in chemical peel treatments, particularly in my patients with melasma and post-inflammatory hyperpigmentation.

In fact, just like I was speaking about glycolic acid earlier, this is an additional therapeutic agent. Should I have a patient who's not getting a response to glycolic acid, I can then do a next treatment cycle with TCA and hope to get a little bit more of that desquamation and epidermal cell turnover.

Moving into a higher concentration, I use it oftentimes 35 to 40 percent for those patients who

really have recalcitrant hyperpigmentation and even some superficial acne scarring. And it's very effective in that concentration as well in a controlled office setting. And though it does have a little bit of irritation and burning at the site of application while I'm doing the procedure, the post-care if patient is instructed correctly is very, very simple, and these patients do really quite well no matter what their skin type.

Then the third indication, which is what I found to be super helpful, is in patients who have pitted acne scars, which we know is a permanent side effect of chronic inflammatory acne, and those scars are very, very difficult to treat, and also for external genital warts.

I'll give you an example. For patients who come in with genital warts, one of the cheapest and quickest things we do in our office is use liquid nitrogen, and we can freeze the warts. If any of you have had warts, you know they're quite easy for a dermatologist to treat. We're able to apply liquid nitrogen, freeze the wart, and hopefully it

will start to reduce in size.

But in patients with darker skin tones, particularly patients of my skin tone or darker, when you apply liquid nitrogen to the skin, you actually risk leaving a really white area on the skin that can be quite noticeable called post-inflammatory hypopigmentation or depigmentation.

So you can imagine that I'm trying to fix someone's wart and get rid of the virus, but in turn I've left them with a white scarring area that's quite visible. And you can imagine if this is on the genitalia of either a man or a woman, this can be quite concerning to patients and can lead to lots of psychosocial implications.

Using TCA, I can actually direct the application of that solution directly on the site of the viral lesion without risking much spread to the surrounding peripheral tissue that liquid nitrogen would do, and therefore cause that pigmentary issue. So I can actually control the application with high-dose TCA much easier than I

can with liquid nitrogen, especially with patients with darker skin tones.

Lastly, I want to mention acne scars because I've had many patients who are teens and young adults in college who come in, who are very distressed from their inflammatory acne scars that almost leave ice-pick like areas and pock marks on their skin. And I think we've all seen that, and that can be very distressing to these patients.

A quick in-office procedure applying high-dose TCA -- and I go up to 85 and 90 percent. And I can actually apply the acid directly into each individual scar without surrounding and damaging the tissue, and have a really nice improvement in these patients' acne scars.

The last thing I'll mention is that you see lots of advertisements for laser resurfacing treatments and lots of cosmetic laser treatments for acne scars, which costs thousands and thousands of dollars. With this ingredient, we can do it for a fraction of that cost. And I'm happy to entertain any questions, and I thank you in advance

for your inclusion on the list.

DR. GULUR: Thank you. Do we have any clarifying questions? Dr. Pham?

DR. PHAM: It's been mentioned previously about the concerns about the higher concentrations and serious reactions. With the in-office application, how are you monitoring for use of the higher concentrations?

DR. DESAI: The in-office application use of the product is very, very simple. And I actually only use this exclusively in office really no matter what the concentration. So in low doses, I'm using it as a peel where we actually apply a liquid solution typically in an alcohol base to the skin, allowing the acid solution to evenly penetrate for usually 2 to 3 minutes.

Then we neutralize it either with normal saline or some sort of neutralizing applicator depending on the type of peel I'm using. We apply post-emollient or thick ceramide-containing moisturizers, sun screen, and the patient's usually discharged. That procedure from start to finish

takes me less than 10 minutes.

If I'm using the higher concentrations, let's say for acne scars or genital warts, that procedure does take a little bit longer because we're very careful to ensure that that solution is only applied at the target site. And I think the key here is that when you're using in an office in concentration, the most important thing is when you're applying the solution, just to apply it very, very slowly and methodically. And that's where the compounding pharmacists come in handy because we can actually get this compounded in more of a viscous or gel-like solution to ensure we're not spreading it to surrounding tissues.

But usually there are no other precautions that are used prior to the treatment except to counsel patients to discontinue use of all retinals- and retinoid-containing products at least a week prior to coming in to see me for the treatment, and then afterwards to limit their sun exposure, wearing sun screen.

These are the sort of procedures where I

tell patients, if you're planning a beach vacation three days after you want to do this procedure, that's not something you want to do. This is something where you want to really limit excess sun exposure for usually 7 to 10 days. That doesn't mean you have to go into hiding, but it means that you really have to make sure you use a little bit of caution. And normal activities can be resumed almost immediately. So I even have patients come in to do this in the middle of a work day, and they can go back to work as long as they're using good photo protection.

DR. GULUR: Thank you very much. Any other questions? Dr. Vaida?

DR. VAIDA: I just have one for the FDA. When they get added to the list, is there going to be like a few sentences or something on the drug? Since there is no monographs and you can look them up, is the FDA going to -- like will the list include like a little paragraph or something on the drug, higher strengths, office use? Although you may not be able to regulate it, is that the intent

of that --

MS. GEBBIA: We do have to go through, as you noted, to make the list a rulemaking process. So we'll issue a proposed rule on a rolling basis where we'll discuss the substances that we're proposing to put on the list, sort of what the evaluation was, what the PCAC said.

My sense is that the entry on the list would be not an explanation or we wouldn't be trying to set standards or describe that. There may be some discussion in the preamble to the rule about what the thought process was and why we're recommending something or not. And of course, we'll get comments. People can comment on the proposed rule when it's available, and during the rulemaking process we also respond to comments.

So it may be incorporated into part of the process, but I -- obviously, we haven't done the rule yet, so I can't say what exactly it will look like. But I think the idea is that they're -- like with the withdrawn and removed list, if you look at those entries, they're just sort of directly about

the substance. It's not a lot of elaboration.

DR. GULUR: Thank you. Any further questions?

(No response.)

Committee Discussion and Vote

DR. GULUR: Thank you very much for your comments.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion of trichloroacetic acid.

Do the committee members have any comments? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. I wanted to thank Dr. Desai for his comments because he made what I wanted to say a lot easier. And that said, I was going to try to clarify a little bit for the committee the difference between the words that are sometimes used and the actual activity as it actually happens.

Most of what's been presented has been for warts. So we all have our own idea of what warts

are. Certainly, very specifically, they're infections by human papillomavirus. However, just like you would think of a spot or a mole, or more specifically a nevus, or even more specifically a certain type of nevus like a junctional nevus, a wart is a common type of lay word used for many different types of skin lesions.

So the data that's presented quite accurately will show that there are other FDA-approved treatments for warts. Probably the reason there are so many is because they are so poor, making it very helpful to have preparations such as TCA, which can be used for specific indications, as Dr. Desai has eloquently presented.

The issue with the commonest treatment, cryotherapy, is the very debilitating hypopigmentation that sometimes occurs in skin of color. However, there are many other skin lesions that are considered warts that may be more specifically thought of by the dermatologists, like seborrheic keratosis or xanthelasma, which is a very common one that was up on the screen, which

are lesions around the eyes that tend to respond very, very well to this treatment and very poorly to many other types of treatment.

So while there are other FDA-approved treatments for warts, there are many of the other conditions which this is used for, where there really aren't any FDA-approved treatments.

So this is a very useful tool, a somewhat destructive tool that can be controlled like the freezing of cryotherapy, or the electrodessication of an electric needle, or many of the other treatments like a laser that affords the ability of the practitioner to be able to direct it specifically to a lesion and create a great deal of efficacy. And it's almost uniformally done under controlled circumstances in the office.

So I was hoping -- I wanted to clarify that. Again, I thank Dr. Desai for helping us understand the scope of its utility.

DR. GULUR: Dr. Carome?

DR. CAROME: So I appreciate John's comments. I do have concerns about the data, at

least for the indications that it was proposed and discussed by the FDA, that there really is very poor data here from clinical trials, much less so than the previous drug we looked at. There is not good data on effectiveness, at least for the indications proposed, and we're talking about many other things it might be used for, for which we haven't discussed. So that raises concerns for me.

DR. GULUR: Dr. Epps, would you like to address that?

DR. EPPS: TCA action is by precipitating proteins, so when you apply it to the skin, it causes a white frosting. So it would be very difficult to have a randomized, double-blind, placebo-controlled trial when what you're applying causes white frosting and a vehicle or another substance does not cause that.

So that's why it's very difficult -- you can compare different strengths of TCA, but it's very difficult to find a substance which would compare and give you a really good clinical trial. Yes, there are active comparators, and we compare them.

The other point I should make, there are over 150 different humanpappiloma viruses. And the reason that there are a lot of treatments for warts -- because none works for everyone, so you need different treatments. And sometimes they're used sequentially. You might use one sometime if someone has multiple warts. Some of them go away, some don't. So the next time you treat, you might use something else.

We're not in the business of treating. I'm a dermatologist, pediatric dermatologist specifically. So that was in my former life. But the reason that they're a lot of treatments is because none works for everyone, and clinicians need options.

DR. GULUR: Dr. Carome?

DR. CAROME: I'm a little astonished by your saying we can't do good clinical trials here because of precipitation. You can actually have hard outcomes about many things: has the scar resolved, are the warts resolved? So I'm a little confused by what you just said about not being able

to do clinical trials.

DR. EPPS: I didn't say they couldn't be done.

DR. CAROME: Okay.

DR. EPPS: That is the data that's available, and that's what was reviewed.

DR. CAROME: Exactly. But you could design much better trials and get definitive data.

DR. EPPS: FDA reviews data. We do not conduct clinical trials.

DR. CAROME: I understand that. I'm not criticizing you for not doing the trials. I'm criticizing the field perhaps.

DR. GULUR: Any further discussion? Any comments?

(No response.)

DR. GULUR: We will now end our discussions and start the vote. The question in front of you is FDA is proposing that trichloroacetic acid for topical use be included on the 503A bulk list. Should trichloroacetic acid be placed on the list? If you vote no, you are recommending FDA not place

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

(Vote taken.)

DR. HONG: Question 2, we have 7 yeses, 1 no, and zero abstain.

DR. GULUR: Thank you. We will now take comments on this. Dr. Vaida, if we could start with you.

DR. VAIDA: Allen Vaida. I voted yes. It was a real tough call. I still have questions on

why it was removed from the USP monograph that I don't think were answered, and still have some of the questions on the studies that were done as Dr. Carome had mentioned. But I voted yes basically on what the dermatologists said, that there is a use for it, although there are some other drugs available.

DR. GULUR: Go ahead, Dr. Pham.

DR. PHAM: Katherine Pham. I voted yes. I also felt that this was a difficult decision. I'm still not convinced by the level of evidence, though I do appreciate thoughts from Dr. DiGiovanna and Dr. Desai regarding the clinical experience with this agent.

Ultimately, I do feel that even though placing on a list may disincentivize evidence to be done in a better designed trial, there is enough widespread use concerning access, and concerns with the serious concentrations seem to be alleviated by the process that's done in the in-office applications. So because of that, the fact that it's an in-office application, as long as there's

close monitoring by the provider, ultimately will swing me to a yes, but it was not an easy decision.

DR. GULUR: Thank you, Dr. Pham. Dr. Wall?

DR. WALL: I voted yes. I felt like there was enough clinical data that there is a sufficient need for it, and I appreciated the comments from the dermatologists of how they need a large armamentarium of medications to treat some of these things, that it is not a one size fits all. So there needs to be flexibility in what they can use, and I felt like they're monitoring their patients appropriately.

DR. CAROME: I voted no because of concerns about the poor quality of data on effectiveness, the availability of FDA-approved and the over-the-counter products, and other compounded products that this committee has allowed to go on the list for the conditions being considered, and again, the fact that this disorders here are not serious or life-threatening.

DR. GULUR: Thank you, Dr. Carome. Dr. Hoag?

DR. HOAG: Steve Hoag. I voted yes. I felt that the pattern of use of the application in the clinic and the -- there are some side effects, but they weren't that severe that it's worth having on the list.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. I voted yes. I think that in trying to make these evaluations, it's a little difficult. I've been in a number of advisory committees. Most of them are for drug approvals, where we see a huge amount of data that's been very carefully collected, with the help of the FDA, in designing well-controlled studies.

On the other hand, in this environment, really what we are often talking about are products that have had a very long history of safe use not only in the U.S. but worldwide. So it's hard, if you're not in that scenario of using them, to be able to get an understanding of exactly what real life is like for the users and the receivers of this.

It reminds me of driving in a car to get

here this morning. Sometimes being on the Beltway, you run into a problem, and if there's traffic, you have to change course. So you may have to get off and go a different direction. You have a GPS that helps you. And if there are more difficulties, you change course again.

That's the scenario for a compound like this in a dermatologist's office, where you will have a variety of different skin lesions, warts, and in some individuals they'll be easy to address with standard interventions, but in others they're not, in which case you have to change course and find something else. And you may then choose the product like this that requires extra effort of having it compounded and having it made, and applying with more restriction.

So you didn't choose that as the first one. You choose that as the route to get around the difficulty. And it makes studies that are carefully controlled difficult to assess, and you're not going to find those in the literature because no one is going to do a large study to look

for the alternate route to the FDA when their first didn't work out.

So I think it would be helpful sometimes to get a broader sense -- I know it's difficult to get that for individuals who are not in that situation -- of how some of these products -- not only this one but others that we will be facing as the committee goes on, how they are practically used, and perhaps why we're not seeing the same level of stringency in the studies that we may be more comfortable with in other environments

So in summary, I voted yes. I think it's a very useful product that has been used by dermatologists safely for a long period of time, but not as a first-line approach for those scenarios where something else needed to be thought of.

DR. GULUR: Ms. Davidson?

MS. DAVIDSON: Gigi Davidson. I voted yes, and I appreciate Dr. DiGiovanna's analogy of taking different courses. I think that's what compounding is all about. It's for individual patient

problems, and not everything works for all patients. My daughter was a swimmer most of her early years, and we struggled with plantar warts for her entire swimming career. And I know how many options there are out there to treat warts, and very few of them work.

I agree with FDA's assessment of the data that is available, and I appreciate the problem with blinding that Dr. Epps brought up. We could do clinical trials, but they would not be blinded. There's no way to blind this drug, so I do appreciate that challenge in finding good data.

I just wanted to mention that for USP monographs, they're not necessarily all clinically based or drug based. This monograph probably was not removed for efficacy reasons or quality reasons. It was probably lack of continued use as maybe an excipient or some sort of vehicle binder, some other reason. But again, I have put in a request to USP to try to find out it was omitted, and I will share that one when I have that data. Unfortunately, the FDA and USP firewalls do not

like each other at all, so I've had to switch to my phone to try to get to the USP database.

DR. GULUR: Thank you. I voted yes as well, and I do find that I share everyone's mixed emotions on this particular issue. I do respect the fact that it's hard to conduct studies, well-controlled studies, when it is not widely used.

But at the same time, I find it hard -- I struggle with thinking that just because it's rarely used, we shouldn't worry about the risks of that treatment. In fact, in many times when you have these kinds of fourth option or fifth option, the risk for patients are actually higher and higher as you go forward.

This particular drug, again, the challenge was that it didn't pose -- or at least we didn't hear of any significant risk. It is widely used in practice. That still does not absolve those of us that are in the science of these votes from making the effort to learn more and ensure that the safety of our patients continues to be primary.

So I would encourage that we look at it from that perspective in spite of the fact that we have voted to put this on, on the list. Thank you.

With that, thank you, everyone, for your participation. We are actually a little bit ahead of time, but we will now have our morning break. Committee members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. Please return to your seats at 10:45.

So I would encourage that we look at it from that perspective in spite of the fact that we had voted to put this on the list. Thank you.

(Whereupon, at 10:25 a.m., a recess was taken.)

DR. GULUR: If all members would please take their seats, we will get started with the session after the break. We will actually now have Dr. Jonathan Jarow present on kojic acid.

(Pause.)

DR. GULUR: Dr. Jarow, if you could give us

a few minutes, we're going to have actually Sara Rothman present on -- or clarify some comments from before.

MS. ROTHMAN: Thank you. I'm Sara Rothman. I'm in the Office of Unapproved Drugs and Labeling Compliance in the CDER Office of Compliance. I just wanted to make a few clarifications to address the earlier discussion regarding registration, GMPs, and sanitary conditions, and the types of things that we're seeing at compounding facilities.

I just wanted to clarify that all of the provisions of the Federal Food, Drug, and Cosmetic Act that apply to conventional manufacturers apply to compounders and compounded drugs unless compounded drugs can qualify for exemptions from certain provisions of the Act if they are compounded in accordance with either Section 503A or 503B.

503A is of course what we're talking about mostly during this meeting. And under 503A, if a drug meets all of the conditions, it can qualify for exemptions from FDA approval requirements, the

requirement to be labeled with adequate directions for use and current good manufacturing practice requirements that remain subject to all other provisions of the Act, including, for example, the prohibition on preparing, packing, or holding drugs under insanitary conditions.

Other provisions that apply include, of course, that you can't have a drug that deviates from the applicable USP monograph in strength, quality, or purity, and you can't have labeling that's false or misleading. There are many other provisions that apply to those drugs.

When we do our inspections of compounders, as Dr. Pham noted, most compounders do not register with FDA unless they decide to elect to become outsourcing facilities. So there are estimates out there of thousands and thousands of compounders that produce drugs, fewer that do sterile, but many that compound drugs. And of the thousands that are out there, we only know of a small number of them based on just prior history, receipt of complaints, information from states, et cetera.

So of the compounders that we know of, we do surveillance, for-cause, and follow-up inspections. When we go out and we do our inspections, we find a wide variation of conditions at the compounders. Some compounders are located in states that have really intensive inspectional programs and oversight programs. Other states, because mainly of resource constraints, aren't able to oversee the compounders as routinely.

As Emily noted, we have on our website a list of inspectional observations. Many of the compounders that have received warning letters have insanitary conditions cited in the warnings letters. There are things that we see like cockroaches and ceiling construction during sterile processing, really conditions that cause a great deal of concern.

We do not cite compounders for violations of current good manufacturing practice requirements unless either they register as an outsourcing facility or they produce drugs that do not meet the conditions of Section 503A. And that's always been

our practice, and it remains our practice.

So there's a wide variation of conditions that we see. I would also note that since the 2012 fungal meningitis outbreak, there have been numerous serious adverse events that we've investigated associated with both sterile and non-sterile drugs.

Recently, we've seen patients hospitalized when they've received non-sterile drugs that are over a thousand times super potent. So we're obviously most concerned about contaminated sterile drugs, but non-sterile drugs have also been associated with serious adverse events.

So I just wanted to clarify that all of the provisions of the Act apply to these entities unless they qualify for exemptions from just provisions that they can be exempt from. And although the states have day-to-day oversight, we do have authority. We just don't know who most of them are because most of them do not register with FDA.

DR. GULUR: Thank you very much. At this

time, we will likely limit the discussion on this topic further. The FDA has promised to do a presentation on this at a subsequent meeting for us, and we'll look forward to that, and have the opportunity at that time to discuss it further.

With that, I will invite Dr. Jarow again to please present kojic acid.

FDA Presentation – Jonathan Jarow

DR. JAROW: Thank you very much. My name is Jonathan Jarow. Good morning, committee members and guests. I will be presenting kojic acid on behalf of the FDA review team, which is listed here.

Kojic acid, 0.05 percent to 10 percent, has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A of the Act for topical use in the following conditions: in the treatment of hyperpigmentation disorders and as a chelating agent for wound healing and prevention of photodamage.

Kojic acid is currently available in

cosmetic formulations and in soap bars. Kojic acid is a small organic molecule. It's pKa is around 7.4. It's soluble in water. It's a naturally occurring chelation agent. It is easily characterized with various analytic techniques.

Kojic acid, however, is very reactive and an unstable compound. It oxidizes easily in air, both as a solid and in an aqueous solution. High temperature, exposure to light, low pH can all accelerate the decomposition or degradation process. It requires special sealing and formulation to protect it from decomposition, although the preserving effects of this are limited. As an example, just UVB exposure in an aqueous solution causes all of kojic acid to disappear within 2 hours, so it can be very unstable, and it's particularly unstable in an acidic environment.

Kojic acid can be obtained from the fermentation of starches and sugars by a variety of microorganisms. Likely impurities include bioburden, residual starting materials, and

degradation products. In summary, regarding the physical and chemical characterization, kojic acid is a small, easily characterized molecule, however, it is very reactive and unstable, and this can affect the stability of compounded drug products.

In regards to pharmacology and toxicology, kojic acid, as I mentioned before, is a chelation agent and an antioxidant. It is also a pigmentation inhibitor in plant and animal tissues and is used in foods and cosmetics to preserve or change the color of products. Kojic acid is used in dozens of cosmetics at concentrations from as low as 0.1 percent to 4 percent. It also has antibacterial and antifungal properties and is produced by many species of aspergillus. Non-clinical published data on topical use of kojic acid is limited.

Kojic acid does not appear to be irritating to the skin or eyes up to 3 percent, and is non-phototoxic at up to 5 percent in available animal studies. At concentrations up to 30 percent, kojic acid does not demonstrate skin

sensitizing ability. The subcutaneous LD50 of kojic acid in mice and rats is 2.7 grams per kilogram and 2.6 grams per kilogram, respectively. The dermal and oral LD50s in Wistar rats are greater than 2 grams per kilogram.

A 4-week dermal study in Wistar rats using doses of zero, 100, 300, and 1,000 milligrams per kilogram per day revealed mildly decreased lymphocyte counts in males and female rats, receiving greater than 300 milligrams per kilogram per day of kojic acid. The no observed adverse effect level of this study was determined to be 100 milligrams per kilogram.

Kojic acid appears to be genotoxic as demonstrated by positive results in the Ames test and chromosomal aberration test in vitro, however, kojic acid does not appear to be genotoxic in an in vivo mice micronucleus assay or an in vivo rat Comet assay. Reproductive toxicity studies in rats demonstrated slight changes in fertility parameters at 900 milligrams per kilogram orally. The results of carcinogenicity studies are mixed, and the

carcinogenetic [ph] potential of kojic acid is unclear.

With limited dermal absorption shown in the in vitro human skin penetration study, the use of kojic acid in the compounding of dermal drugs may be reasonable from a pharmacologic and toxicologic perspective, however, non-clinical data suggests that its possible genotoxic potential and equivocal carcinogenicity data are of some concern.

In summary, there's limited published non-clinical data on topical use. It appears to be not irritating to skin or eyes at concentrations up to 3 percent. It's not phototoxic up to 5 percent. In rat studies, we've seen a mildly decreased lymphocyte count genotoxicity as observed in in vitro studies but not in vivo studies.

Reproductive toxicity suggests lack of developmental or reproductive toxicity. Carcinogenicity is equivocal, and toxicokinetics demonstrate some dermal absorption but quite limited. Studies in rats did show, however, placental transfer and milk secretion of kojic

acid.

In regards to human safety, we performed two searches for spontaneous adverse events with kojic acid. The first was of the FDA FAERS database by the Office of Surveillance and Epidemiology, and the second was by CFSAN of its CAERS database. Neither of these searches found any reports for kojic acid. It may be that the reporting in these databases may not be sufficient to link a report of an adverse event to a product containing kojic acid.

The available data suggests that the topical use of kojic acid may be associated with local irritation. Generally, reported adverse reactions appear to be transient and manageable with standard procedures. There have also been cases of allergic contact dermatitis documented in literature reports and confirmed with patch testing. There have been no reports of systemic adverse reactions associated with kojic acid.

Both in vitro and in vivo studies have demonstrated the ability of topically applied kojic

acid to penetrate intact skin and lead to systemic exposure. There's been no studies of non-intact skin or wounds to determine whether the exposure is greater in that setting.

In 2012, the European Commission Scientific Committee on Consumer Safety reevaluated the non-clinical and clinical data regarding the safety of kojic acid and stated the following. Reexamination of the available data for kojic acid used as a skin whitening agent at a concentration of 1 percent in leave-on creams, which are generally applied to the face and/or hands, leads to the conclusion that it is safe for consumers.

There are products with established safety approved for the treatment of hyperpigmentation disorders such as melasma. Tri-Luma is an FDA-approved product for topical use for treating this. For indications related to iron chelation by kojic acid, there are a number of products, both devices and drugs, approved for wound healing. There are no approved products for photodamage prevention.

In summary on human safety, clinical data

suggests that the adverse effects of topical kojic acid are minor, transient, and manageable. Data regarding the safety of kojic acid as a single active agent in the treatment of hyperpigmentation disorders are limited. The data are confounded by the use of formulations with multiple active ingredients and poor trial designs without adequate controls. Most trials include sunscreen application as a concomitant procedure.

Regarding the use of wound healing, the safety of the proposed concentration up to 10 percent has never been studied in open wounds. There are no available data regarding the systemic exposure for this use, which may depend on many clinical variables included but not limited to the size of the wound and presence of infection. There are no safety data on kojic acid in prevention of photodamage.

Moving on to effectiveness, the majority of the trials evaluating the use of kojic acid in the treatment of melasma or hyperpigmentation disorders included combination products containing kojic acid

compared with active controls. These combination products contained other topical therapies such as retinoids, hydroquinone, glycolic acid, and botanical ingredients. All of the trials used adjunctive measures such as sun protection with sunscreens and protective clothing.

Many of these trials showed improvement in the severity of melasma compared to baseline using kojic acid combined with products either as a topical agent or with a peeling agent. However, the data are often confounded by the use of formulations with multiple active ingredients, inappropriate comparators, poor trial designs, incomplete descriptions of statistical methodology, and variable outcome measures.

The standard criterion of treatment success used by FDA for approval of drugs for this disorder is clearance of melasma, and this is not usually presented in the reports. Thus far, there are insufficient quality data from clinical trials to assess whether kojic acid aids in the treatment of melasma or other disorders of dispigmentation.

In addition, the clinical data from such trials may only provide limited support for extrapolation to use in a compounding setting because of formulation differences, especially considering the instability of kojic acid, which may be aggravated by the presence of acidic peeling ingredients often used in combination.

I will review three of the eight studies that we found. Hyperpigmentation disorders. In 1999, Lim evaluated 40 Chinese women with epidermal melasma in a double-blind, randomized, within-subject, 12-week trial comparing hydroquinone 2 percent with glycolic acid 10 percent, with add-on therapy of kojic acid 2 percent gel. The difference in clearance of melasma was not significant different between the treatments, and the p-value was 0.9.

In a study by Deo in 2013, he conducted a 12-week, randomized, single-blind, parallel group trial of 80 adults with melasma comparing kojic acid alone at 1 percent, kojic acid combined with hydroquinone, kojic acid with betamethasone

valerate, and kojic acid with the two other agents.

Information on the rate of clearance of melasma in the study subjects was not provided in this report, but they used the reduction of the MASI score, and this was achieved in the following percentages in the various groups, so it ranged from 59 percent to 36 percent. Of note, all of the arms had kojic acid in them. The fact that kojic acid combined with other agents did less well than group A makes it very difficult to interpret this study.

The next study by Garcia in 1996 conducted a 12-week, randomized, active-control, bilateral comparison, so a split-face trial, in 38 subjects with melasma comparing kojic acid with glycolic acid to hydroquinone to glycolic acid.

The clearance rates for melasma were not provided, while reduction in hyperpigmentation showed the following percentages, which was not statistically significant. Efficacy of kojic acid 2 percent in combination with glycolic acid as gel formulation is not established. Clearance rates

for melasma are unknown for this study.

Iron chelation uses, it was nominated for both wound healing and photodamage prevention. There is no published human clinical experience to support use of kojic acid in wound healing or prevention of skin photodamage. There was one published animal study of kojic acid as an iron chelator to promote wound healing with an active control and a placebo control. The active control, deferiprone, was superior to kojic acid, and kojic acid was not found to be better than vehicle.

One published study of kojic acid used in hairless mice as an iron chelator for photodamage prevention, kojic acid prevented wrinkling from solar-simulated UV irradiation for 20 weeks.

The seriousness of the conditions for proposed use of kojic acid, hyperpigmentation disorders, and photodamaged skin are not serious conditions per se, but pathologic changes predisposing to skin cancer may be associated with photodamage. Wounds can be serious conditions depending on the location, size, depth, concomitant

fluid/electrolyte loss, vascular supply, free radicals, and wound infection.

In summary on effectiveness, most clinical trials assessing treatment of melasma included use of kojic acid in combination with other drug substances. It is very difficult to quantify the effect of kojic acid alone. Insufficient quality data from clinical trials makes it difficult to assess whether kojic acid aids in treatment of hyperpigmentation. There is no human clinical data to support the use of kojic acid in either wound healing or prevention of photodamage.

In regards to the historical use of kojic acid in compounding, kojic acid has been used often in combination with other substances in pharmacy compounding in the United States for decades. The most common uses are melasma and other hyperpigmentation disorders. The extent of use cannot be precisely determined. Kojic acid products are regulated in Japan as quasi-drugs. It is not in the USP or European, British, or Japanese pharmacopeias.

The recommendation, a balancing of the four evaluation criteria weighs against kojic acid being added to the list of bulk drug substances that can be used in compounding under 503A of the Food, Drug, and Cosmetic Act. The criteria include physical and chemical characterization. The key finding for this criteria is that it is highly unstable unless adequate measures are taken to stabilize this.

It is certainly possible to do that, but without any USP monograph, there will be no standardization of how this is compounded in practice. And as I mentioned before, it can decompose as rapidly as 2 hours after exposure to light.

The safety, it appears to have a very good safety profile. The safety findings, the adverse events are all mild, transient, and manageable. Effectiveness, there's very little data to support that this drug, kojic acid, has any substantial effect in the management of pigmentation disorders, and there's no evidence whatsoever on wound healing

or photodamage prevention.

In terms of historical use in compounding, kojic acid has been compounded for use in the treatment of hyperpigmentation skin disorders such as melasma in the United States and other countries for decades, often in combination with other substances. The extent of use cannot be precisely determined. Thank you very much.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Jarow.

At this time, we will take any clarifying questions from the committee members. Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. You mentioned that there were a number of preparations, cosmetic preparations available. Actually, a quick Google search shows quite a bit. Is there any sense whether there's any active kojic acid in any of those, or is there any understanding as to how people may have tried to stabilize the product in those preparations?

DR. JAROW: Yes. There was one study that

we found, and I don't have the reference up here with me, where they looked at a variety of cosmetic products for the content of the labeled ingredients of them, including kojic acid. And someone help me with the numbers. I think it was approximately half that were labeled to have kojic acid, had kojic acid present.

So it can be maintained in the product for a period of time. The stability in these cosmetic products is unknown. There was actually one product that didn't have kojic acid labeled as an ingredient that they found some kojic acid in it. So we don't really know for -- it's hard to make any firm conclusions regarding that.

In vitro studies have shown that you can stabilize kojic acid, particularly if it's an alkaline pH, and there are ways to stabilize it. The problem is there's no standard formulation for this that would be used. And if it's on the list for 503A, that would require that it be made in a fashion that is stable.

DR. DiGIOVANNA: So when you say that they

found kojic acid in it, you would mean -- you would assume that would be active kojic acid.

DR. JAROW: Yes.

DR. DiGIOVANNA: Yes.

DR. GULUR: Dr. Carome?

DR. CAROME: Did that same study address how much kojic acid it was, the amount?

DR. JAROW: So that's the problem. So they did measure it, and they could tell you the amounts. And I don't remember the amounts off the top of my head. If there's someone at the table that has that reference handy, we can supply that to you because I don't know if it was in the review. But nevertheless, it was not listed as to how much was actually put in. We don't know for certain what was put in when it was made.

DR. GULUR: Dr. Pham?

DR. PHAM: I just wanted to clarify under the animal data or non-clinical data, there were studies that suggest a lack of developmental or reproductive toxicity, but then with the melasma and pregnancy in rats, it showed that it did pass

to the fetus and possibly get excreted in milk. So I'm just trying to make the connection between the lack of developmental toxicity in one bullet point, but then the possible placental transfer in the animals.

DR. JAROW: Right. So the animal studies did not demonstrate any developmental or reproductive toxicity. However, there could be exposure to nursing infants through breast milk or fetuses through the placenta.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Yes. Just as a follow-up with the other products, too, when I was looking for the concentration of the glycolic acid in the Proactive, I see several of their products also advertised that it contains this, but I don't see any concentrations in that either.

MS. GEBBIA: Sorry. I can help. And Dr. Ganley, please step in if I get it wrong. But my understanding is that for the OTC products, it's confidential what the concentrations are. So they are required to list the ingredients but not the

concentrations. So that's why you didn't see that when you looked.

DR. GULUR: Any further questions from the committee members?

(No response.)

DR. GULUR: Thank you very much, Dr. Jarow, for your presentation.

DR. JAROW: Thank you.

DR. GULUR: We will now proceed with nominator presentations. We have one presentation on kojic acid, Mr. Tom Wynn from Fagron.

Nominator Presentation - Tom Wynn

MR. WYNN: Thank you all for allowing me to come today. My name is Tom Wynn, and I represent Fagron North America, and we're here with the nomination of kojic acid.

Kojic acid, as the FDA has stated, is a fungal metabolite, certain species of acinetobacter and penicillium. It's even produced in some fungus as well. Its depigmentation properties originate from a potent inhibition of tyrosine by chelating copper at the active site of the enzyme. So it's

showing its chelation ability right at the site of the receptor in order to cause its response.

A key factor is its skin lightening effects are not irreversible. It's a slow competitive inhibition of tyrosine. And I think this can be important because whenever we're talking about a receptor that we want to modulate, we don't want to have any kind of irreversible response to that receptor and damage it, and kojic acid does show the ability to not damage the receptor while it's producing its effect. It acts as an antioxidant and free-radical scavenger, and has been shown also to have some antibacterial activity as well.

As far as safety, what I found is in mammalian dominant lethal assay, kojic acid was proven negative, so it was not passed on from male to female. In a 14-year dermatological study in humans, kojic acid was found to have no adverse local effects and no adverse systemic effects.

In another study on 6 menopausal women, volunteers received a single dose of kojic acid in topical cream. The application of 1 percent cream

at a 500-milligram dose was applied both to the hands and face. Kojic acid did not undergo any type of enterohepatic recirculation, or circulation, and resulted in a maximum plasma level of 1.54 nanograms per mL. No adverse effects were observed in any of the participants in this study as well.

In another study, it provided that exposure to Japanese populations to kojic acid through consumption, usually through miso and soy sauce, could be as much as 103 milligrams per day. Kojic acid is regarded by the Japanese Ministry of Health and Welfare to be safe when it's added to foods, and it actually can be found in a variety of foods.

If we look at this slide here, it just kind of gives an idea of where you're going to find kojic acid and different references on how they looked at the different amounts that are in those types of foods. So it's something that you commonly ingest, a lot of times if you're taking in, especially getting into more affirmative foods because that's really how it's mainly produced.

Another study, we looked at a penetration study of human skin found that the flux rate of kojic acid at 24 hours was 0.142 to 0.65 micrograms per centimeters, or 0.698 percent of the applied dose. So not really a whole bunch was getting through I guess within 24 hours. There was no histopathological changes associated with it. And based on the changes observed in the white blood cell counts, a NOAEL of 100 milligram per kilogram a day [indiscernible] was established.

Also, in another study, we looked at the treatment of cholasma, or tan or dark discolorations, of 107 patients, where 2.5 percent kojic acid was applied twice a day for a mean period of 2 months. Only two developed skin sensitivity out of the 107, and when they reviewed the actual sensitivity they had, they did a patch test with the actual base they were using and found the sensitivity was more likely due to the base than the actual kojic acid preparation that they had made.

So with the evidence of safety, NOAEL, or

the no observed adverse effect levels, determined at which there's no biological, statistically significant increase in frequency of severity and adverse effect. It's a lot of times used in clinical trials to establish a safe starting dose.

This becomes a little bit more important when the FDA did mention a study that was done, or review, from the scientific community on consumer safety. They did look at the absorption of kojic acid, and they did determine at a 1 percent dose, that it was safe to be utilized that way.

This is kind of the NOAEL that they came up with from that particular review. The thing I find most important is if we look at the no observed adverse effect level, it's 6 milligram per kilogram body weight per day.

Now, the FDA does have a guidance out that they utilize for determining -- this was more from -- taking this dose of the no observed adverse effect from 6 milligram per kilogram per body weight per day. And you can convert that over to an actual milligram -- excuse me, milligram per

meter squared for a topical dose. In humans, they would say then to take that 6 and multiply it by 37, and you wind up within 222 milligrams of a dose that they would find to be safe based on this particular NOAEL that you could utilize in a patient.

Now, keeping that in mind, we are nominating this for a dose from 0.5 to 10 percent, so it comes down more to not really the strength or the percentage, but to how much in milligrams we're actually going to deliver based on the preparation that we have. Even if you had a 10 percent kojic acid that was prepared, you then could apply 1 gram twice a day in different spots, and then wind up within that 200 milligrams.

So I think more important here is looking at not so much that the safety was just in 1 percent, but the safety can actually be in more percentage of doses if we'd look at the actual milligrams based on this NOAEL that we're allowed do deliver. And this is just the other half of that.

Mutagenicity, kojic acid appeared to be

mutagenic in bacterial mutant assays, gene mutant assays, but these findings could not be confirmed in hamster or mouse lymphoma testing assays. Testing in sunlight had no relevant influence on the mutagenic potential, meaning that when creams were applied, that actual exposure to sunlight was not making that particular kojic acid preparation any more mutagenic.

In vivo testing showed no DNA adducts. In liver and thyroid, there was no clastogenetic findings in the liver, stomach, or colon. This suggests that kojic acid is not DNA binding. Female mice dermally exposed to 0.3 to 3 percent kojic acid for 19 weeks showed no initiation or promotion of potential for skin carcinogenesis. Kojic acid was not found to be mutagenic in in vivo gene mutation assay tests and in transgenic mice.

Stability of kojic acid. Stability is something that really was one of the main focal points of the FDA's argument, that it's difficult to maintain stability of kojic acid. There was a study that I found that looked at microemulsion

surfactants of lecithin using kojic acid in various strengths. They found an increased stability of pH 5 while you're using these types of lecithin microemulsions.

Kojic acid is subject to oxidation in the presence of air and heat, but stability can be achieved with chemical antioxidants such as sodium metabisulfite, EDTA, ascorbyl palmitate, and BHT, very similarly to what we do to help maintain the stability of some of the commercially available preparations when we're actually putting them together.

This is also a study that Fagron did on kojic acid, and they put it in two different of their particular bases. They did it in Nourivan, an antioxidant which contains some of those antioxidants that I mentioned, and they did a 4 percent concentration. They also put it in Fitalite cream, which is just a basic vanishing cream that really doesn't have any of those antioxidant properties.

They found that after 30 days, both fell

within the recommended BUD at 795 to be compliant to be stable, or listed as stable, for that beyond-use date. So we actually have a 30-day BUD, and this has been done with other companies as well doing their own studies to prove that there is stability in the bases that they have.

When we talk about stability and compounding, we're not really looking like we are for cosmetics or for something that's commercially available, but we don't need two years. Thirty days is very appropriate because we can put something together, and we want that patient to return. We want to see them again so then we can evaluate how things are going. So 30 days is well appropriate for a BUD to have in something like this.

Now, if we look a little bit at efficacy, here's a study with, again, the combination of glycolic and hydroquinone or kojic acid in the treatment of melasma. We did 39 patients, kojic acid on one side of the face, hydroquinone on the other. The patients applied the cream to each side

of the face for 3 months. And again, what they saw was that 28 percent had more dramatic reduction, and 21 percent had more dramatic improvement with hydroquinone.

So again, it was mentioned that this may not be statistically significant between the two, but it does show that at least it was being equally as effective as the hydroquinone in the actual treatment of the menasia [ph ??] [melasma].

The use of chemical peelings treatment is another study we looked at, and there were 20 patients with diffused melasma [?], were treated with a solution of 50 percent glycolic acid and 10 percent kojic. Treatments were applied, left on for 15 minutes, and then removed, and this was done biweekly for 3 to 6 months. Six patients showed complete regression and 12 showed partial. No side effects were reported. So we did actually have 50 percent of those patients actually show a complete regression of that particular hyperpigmentation disorder.

Another study, again this is another

combination of hydroquinone -- of betamethasone valerate, and it was kind of one of the bigger ones, and we looked at kojic acid by itself. I know the FDA mentioned this one as well. But the kojic acid 1 percent did show with the MASI score, a 58.72 percent. And I know they did mention that there was no documentation of how much of the regression that was there. But we were showing that there were some depigmentation and coloration based on this particular study.

I just want to throw out a little bit about some of the things that are out there that are available to be utilized for different hyperpigmentation disorders. Hydroquinone is one, and it does have a known instability due to oxidation, which would be very similar to what kojic acid has. It's a well known cause of ochronosis. Ochronosis is something that is considered rare. So the mentioned rare in the studies that I looked at.

Then I tried to determine, well, how rare is that; how do we define rare. I did find studies in

India that were looking at the prevalence of this particular disorder in that population, and they looked at probably 100 people and got about 0.9 percent, which doesn't seem very significant. But if we ramp that up and say, well, let's estimate that, there's 300 million people in the U.S. That may be 3 million people that actually could come down with this particular disorder. And we know that hydroquinone is something that does push that into effect. It's one of the actual stimuli to cause that. So something to keep in mind, even though it's a rare effect, that it could be a lot more significant based on the U.S. population.

Possible toxic to melanocytes. This is an example where it can have some irreversible effects on the actual receptors. We talked about kojic really doesn't do that. They combine and let go, and allows a receptor to not be damaged. It did cause cancer in rodent studies. And topical toxicity from hydroquinone arises from a strong oxidant that rapidly converts to melanocyte toxic

products. Dihydroxy benzoquinone and p-benzoquinone and those can actually cause destruction of the melanocytes altogether.

A couple of other things. Mequinol, I am not sure. I was having trouble finding if this one is still currently available on the market. I did see some listings for it. It's an competitive inhibitor of the melanocyte substrates. It was never really considered super effective, and pigmentation can return over time from that treatment. Then we have retinoids. Retinoids, again they can be strong irritants. They tend to have a bit more, I would believe, dermatitis, erythema, dryness, and scaling.

These are some of the references that we have. So I guess keeping in mind what we talked about, definitely kojic acid is something that does bind as a chelator to the receptor site. It is a irreversible. It is something that doesn't have as many of the possible side effects as some of the commercially available items.

To me, it's kind of thinking of you don't

always need a cannon when you're going after something of this nature. It's nice to have something that might be considered a bit milder, then maybe we could do as an additive effect to some other ingredients, maybe such as glycolic acid or some of the other things in the study, where we're going to be able to help with patients and not have to bring out something as strong as maybe some of the commercially available ones that are out there.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

Do the committee members have any clarifying questions for our presenter?

(No response.)

DR. GULUR: All right. Thank you very much. You do?

DR. HOAG: I'm just curious how prevalent or how widely used is this.

MR. WYNN: As far as --

DR. HOAG: Number of prescriptions.

MR. WYNN: No. I have not been practicing

in the pharmacy for a number of years, so offhand, I'm not sure the number of prescriptions. That may be something that's going to come up in the open discussion because I know that someone's going to be talking about that as well, and maybe can answer more to that question, to how much in their practice they see kojic acid.

I know we talked about it being commercial -- excuse me, available OTC. There are some issues with stability there. But I think it's something -- that, again, it's a tool. We need other tools that can be utilized in dermatology to treat some of these conditions, and we need options.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. So if I were to ask you to make a preparation of this for me, would you recommend -- how would you recommend it be made so that it would be stable?

MR. WYNN: Sure. If it was me, I would consider either using a product like Nourivan because I already know that there's a published

study showing it is effective for 30 days. So I would go ahead and utilize that base, or if there was another supplier who had the study for me, I would utilize that base.

If that was unavailable to me, then I would consider the antioxidants that were mentioned before. BHT is very commonly used, like 0.1 percent; sodium metabisulfite, 0.2. You can do ascorbyl palmitate, 0.5 to 1 percent. You can do vitamin E and add that in there, too, to 0.1 percent; a lot of antioxidants that you can add to maintain that stability. And again, I'm looking to go 30 days. I don't need to go for years. I just need to go for that 30 days for your patient so that we can go ahead and start the treatment process for whatever pigmentation disorder they have.

DR. GULUR: Mr. Mixon, did you have a question still?

MR. MIXON: Not a question, just a comment. In my experience, it's widely used as a component of preparations used on the skin.

DR. GULUR: Ms. Davidson?

MS. DAVIDSON: I had one question about your Durabrand, I think you called it, stability study. You referenced in the slide that the stability indicating assay was performed according to EP and USP monographs. I'm not aware that there are any monographs for kojic acid in any of the world pharmacopeias. So could you clarify how you did your --

MR. WYNN: Do you mean on the Fagron study?

MS. DAVIDSON: Yes.

MR. WYNN: Yes. What I was mentioning was that you have to fall within the 10 percent rule. So anytime that you're doing a study to make sure that it's actually effective -- just like if I would send off a potency study of something that I did in my pharmacy, I wouldn't want it to fall within the USP 795 guidelines of what something needs to be to be effective.

So they give you that 90-110, and that's really what I was referring to, that those guidelines are there to help us make sure that we

make continually effective preparations, and that's the guidelines I was looking at.

Now, the exact effectiveness, we didn't actually put into that study, something I could probably get. I'm sure it was probably better than that. Most of the time when I did my own in my own pharmacy, I was even looking more stricter. I was trying to keep things within 5 percent. I wanted 95 to 100. But we get 90.

MS. DAVIDSON: To clarify, that's not effectiveness; that is strength that you're talking about. But I was concerned about that and also the study that Dr. Jarow mentioned, that looked at the assay of potency of the cosmetic products. I've looked and looked, and I can't find a stability-indicating assay to determine the recovery of that. So I'm concerned that there may not be the ability to determine exactly how much kojic acid there is in something, number one.

The other question I had was I found, in preparation for this meeting, quite a bit of reference to kojic acid dipalmitate being a much

more stable presentation of kojic acid. And I wondered if the providers of kojic acid provide that salt of kojic acid since it seems to be relatively more stable.

MR. WYNN: Correct. No, not at this time. I did see those as well, and that's not something that currently is available from suppliers that I know of.

MS. DAVIDSON: Okay. I couldn't find that it was either. I just wanted to see if there was something I didn't know.

I have one final question. It's more a comment. Even though you might be able to formulate a stable preparation of kojic acid, I was concerned about the concomitant use of really acidic co-therapies that Dr. Jarow mentioned, and it might really decrease the efficacy of kojic acid by completely inactivating it at low pH.

MR. WYNN: Well, one thing I mentioned in that one study with the microemulsions, that they found it stable to ph 5. So it would be something to where you could consider making sure that pH is

high enough to prevent that. So these are things, again, that you can look at while you're going ahead and adding it in and making your preparation. But I did notice that in the particular creams that we put them in, we did not look at that in the Fagron studies. There was an HPLC study looking at the actual amount that came out in the end, and they didn't do that to that effect. But it could be done.

MS. DAVIDSON: And I guess that's my concern, is even though you might make a perfect compound, and somebody could come up with a formula for a perfect compound, there would have to be counseling of those patients to not use anything else that had a real acidic pH because it would inactivate the kojic acid since it is so unstable in the presence of acid. So that was just a comment more than a question.

DR. GULUR: Thank you. Yes?

MS. BORMEL: We just wanted to clarify that the kojic acid that is in the OTC products, it's in as an inactive ingredient.

DR. GANLEY: Just to clarify that further, it's an OTC drug product.

MS. BORMEL: Correct.

DR. GULUR: Yes, Dr. DiGiovanna?

DR. DiGIOVANNA: Perhaps he can clarify a little more. If you look on the Web, there's a wide variety of cosmetic preparations that are not drug products that advertise some specific concentrations of kojic acid. A study that Dr. Jarow was talking about I think was in looking at products that actually somehow managed to achieve what they said they were going to achieve. Was that the cosmetic products, or was that only the OTC drug products?

I guess what I'm getting to is part of the balance of the assessment here is how difficult or how easy is it to actually make an effective product because it seems to me that one of the real issues is the ability to actually compound an effective product, a stable product.

DR. JAROW: So those were cosmetic, not drug products, in that study. So you can look at it as

cup half full or half empty. The fact that half of them that said they had kojic acid in it had it is potentially a good sign that you can do it. Half of them didn't. But we don't -- it's not the same oversight of cosmetic products, so just because it's listed as an ingredient, we don't know that it was actually put in that specific cosmetic. Moreover, we don't know the exact amount, or at least it wasn't stated in the study. Again, there was just one product, which didn't have it listed as an ingredient, that they found it.

So again, I'm not sure how much you could take home from that other than the fact that it is -- we certainly recognize that it's possible to create a formulation of kojic acid that may be stable under certain conditions, and that's all we can say.

DR. DiGIOVANNA: But also that a number of over-the-counter producers have actually done that. They've actually -- different manufacturers have managed to accomplish this apparently without some extraordinary unusual apparatus or jumping through

hoops. I mean, it's not a rare thing for them to do.

DR. JAROW: I can't speak to the apparata, but it's certainly possible. The question is will it be done and stored -- even just the compounding pharmacy receiving the substance, how will it be stored there and what will happen to it while it's at the compounding pharmacy. Even before it goes out, there won't be any testing.

DR. GULUR: Yes, Ms. Davidson?

MS. DAVIDSON: Just one more clarification. USP recently revised its general notices to take out the 90 to 110 percent requirement, and it's now monograph-specific. So if you are shooting for a USP standard, you need to go to the individual monograph for that product, that substance, or that preparation to find out what your expected strength range is. I didn't know if that was common knowledge or not, but I did want to make that clarification.

DR. GULUR: Thank you, Ms. Davidson.

Yes, Dr. DiGiovanna?

DR. DiGIOVANNA: So another question maybe for Dr. Davidson. If there isn't a monograph, then how does a compounding pharmacist go about determining how to compound something?

MS. DAVIDSON: Mr. Wynn did allude to the USP defaults, and so you have to use professional judgment on how to put some things together. But after you do that, there are limitations on the beyond-use data, which would be the expiration date equivalent for a manufactured product that you can assign to that, which are pretty conservative. And he mentioned 30 days, which is the default for water-containing topical compounds. But it is much better to have a monograph if possible.

DR. GULUR: Yes?

MS. BORMEL: Just another clarifying comment. If kojic acid is in an over-the-counter cosmetic, it's not active. Once it becomes active, as doing something pharmacologic, it would be a drug. And so we're looking at it in this arena, and as it was nominated, which is as a drug to be placed on the 503A bulks list.

DR. GULUR: Thank you. Yes, Dr. Braunstein?

DR. BRAUNSTEIN: So it seems to me that one of the reasons -- one of the aspects of this product or this chemical that we're discussing is whether it's difficult to compound. And actually there's a separate list that talks about difficult to compound products. I mean, is this really a -- should really we be talking about whether this should be on the list, on that list?

But related to that, I have a separate question for the agency. And that is, if for example there were formulations of kojic acid that could be demonstrated with appropriate studies to be stable, would that be something that instead they might come back with to propose be put on the 503A list? I mean, I'm just trying to understand what the different rules are here regarding something like this.

MS. GEBBIA: With respect to difficult to compound, the reason this came up is because one of the criteria for the bulk drugs substance list is physical and chemical characterization, and we

consider stability to be part of that, and that's why it's come up. With respect to formulations, this is a bulk drug substance list, and so it's not really this first specific formulation. So we have to take that into consideration when we're deciding whether or not something should go on the list.

Open Public Hearing

DR. GULUR: Thank you all. At this time, thank you very much for your presentation. We will now proceed to hear the open public hearing speakers. Please introduce yourself again.

DR. DESAI: Thank you, Madam Chair. Seemal Desai, board certified dermatologist speaking on behalf of the American Board of Dermatology Association, as well as the American Society for Dermatologic Surgery Association. And thank you for allowing me to speak.

I'd like to thank Dr. Jarow for his thorough presentation on the characteristics of this product, and overall, I do agree with much of what he stated behind the science. However, I must disagree with one component of the presentation,

which I think should be the most important thing that the committee looks at on this drug, is that melasma and hyperpigmentation as a disease state is a multifactorial disease. And therefore, the studies for any chemicals or products to treat these diseases tend to not be studying the ingredient as a monotherapy.

I suspect the committee has concerns that the kojic acid studies have not been done entirely in large cohorts as a monotherapy ingredient. One of the reasons for that is because melasma as a disease state really does not respond to monotherapy drug treatment. And a lot of what we've talked about this morning with the other products, and now with kojic acid, is that these conditions really require a multifactorial approach, and really me as a provider using what I have in my therapeutic armamentarium to combine therapy for my patients.

I do find kojic acid actually to be very beneficial in my patients, but I will comment that this is not meant to be first-line treatment for

melasma. And many of you've heard this morning, we've talked about Tri-Luma, which I do not have a conflict of interest with, by the way, but I'll mention it because it's been discussed.

Tri-Luma contains hydroquinone, and hydroquinone is the gold standard as a skin lightening agent due to its inhibition of tyrosinase. The problem is that hydroquinone monotherapy can be very irritating and has a lot of side effects, and therefore, it's been combined with a topical steroid and a retinoid to make the Tri-Luma or tri combination.

The problem is that when I'm treating melasma, as I mentioned to you earlier, this is a chronic condition. It does not go away. I can get patients better, but the pigment is always lurking in the background. And therefore, they need to be on some sort of maintenance therapy.

Hydroquinone or Tri-Luma cannot be that maintenance therapy. And the main reason it cannot be that maintenance therapy is because if I have someone use it uncontrolled for weeks and weeks and

weeks and weeks, I risk that patient getting permanent disfigurement from hydroquinone pigment, which is called exogenous ochronosis. And I have had many, many patients who have had exogenous ochronosis who have used uncontrolled amounts of hydroquinone for long periods of time without being supervised.

Let me just describe to you what exogenous ochronosis is. It is a very disfiguring condition because what it does is small blue, particle-like dots develop along the face, particularly on the upper cheeks bilaterally. And once those pigment drops and ochronotic deposits are in the skin, they cannot be removed. There is no cream, there is no laser, there is no peel that's going to get rid of that ochronotic pigment.

So what I tell my patients is I'm going to give you this triple combination hydroquinone-based therapy for 6 to 8 weeks max, and at that junction, if you're not doing any better, or if you are better and I need to maintain you, that's when I'm going to incorporate something like kojic acid or

azelaic acid to keep things going because I know that even though this is a milder lightening agent that does not work as well, I know I'm not putting you at risk of a permanent side effect from your condition by treating it with the gold standard.

So in my opinion, what we really need to look at is that though this may not be a very prevalent drug that every dermatologist uses, those of us who specialize in pigmentary disorders, like myself and many others throughout the U.S. and abroad, really find this to be a very safe, effective, additional option to keep people going on therapy while we're trying to figure out what else I can do to make their pigment better. And that may be the glycolic acid chemical peels we talked about this morning. That may be the TCA peels. That may be using azelaic acid. That may be doing laser.

But the point is that we have to do something because if you stop the gold standard hydroquinone, which you should to avoid ochronosis, what are you going to do to keep these people from

getting the pigment coming back with a vengeance?

Unfortunately, what happens in many societies and in many cultures is these patients who have this recurrent hyperpigmentation end up having a lot of psychosocial impact from this disease. I've had two patients who have been suicidal because of their melasma coming back. One of those patients actually also had post-partum depression and had recurrent melasma after the third pregnancy.

So this is a serious condition, and though Dr. Jarow mentioned that it's not serious medically, and I do understand his implication of that, it is serious to my patients who are suffering from the disease, and it's important that I have these other options to treat them. So I'm happy to entertain any questions regarding that specifically.

DR. GULUR: Questions for our presenter? Yes, Dr. Wall?

DR. WALL: I actually have three questions. One, I guess one you answered as sort of where you

use it in therapy. What would happen if that was not an option for you anymore? And number two, have you seen any types of side effects that we have not reflected upon today?

DR. DESAI: So in terms of side effects, I've actually found this to be pretty non-irritating. Now, I will say in full fairness, anytime I prescribe a topical, especially a compounded topical, which in my practice usually contains a retinal or a retinoid like the Tri-Luma combo, or when I compound kojic acid with my retinal and steroid, I do counsel the patients that irritations, redness, and dryness is a very common side effect. And I have to disclose that, and I let everyone know that in advance. Overall, this is very well tolerated.

I will also mention that I make sure the patient is only using this at night. And to Ms. Davidson's comment, I think it's important to mention that these patients are also careful about what they're using concomitantly at the same time, especially with cosmeceuticals and other products.

So usually when I'm prescribing something like this for maintenance, it's usually as a compound, and that's all they're using, except for sunscreen. It's at bedtime to avoid UV light and stability, and then they use a sunscreen throughout the day, and then I usually follow the patient up again in 6 weeks, and then move on.

To answer your second question, what if I didn't have this, well, in full fairness, if I didn't have it, there are other things I could use, especially the chemical peel treatments, and then third-line, the laser treatments. The problem with those is access for many patients to be able to afford those therapies in my practice, and how they're going to be able to come in oftentimes to do those treatments.

Physical modality therapy for pigmentary disorders, which includes peels and lasers are great things to do, and I do them all the time. But each and every patient can't afford coming in and spending $125 every 2 weeks for a chemical peel treatment that they're going to have to do five

times, or come in for a several-hundred dollar to several-thousand dollar laser procedure.

So yes, there are other things I could do, absolutely. However, I think it would limit access to care for many of the patients, especially my underserved patients, which we treat a lot in the inner city part of Dallas who have skin of color and don't have insurance, where I can still get a compound for a decent price.

Yes, Mr. Mixon?

MR. MIXON: As a compounding pharmacist, we know that hydroquinone is unstable. We know that kojic acid is unstable. We know how to prepare these drugs so they are relatively stable. You know, it's not up to us to decide what the patient needs; that's his job. Our job is to make it and make it correctly, and I think we can do that. And I don't think that this committee should take this drug out of his box of tools that he needs to take care of his patients.

DR. GULUR: Ms. Davidson?

MS. DAVIDSON: Dr. Desai, have you used the

kojic acid containing OTC products, realizing they're not monotherapy? And we don't know what the concentration is, but what's your impression of those?

DR. DESAI: So I was following that discussion intently about the OTC formulations, and there is actually one cosmeceutical formulation that I have tried. There are several different companies that make it. There is one company in particular -- I won't mention the name just for conflict-of-interest reasons -- and I have tried that product.

The problem with that product is the cost. It is, the cosmeceutical that I can dispense in office and the ones that I trust because they have at least some science behind them, they're very, very, very expensive, and many patients can't afford those cosmeceutical products. In fact, the one that I do dispense in my office if a patient really wants that in lieu of a compound, a one-month supply is about $96.

So these aren't inexpensive things we're

recommending. Granted, patients who have pigmentary disorders, a lot of them come to see me are so frustrated, they will spend the money to get better. But if I can offer them something where I know I'm not having them spend as much money that has a good effect, and I know that I can do that in a controlled setting with continuous follow-ups, I'd be doing a disservice to my patient, just forcing them to use a more expensive option.

DR. GULUR: Go ahead.

MS. DAVIDSON: And one final question.

DR. DESAI: Sure.

MS. DAVIDSON: Could you characterize maybe a percentage of your patients that you use this in?

DR. DESAI: And that's a very valid point, is that this, again, is not my first line by any means. But the kojic acid discussion about maintenance therapy I bring up with each and every one of my hyperpigmentation patients, because when someone comes to see me on their first visit, I have a detailed discussion about the journey we're going to take together in trying to get their

condition better.

What I set from the ground work is that this is not a one time, come in and see me one day, and you're good kind of thing. This needs to be a relationship that happens long term to prevent you from relapsing and recurring. I always mention when I write that triple combination therapy on visit one that you are not getting any refills.

This is meant to be used for no more than 8 weeks. And if you don't want to come back and see me, that is fine. But if I would have you continue using this and not switch you to a second-line topical like kojic acid, or azelaic, or peels, then I'm doing you a disservice and only going to create another problem for you down the road.

DR. GULUR: I'm sorry. I'll clarify again. I didn't understand. How many patients do you use this on?

DR. DESAI: I couldn't even give you an exact number, but I can tell you that, for example, on a daily clinic, I see usually 10 to 12

hyperpigmentation patients per day. At least half of those are on a second-line topical agent, including kojic acid. If you wanted me to quantify that, maybe 10 to 15 patients a week are on some formulation that contains this and/or azelaic.

DR. GULUR: And is kojic acid your primary treatment when you move to the second line? Is it what you're depending on? What other agents are in the compounded mix you dispense?

DR. DESAI: I'm glad you asked that. I actually still compound it with a retinoid and a topical steroid. And what's really easy for me to do is explain to the patient, your Tri-Luma product contains three ingredients, one of which is hydroquinone. At the end of 6 weeks, we're just going to drop that hydroquinone ingredient and add this other ingredient instead.

So we really just incorporate the kojic acid and/or the azelaic acid in there. And the way I usually choose that oftentimes depends on the patient's pregnancy status and nursing status. And I'll clarify that, because women who are pregnant,

I can use azelaic acid, which is a pregnancy category B. I wouldn't use this ingredient, for example.

Also, azelaic acid has become harder and much more expensive to get because the concentration that we usually have studied in melasma is 20 percent, but the brand formulation we have here is 15 percent that's actually being marketed. So it's a matter of figuring out which one the patient can either afford and/or have access to with their insurance. I use between azelaic and kojic both.

DR. GULUR: And what is the percentage of kojic acid?

DR. DESAI: I like 3 percent.

DR. GULUR: You use 3 percent.

DR. DESAI: I use 3 percent.

DR. GULUR: And you're very convinced that it's stable in the formulation that you are -- after hearing the concerns here?

DR. DESAI: I think the instability concerns are valid. I have no reason to refute that. I've

seen the data as well. In fact, as I mentioned earlier, I'm on the International Board of the Pigmentary Disorder Society, and we've brought this up at a global consensus conference that we had in Delhi earlier this year.

I think instability for all of our hyperpigmentation products is an issue, and that's one of the reasons that we don't have a good product to treat these conditions because, one, of their pharmacodynamics and, two, we don't have large randomized controlled trials. In my experience, I have not had any issues with this ingredient, and I've found it to be very well tolerated.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. Just wanted to make one comment. And that is that in addition to the issue of cost of cosmeceuticals or cosmetics, there's also the issue of content over time, in that in various products, the formulations are often proprietary and can be changed at any time without the knowledge of the

user, and certainly without the knowledge of the physician. And if you are actually using a product that you are observing, it's a bit easier for you to determine the lack of efficacy than if a patient is purchasing something and the formulation's been changed and it no longer has the activity. It's very difficult to determine that there's actually been a change.

So I think it's useful for the committee members to understand that in the real-world practice, merely the fact that a cosmeceutical with the active agent is available is not the same thing as having it available to be compounded and then used under the observation of a physician.

DR. DESAI: Ma'am, may I make a comment?

DR. GULUR: Before you do that, just for the committee members' benefit, all discussion should be maintained for later. We would request that you only direct clarifying questions to the presenters at this time.

DR. DESAI: Madam Chair, may I comment to that just for the committee's sake?

DR. GULUR: Yes.

DR. DESAI: Thank you for bringing that up. And that is the exact reason, which is why I don't dispense a lot of cosmeceuticals in my practice, because I honestly don't know what's in them. The issue with why the compounding of pigmentary disorders medications is so important and for me to have control is because in many countries, and even here in Dallas, in D.C., in New York, you can go into an ethnic food store, or into a retail store in certain parts of the city, and you can buy products containing 8-10 percent hydroquinone, containing high-potency topical steroids in OTC formulations.

I have many of my patients -- Dallas has a very large Indian population. Many of these patients when they go back to India or to the subcontinent can actually buy clobetasol and 8 percent hydroquinone combinations OTC. Then they come back here using these products, thinking they're getting better, and then I see the side effects not knowing what they've been using.

So it's really important to be able to control what we're using as best as possible. So I think that's a really important point for the committee to know.

Committee Discussion and Vote

DR. GULUR: Thank you very much. We will end the open public hearing portion of this meeting, and we'll no longer take comments from the audience.

We will now begin the panel discussion of kojic acid. Dr. Pham?

DR. PHAM: I just wanted to comment on the known instability of hydroquinone because that keeps getting brought up as a comparator. But that said, if that's a component of the FDA-approved product, then that means it's actually going through the rigorous testing of the approved products, which also will speak to why there may be a difference in price, because you are taking this product through the NDA, through the testing, going through the current manufacturing practices to produce the product.

So to say, well, it's just as potentially unstable, that's fine, but then this product should also go through the same rigorous testing to validate, the same stability in that combination. There are a lot of other combination products that go through the NDA approval process, and I feel like if this is something that shows significant population need, it should also go through that testing.

There are still questions about its stability. It would then get the appropriate labeling to warn also concomitant topicals in that areas, things that may deactivate the product. I feel like there's a lot of safety that comes through taking this through the NDA process. And I still have a lingering question about the potential with the placental transfer regardless of whether there is documented developmental toxicity or not. Again, you're not going to get that information unless it goes through more rigorous studies.

So I feel like we need to think about incentivizing the drug approval process for this

potential --

DR. GULUR: Thank you. Any other comments?

(No response.)

DR. GULUR: If not, we will move forward now. We will end our discussion and start the vote. The question put forth is, FDA is proposing that kojic acid not be included on the 503A bulk list. Should kojic acid be placed on the list?

If you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP, or NF monograph, or a component of an FDA-approved drug.

If there 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.

(Vote taken.)

DR. HONG: Question 3, we have 3 yeses, 4 nos, and 1 abstain.

DR. GULUR: All right. We will start with the comments on the votes. Dr. Vaida?

DR. VAIDA: Allen Vaida. I voted no. I'm not convinced of the effectiveness, and I also am not convinced that the amount in the product is actually what may be there in a week or so because of the stability.

DR. PHAM: Katherine Pham. I voted no for similar reasons regarding its effectiveness and still some concerns about the reactivity of the active ingredient as well as some lingering questions about toxicity.

DR. WALL: Donna Wall. I voted yes because I think that there is a place. Granted it's further down the chain of where you need to use it in your therapy, but I think it's an option that is needed and appears to be watched by the dermatology community.

DR. CAROME: Mike Carome. I voted no because of the concerns raised by the FDA about stability of the product and the efficacy data lacking.

DR. HOAG: Steve Hoag. I abstained because I agreed with everything that was said by everyone. One of the problems is the stability of these compounds. I know how complicated formulations are, and so I just really worry about having the correct amount of drug. And then also, I can see the point of view of this as a treatment. Obviously, it must have some efficacy or people wouldn't be using it. I don't know if that's the scientific justification. So I stayed in the middle.

DR. DiGIOVANNA: John DiGiovanna. I voted yes. I think the FDA's position was that this assessment was a balance. There are no real safety issues. It appears to be efficacious for individual patients. As I think the discussion has held before, for most of these compounding issues, they are of greatest value for the unusual patient,

and it's not likely that we are going to see them go through the NDA process, the IND process. And I think it's useful for us to understand what we are trying to add to patient care.

The issue of stability is, of course, of concern. However, it seems that a number of over-the-counter companies and a number of cosmetic companies have successfully been able to do this, and it seems to not be a barrier under certain circumstances. So I think in my balance, this was a product that should be available for its limited use.

MS. DAVIDSON: Gigi Davidson. I, in preparation for this meeting, came prepared to vote no on this because of the quality attributes for this bulk drug substance when prepared as the compound. But after hearing Dr. Desai's presentation, Dr. DiGiovanna's contributions to that, I now believe that it is a therapeutic tool that dermatologists do need, so I voted yes.

I think the stability issues, although significant, can be addressed. Mr. Wynn convinced

me that there are chemical ways to destabilize this preparation, and then again, Dr. Desai alluded to the fact that patients are counseled to not use concomitant therapies that might contribute to the instability of this.

I also feel that in the compounding arena, this substance will be restricted more carefully to supervision under a physician to observe for adverse effects or lack of efficacy, which is my bigger concern. There isn't a safety signal here in my mind, but lack of efficacy is. And as opposed to forcing people to use cosmeceuticals because we don't put this drug on the list, I think it pulls it back into the triad relationship so that it can be monitored, and the adverse events from hydroquinone are very, very serious and very concerning.

Adjournment

DR. GULUR: I voted no on this and agreed with the FDA. And the concerns were primarily on the stability of this formulation. I respect completely my dermatologist colleagues who feel

like this is necessary and useful in their practice, but at the same time did not hear anything convincing as far as they can be sure that they are getting a stable product, that the patient is receiving a stable product. And instructions on how best to use it, et cetera, can be provided. But nonetheless, again, we're not really certain, in this circumstance, what this patient is receiving. And just from that aspect, it seemed a little bit more difficult to vote otherwise. Thank you.

We will now break for lunch. We will reconvene again in this room in one hour from now at 1 p.m., five minutes short of an hour, but at 1 p.m. nonetheless. Thank you.

(Whereupon, at 12:05 p.m., the morning session was adjourned.)

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

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director of Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

John J. DiGiovanna, MD

Senior Research Physician

DNA Repair Section

Dermatology Branch

Center for Cancer Research

National Cancer Institute

Bethesda, Maryland

Padma Gulur, MD

(Acting Chairperson)

Vice Chair, Operations and Performance

Duke University School of Medicine

Department of Anesthesiology

Durham, North Carolina

Stephen W. Hoag, PhD

Professor

Department of Pharmaceutical Science

University of Maryland, Baltimore

Baltimore, Maryland

Katherine Pham, PharmD, BCPS

Senior Officer

Drug Safety Project

The Pew Charitable Trusts

Washington, District of Columbia

Allen J. Vaida, BSc, PharmD, FASHP

Executive Vice President

Institute for Safe Medication Practices

Horsham, Pennsylvania

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

William Mixon, RPh, MS, FIACP

(Industry Representative)

Former Owner

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.)