FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Thursday, June 23, 2016

8:29 a.m. to 11:17 a.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)

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(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

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PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Donna **Wall, PharmD**

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING DRUGS ADVISORY COMMITTEE

INDUSTRY REPRESENTATIVE 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

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

(8:29 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning. 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 contacts for this open session meeting, Mr. Chris Kelly and Ms. Lindsay Meyer. If you're present, please stand so everybody can see you. Over there. Thank you.

Good morning. My name is Jurgen Venitz. I'm the chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee into order.

We will now ask those at the table, including FDA staff and committee members, to introduce themselves starting with the FDA to my left and moving along to the right side ending with one of the industry representatives,

Dr. Ned Braunstein.

So let's start to my left, please.

DR. BRAVE: I'm Michael Brave, a medical officer in the Office of Oncology Drug Products, in the Hematology and Oncology Drug Products.

MS. GEBBIA: Emily Gebbia, CDER, Compliance.

DR. GANLEY: Charlie Ganley, from the Office of New Drugs.

MR. FLAHIVE: Jim Flahive, CDER, Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. DOHM: Julie Dohm, agency lead on compounding.

MS. BORMEL: Gail Bormel, Center for Drugs, Office of Unapproved Drugs and Labeling Compliance.

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

DR. GULUR: Padma Gulur. I'm a professor of anesthesiology at the University of California, Irvine.

DR. HONG: Cindy Hong. I'm DFO for Pharmacy Compounding Advisory Committee.

DR. VENITZ: Jurgen Venitz, clinical

pharmacologist and professor at the VC School of Pharmacy.

MS. DAVIDSON: Gigi Davidson. I represent the United States Pharmacopeia.

MR. HUMPHREY: William Humphrey, director of pharmacy, St. Jude Children's Research Hospital.

DR. HOAG: Steve Hoag, professor of pharmaceutical sciences at the University of Maryland, Baltimore.

MS. JUNGMAN: Elizabeth Jungman, director of public health programs at the Pew Charitable Trusts.

DR. PHAM: Katherine Pham, NICU clinical pharmacy specialist at Children's National Medical Center.

DR. VAIDA: Allen Vaida. I'm a pharmacist at the Institute for Safe Medication Practices.

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

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

MR. MIXON: My name is Bill Mixon from Hickory, North Carolina. I'm the non-voting industry member.

DR. BRAUNSTEIN: Ned Braunstein from Regeneron Pharmaceuticals. I'm the non-voting pharmaceutical and biotech industry rep.

DR. VENITZ: Thank you, everyone. Let me then read for the official record.

For topics such as those being discussed at today's meeting, 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 be allowed to speak into the record only 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 only. We are aware that the 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 lunch breaks or other breaks.

Today, we will cover six bulk drug substances nominated for inclusion on the list of bulk drug substances that may be use to compound drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act: chrysin, cesium chloride, sodium dichloroacetate, pyruvic acid, tea tree oil, and 2,3-DMPS.

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

This afternoon, we will also hear presentations from FDA on expanded access to investigational new drugs and ask clarifying questions.

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 the federal ethics

and conflict of interest laws covered by but not limited to those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest when the interest of the 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 the purposes of 18 U.S.C. 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 the morning, the committee will discuss six bulk drug substances nominated for inclusion under Section 503A bulk drug substances list.

FDA will discuss the following nominated bulk drug substances: cesium chloride, chrysin, sodium dichloroacetate, pyruvic acid, tea tree oil, and 2,3-dimercapto-1-propanesulfonic acid, DMPS.

The nominators of these substances will be invited to make a short presentation supporting the nomination. In addition, during the afternoon, the committee will receive updates on certain issues to follow up on discussions from previous meetings including the option for obtaining access to

investigational new drugs under expanded access.

This is a particular matters meeting during which specific matters related to the six 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 Board of Pharmacy and that Ms. Gigi Davidson is a representative member from 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 the financial or other stakes in the particular matters before the advisory committee.

With respect to the FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein and Mr. William Mixon are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry.

Their role at this meeting is to represent industry in general and not any particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals, 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 need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the bulk drug substances at issue. Thank you.

DR. VENITZ: Thank you.

Dr. Carome, would you please make a disclosure statement for the record?

DR. CAROME: Mike Carome. I am the director of Health Research Group of Public Citizen and I would like to disclose that in 1999, Public Citizen submitted comments to an FDA docket and presented testimony at an FDA advisory committee regarding products nominated for inclusion on the 503A bulk drug substances list.

As part of the comments, Public Citizen urged the FDA not to include 2,3-dimercapto-1-propanesulfonic acid or DMPS and also characterized DMPS as an example of the abuse of pharmacy compounding.

In today's session, the committee will consider six bulk drug substances nominated for inclusion under Section 503A bulk drug substances list as they relate to the issue of whether they are appropriate for inclusion on the list of bulk drug substances that may be compounded in accordance with 503A of the FDCA.

These discussions will include the bulk drug substance DMPS. I will be participating following in the deliberations of this session of the meeting and will vote on all but the one question posed to the committee regarding DMPS.

I'd like to note for the record, as I've noted before, that Public Citizen disagrees with the FDA's policy on so-called non-financial conflict of interest both in terms of its concept and implementation. Thank you.

DR. VENITZ: Thank you, Dr. Carome.

That will be the start of our presentations. Our first presentation will be from Dr. Julie Dohm at FDA. But before she gets started, I would like to remind to public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the committee.

Dr. Dohm, please?

FDA Introductory Remarks – Julie Dohm

DR. DOHM: Good morning. I would like to welcome you to the fifth meeting of the Pharmacy Compounding Advisory Committee. Again, I am Julie Dohm, senior science advisor for compounding at CDER and the agency lead on compounding issues.

As you may be aware, after 25 years of dedicated service at FDA and 41 years in government, Jane Axelrad, associate director for policy at FDA CDER, retired from federal service on April 29th.

Jane was a driving force behind many high profile activities, including the many legislative,

policy, surveillance, and high profile activities related to drug compounding oversight.

As the audience well knows, she set the stage for the continued worked that must be done on the compounding program, including that for the advisory committee. It goes without saying that Jane is and will continue to be missed.

I look forward to continuing this important work with all of you. I feel fortunate to have been given the opportunity to become an integral part of the compounding program.

Already, I've had the pleasure of working on fascinating and complex issues at the intersection of law, science, and policy, and I feel that my background has prepared me for this work.

I have bachelor's degrees in biochemistry and chemistry from the University of Chicago and a PhD in biology from Johns Hopkins University where I studied the effect of a drug on the interactions between a transcription factor and its cognate DNA binding site.

After graduate school, I became a

post-doctoral fellow at Northwestern University, researching the role of DNA mechanics in transcription regulation.

During my post-doc, I decided that I wanted to go law school. I earned my J.D. from the University of Pennsylvania Law School, and then I clerked for federal judges in the U.S. Court of Appeals for the federal circuit and the U.S. District Court for the District of Maryland.

Following my clerkships, I joined FDA's Office of Chief Counsel as a civil litigator, representing FDA with the Department of Justice in enforcement, defensive, and third-party litigations, both at the trial and appellate levels. I also served a detail as drugs counselor in FDA's Office of Chief Counsel, advising CDER on legal issues relating to generics and biosimilars.

Enough about me and turning back to the meeting today, we will discuss the six bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding by entities seeking to qualify for the

exemptions under Section 503A.

As others have mentioned, those are going to be chrysin, cesium chloride, sodium dichloroacetate, pyruvic acid, tea tree oil, and DMPS.

At today's meeting, we are trying a slightly different approach in the presentation of information. Previously, we had scheduled a few bulk drug substances to be addressed at each open public hearing.

Now, we have scheduled time after each bulk drug substance presentation for the nominators to speak and then we will hold an open public hearing on that drug substance before going on to consider the next substance.

This allows the committee to focus on one bulk drug substance at a time just prior to the vote on that substance. In addition, during the afternoon, we will review FDA's expanded access investigational new drug program.

Our intent is to provide you with more of the nuts and bolts of that program than we have

during prior Pharmacy Compounding Advisory Committee meetings.

Dr. Jarow, senior medical advisor for CDER, will be giving that presentation, and he will be available to answer questions after he completes it.

I would also like to provide you with an update on policy documents issued by the agency since the committee last met in March. In April, FDA issued three draft guidance documents that describe FDA's proposed policies concerning, one, the prescription requirement in Section 503A, two, how the agency intends to apply the prescription requirement in Section 503A to compounding in a hospital or health system pharmacy, and, three, the definition of the term facility in Section 503B of the Act.

Each draft guidance document is available for public comment for 90 days. The comment periods for each of those draft guidances will close on July 11th.

The first draft guidance is entitled Draft

Guidance Prescription Requirement under Section 503 of the FDCA. It describes FDA's proposed policies concerning certain prescription requirements for compounding human drug products for identified individual patients under Section 503A.

It addresses compounding after the receipt of a prescription for an identified individual patient, what is called anticipatory compounding, and compounding for office use, also known as office stock.

The draft guidance states, among other things, that a compounder can fill a prescription for compounded drugs under Section 503A only pursuant to a patient-specific prescription.

Hospitals, clinics, and healthcare practitioners can obtain non-patient-specific compounded drug products or office stock from compounders registered as outsourcing facilities under Section 503B.

The second guidance is entitled Draft Guidance Hospital and Health System Compounding Under the FD&C Act. Pharmacies located within a

hospital or standalone pharmacies that are part of a health system frequently provide compounded drug products for administration within the hospital or health system.

This draft guidance describes FDA's proposed policies regarding the application of Section 503A to drugs compounded in state-licensed hospital or health system pharmacies for use within that hospital or health system.

Specifically, the draft guidance states that drug products compounded by a licensed pharmacist or licensed physician that are not compounded in accordance with all of the provisions of Section 503A may be subject to regulatory action for violations of the new drug approval, adequate directions for use, and current good manufacturing practice requirements of the Act.

However, FDA does not intend to take action if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription or order provided that three things happen.

First, the drug products are distributed only to healthcare facilities that are owned and controlled by the same entity, that owns and controls the hospital pharmacy, and that are located within a one-mile radius of the compounding pharmacy;

Two, the drug products are only administered within the healthcare facilities to patients within the healthcare facilities pursuant to a patient-specific prescription or order.

Three, the drug products are compounded in accordance with all other provisions of Section 503A and any other applicable requirements of the FD&C Act and the FDA regulations. For example, the drug products are not made under unsanitary conditions or being misbranded.

The third draft guidance is entitled Draft Guidance Facility Definition Under Section 503B of the FD&CA. Section 503B defines an outsourcing facility, in part, as a facility at one geographic location or address.

This draft guidance seeks to answer

questions received from outsourcing facilities and other stakeholders about the meaning of the term facility, such as whether multiple suites used for compounding human drugs at a single street address constitute one or more multiple facilities, or whether a single location where human drugs are compounded can be subdivided into separate operations that compound under different standards.

In the draft guidance, FDA has proposed to interpret facility at one geographic location or street address to mean a business or other entity under one management, direct or indirect, engaged in human drug compounding at a geographic location or street address.

The agency considers all activities, equipment, and materials part of such facility if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings located in close proximity to one another.

As noted above, all drug products compounded

in an outsourcing facility are regulated under Section 503B and subject to CGMP requirements. These conditions cannot be avoided by segregating or subdividing compounding within an outsourcing facility.

Last, on June 9th, the agency issued two final guidances, one on the interim policy in compounding using bulk drug substances under Section 503A and the other on the interim policy in compounding using bulk drug substances under Section 503B.

These final guidances set forth the agency's interim regulatory policy concerning compounding using bulk drug substances under Sections 503A and 503B respectively while FDA is developing the lists of bulk drug substances that can be used in compounding under each of those sections.

With respect to the bulk drug substances nominated for use in compounding under Section 503A, until a substance has been evaluated and is identified in a final rule as being included or not included on the 503A bulks list, FDA does

not intend to take action against a state-licensed pharmacy, federal facility, or licensed physician compounding a drug product using a bulk drug substance that is not a component of an FDA-approved drug product and is not the subject of an applicable USP or NF monograph, provided that the following conditions are met.

First, the bulk drug substance appears in 503A, Category 1, on FDA's website. A bulk drug substance in Category 1 may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for FDA to evaluate it, and has not been identified by FDA as a substance that presents a significant safety risk in compounding prior to the publication of the final rule.

The substances that FDA has identified to present a significant safety risk and that are not eligible for this interim policy are included in Category 2 listed on the same webpage.

In addition, substances that were nominated with insufficient supporting information for FDA to

evaluate them appear on the webpage in Category 3.

If such substances are renominated with adequate supporting information for FDA to evaluate them, FDA will consider which category these substances should be placed after it completes its evaluations of the substances that currently appear in Category 1.

Renominated and newly nominated substances are not eligible for the policy until they've been placed affirmatively in Category 1.

The second condition is that the original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under Section 510, including foreign establishments that are registered under Section 510(i) of the Act.

The third condition is that the bulk drug substance is accompanied by a valid certificate of analysis. And fourth, the drug product compounded using the bulk drug substance is compounded in compliance with all of the other conditions of Section 503A.

With respect to the 503b bulks list, until a substance has been evaluated and a final Federal Register notice is published identifying the substance as being included or not included on the 503B bulks list, FDA does not intend to take action against an outsourcing facility for compounding a drug using a bulk drug substance that does not appear on the 503B bulks list and that is not used to compound a drug that appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, provided that the following conditions are met.

First, the bulk drug substance appears on 503B, Category 1 on FDA's website. Like 503A, a Category 1 substance may be eligible for inclusion on the 503B bulks list, was nominated for inclusion on that list with adequate supporting information for FDA to evaluate it, and has not been identified by FDA as a substance that appears to present a significant safety risk in compounding prior to the publication of a final notice in the final Federal Register.

FDA has also posted Categories 2 and 3 on its website of bulk drug substances that are not eligible for this policy because they appear to present significant safety risks or were not nominated with adequate supporting information for FDA to evaluate them.

If substances currently in Category 3 are renominated with adequate supporting information for FDA to evaluate them, FDA will consider which category these substances should be placed in after it completes its evaluation of the substances that currently appear in Category 1.

Renominated and newly nominated substances are not eligible for the policy until they have been placed in Category 1.

The second condition, like 503A, is that the original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under Section 510 and, again, including foreign establishments that are registered under 510I.

Third condition is that the bulk drug

substance is, again, accompanied by a valid certificate of analysis.

The fourth condition is that if the bulk drug substance is the subject of an applicable USP or NF monograph, the bulk drug substance complies with that monograph.

Fifth, the drug product compounded using the bulk drug substance is compounded in compliance with all the provisions of Section 503B.

In addition, FDA does not intend to take action against an outsourcing facility for compounding of a drug product using a bulk drug substance that is not on the 503B bulks list if the drug compounded from the bulk drug substance, one, appeared on the FDA's shortage list within 60 days of distributions and dispensing and, two, was to fill an order that the outsourcing facility received for the drug while it was on FDA's drug shortage list.

These guidances appear on the FDA's compounding website under the section titled Regulatory Policy.

I would like to thank you for your participation on the Pharmacy Compounding Advisory Committee, and I look forward to a productive meeting and to our continued work with you.

Thank you.

DR. VENITZ: Thank you, Dr. Dohm. Speaking on behalf of the committee, let me welcome you and we're all looking forward to working with you as our agency lead.

Let me also take the personal privilege of thanking your predecessor, Dr. Axelrad, for her tireless work for getting us all started, and I hope she enjoys her retirement.

Now, we're proceeding to our first order of business, which is the review of chrysin. The FDA presenter is Dr. Michael Brave. He is a medical officer in the Division of Oncology Products and will introduce FDA's review.

Presentation - Michael Brave

DR. BRAVE: Good morning. I'm Dr. Brave from the Office of Hematology and Oncology Products, and I reviewed the nomination for

chrysin. I'd like to thank my colleagues listed here for also reviewing this nomination.

Chrysin has been nominated for compounding as an aromatase inhibitor, which prevents the conversion of testosterone to estrogen for the treatment of quote, "high estrogen and low testosterone."

The proposed route of administration is topical. The references provided in the nomination contain only nonclinical information. Chrysin is currently available as a dietary ingredient in dietary supplements.

Chrysin is a flavone found in plants such as the blue passion flower and in propolis or bee glue. Epidemiologic studies suggest that chrysin may have anticancer and chemopreventive properties.

Chemically, chrysin is a small molecule that can be easily characterized, and it is stable under ordinary storage conditions for topical dosage forms.

Chrysin reportedly has activity against cancer cell lines in vitro. In addition, xenograft

studies suggest several potential mechanisms of action, including carcinogen biotransformation, free radical scavenging, and modulation of cellular pathways linked to inflammation, proliferation, differentiation, and metastases.

Systemic exposure to ingested chrysin in humans is low due to poor oral bioavailability, and rapid metabolism, and elimination.

In healthy male volunteers, after a single oral dose of 400 milligrams, mean plasma concentration of chrysin remained less than 0.1 millimolar due to pre-systemic intestinal, and hepatic glucuronidation, and sulfation, and efflux of metabolites back into the intestine for hydrolysis, and fecal elimination.

It is therefore not surprising that in a study published by Gambelunghe and colleagues, oral chrysin had no observable effect on testosterone metabolism in healthy male volunteers.

In summary, we considered the following factors in evaluating the effectiveness for chrysin for the proposed indication. Nonclinical data

suggests that chrysin has biological effects, which could support a rationale for its development as a chemopreventive agent or as an adjunct to chemotherapy.

Chrysin is sold and is readily available as a nutritional supplement, and we found no published reports of chrysin toxicity. Thus, chrysin may be relatively safe at usual dietary doses.

Nonetheless, no clinical trial has, to our knowledge, ever been conducted with an objective to demonstrate clinical anticancer activity. We are also unaware of any preclinical or clinical data regarding chrysin administered topically. Finally, FDA-approved testosterone replacement products are available.

Clinical trials with chrysin have not, to our knowledge, been done. However, we found no reports of toxicity attributable to chrysin in the FAERS database or in published literature.

We found insufficient information to determine how long chrysin has been used in pharmacy compounding. Currently, oral and topical

compounded formulations of chrysin are advertised on the internet.

In summary, chrysin is chemically well-characterized and expected to be stable in topical formulations. Although nonclinical data suggests that chrysin has biological effects, which could support a rationale for its development as a chemopreventive agent or as an adjunct to chemotherapy, no clinical trial has been conducted, to our knowledge, with an objective to demonstrate clinical anticancer activity.

We also found no clinical studies that demonstrate the efficacy of topical or oral chrysin as an aromatase inhibitor for treatment of quote, "low testosterone or high estrogen."

Several FDA-approved testosterone replacement formulations are already marketed, as are several aromatase inhibitors for the treatment of breast cancer in postmenopausal women.

Clinical safety information is scant and is mostly derived from the use of orally ingested chrysin as a nutritional supplement. No

information was found to assess the safety of topically applied chrysin.

There is insufficient information to evaluate the historical use of chrysin in pharmacy compounding. Chrysin does appear to be compounded currently and is promoted for use primarily with regard to bodybuilding and men's health.

Based on a balancing of the four evaluation criteria articulated in the Federal Register, we find that chrysin is not a suitable substance for the bulk drug substance list under Section 503A of the Food, Drug and Cosmetic Act. Therefore, we recommend that it not be included on the list.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Brave.

Any clarifying questions by any of the committee members?

Go ahead, Dr. DiGiovanna.

DR. DiGIOVANNA: Yes. Dr. DiGiovanna. You have in the materials that chrysin is sold as cosmetics. Is it widely sold? And if it's not on the bulk drug substances list, will it still be

available under those ways that it's sold now?

MS. BORMEL: This is Gail Bormel. I'll answer that. We're only addressing the chrysin nomination for the 503A bulks list. It's used as a drug for that. So if it's sold in other forms, for cosmetics, et cetera, this would not affect that.

DR. VENITZ: You mentioned it has insufficient safety information. What about potential expected toxicity based on the structure and the suspected biologic activities? Are there any theoretical risks since we --

DR. BRAVE: I don't know.

DR. VENITZ: I'm sorry. You said --

DR. BRAVE: I don't know.

DR. VENITZ: You don't know. Okay.

Any other questions?

(No response).

DR. VENITZ: Thank you, Dr. Brave.

Then we have our nominator's presentation. The nominator for chrysin is Mr. Wynn from Fagron.

Presentation - Tom Wynn

MR. WYNN: Thank you very much for having me

today. My name is Tom Wynn, and I'm from Fagron. We really appreciate you giving this chance to speak about our nomination for chrysin.

So chrysin, as was mentioned, is a naturally-occurring bioflavonoid. It is found in passion flower, Indian trumpet flower, honeycomb, chamomile, oyster mushrooms, as well as in tomato skin, fruit skin, and other foods as well. So we do ingest quite a bit of chrysin through our normal diets probably every day.

Bioflavonoids, like chrysin in the plant, their purpose, they would act as chemical messengers. They're necessary in the production of pigmentations involved in -- excuse me -- UV filtration and influence symbiotic relationships and nitrogen fixation.

They also have been found to have bioflavonoids, such as chrysin -- they have antibacterial properties as well.

So the FDA has stated in their evaluation of chrysin that it is easily characterized, relatively stable, and it's a small molecule. It's true.

Chrysin actually has, as far as being small, a molecular size of only 254 grams per mole, and that molecular weight is consistent with that of steroid hormones. And actually, it's a bit smaller than most of them that are currently available that are used topically.

Then they also mentioned that oral supplementation, that the bioavailability is relatively low, also true. Same study here that he mentioned before is that 400 milligrams of chrysin did not really get very much absorbed through the gut.

There is some talk of it having some activity in the gut as well, but the actual systemic absorption was low.

Keeping that in mind, the first thing we're going to think of when we have something that has low bioavailability is, does it have topical administration feasibility?

We did mention that it has a very low molecular weight. That being said, we know, based on this study here on transdermal routes, that if

something has a molecular weight less than 500 Daltons, that's a very good candidate for transdermal absorption.

It also mentions that unionized entities have better absorption and chrysin is non-polar, so it has some capabilities of being able to be utilized topically based on just its normal structure and its ionization.

Efficacy potential; if we get away from just the transdermal part and just talk about can there be efficacy to actually use chrysin? And in this study here, they looked at its ability to inhibit human aromatase. Besides chrysin, they looked at others.

What they found was that these bioflavonoids, such as chrysin, did actually have the ability to bind to the active site of aromatase and then actually cause activity.

Also, another study where they actually looked at chrysin again, and this one was done in Leydig cells. They were looking at, does it have potential to enhance steroidogenesis?

What they found with these results that chrysin did actually show the potential to induce -- they didn't really induce the gene expression, but they were able to actually increase the functionality of the Leydig cells based on cyclic AMP stimulation.

They're allowing that process to continue easier and thereby increasing the aromatase activity in kind of a roundabout way, maybe not exactly hitting the enzyme but actually affecting the cyclic AMP, which then goes ahead and affects the aromatase.

Another one here -- this one talks about the beneficial effects of chrysin and again in animals. This one, we looked at recently isolated from passion flower, administered to two-year-old male rats for a period of 30 days.

They saw a significant improvement in overall sexual function in the rats compared to the control rats. Both had increased sperm count, greater fertilization potential, greater litter size, and they definitely showed a change by adding

the chrysin to this rat's diet.

The next one, we also look here at beneficial effects of chrysin on the reproductive system again in rats. In this one, we were divided in two groups. Rats were given a control corn oil.

Chrysin was administered at a dose of 50 milligrams per kilogram per day. And the results indicated that chrysin significantly increased both GSH, CAT, GSH-Px, and copper-zinc-SOD levels, but it did not change the formation of the TBARS which is the tissue thiobarbituric acid reactive.

In addition, sperm motility, sperm concentrations, and serum testosterone levels were significantly increased. So here, we're actually showing that the testosterone levels were increased by the addition of chrysin.

Now, if we look at mutagenicity, the FDA points to studies in bacteria strains using the Ames test. Within the study that they actually presented, the study looked at all bioflavonoids and actually found that chrysin was the only one

that showed negative mutagenicity across every strain tested.

This was done using the Ames test which -- and the study listed below is actually proven to be a very sensitive test. It has greater specificity and predictability over all forms of mutagenic testing. Within the test that they actually provided, it actually showed that chrysin had negative mutagenicity.

This is that actual test here. This was the article that was submitted, and it said, finally, chrysin, which has only two hydroxyl groups, did not induce mutagenicity activity in any of the bacterial strains used.

Then they also mentioned in their evaluation about neurotoxic effects. Chrysin has been shown, in this study, that it actually had neuroprotective effects.

Here, polyphenolic compounds, especially flavonoids, are known to the most common chemical class of phytochemicals which possess a multiple range of health-promoting effects.

Chrysin, belonging to the flavone class, is one of the more important bioactive constituents of fruits, vegetables -- we went over that -- but chrysin possesses potent neuroprotective effects and suppresses neuroinflammation.

Here, in this study, we're actually showing that instead of having negative effects, it actually does have positive effects and is actually neuroprotective.

Now, another study, one that they also submitted in their actual review of chrysin, was neuroprotective efficacy of chrysin against cisplatin-induced toxicity via attenuation of oxidative stress. This came out of the Journal of Pharmacy and Pharmacology.

In that study, they actually found that chrysin suppressed the cisplatin-induced renal injury. Actually, having chrysin along can actually suppress any kind of ill effects that cisplatin can cause while we're actually trying to treat the tumors in that that we use cisplatin for.

Chrysin also has hepatoprotective effects.

In this study here, we looked at the antioxidant status in hepatitis in rats. The treatment with chrysin was 25, 50, and 100 milligrams per kilogram of body weight.

Within that, these findings demonstrate that chrysin acts as hepatoprotective, antioxidant agent against D-galactosamine-induced hepatotoxicity. This is just another example where it's actually causing positive and not negative effects.

We also have another study here where the influence of chrysin on hepatic markers and lipid profile, rats again are treated with different concentrations, 20, 50, and 100.

It also decreased the level of cholesterol, phospholipids, triglycerides, free fatty acids in plasma and tissues of liver and kidney. Chrysin exhibits hepatoprotective and antihyperlipidemic activity. This is another study again showing the positive effects of chrysin on those parameters.

Chemoprotective effects, this is something that the committee did talk about and possibly said that they do see potential for it there. This is a

study here that talked about findings that might suggest that possible chemopreventive activity of chrysin in early step of colon tumorigenesis. So this is just another study again showing positive effects in looking at the chemoprotective effects.

The next one here, this study, chrysin promotes tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in human cancer cell lines. In this study, we find that pre-treatment with chrysin could promote the cell death induced by TRAIL according to morphological changes and appearance in four human cancer cell lines.

All data indicate that chrysin can enhance apoptosis in induced trials. This is actually a trial that they did, and they found that chrysin did have chemoprotective effects.

In conclusion, there are reference studies that do look at the aromatase inhibition of flavonoids, as well as chrysin. Chrysin is a good candidate for topical and transdermal delivery.

Historically, it's been effective used at

much lower doses when it's commonly used orally because of low bioavailability. So again, it has the potential there to be done transdermally.

Animal studies suggest that chrysin supplementation will improve sperm count, fertility, suggesting that it improves free testosterone levels. In the Ames test referenced by the committee, chrysin did not induce any mutagenic activity. Studies have shown that chrysin is neuroprotective, chemoprotective, and has hepatoprotective properties.

That's all I have.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Mr. Wynn.

Any clarifying questions by the committee? Dr. Jungman?

MS. JUNGMAN: I was wondering if you could talk a little bit about if there's a clinical need here that chrysin fills that's not being filled by FDA-approved products.

MR. WYNN: Sure. With chrysin, one of the things we can look at is -- we talked about is the

safety profile. In long-term use, with a lot of the commercially available products that are out there that are used for aromatase inhibition, I mean, a lot of the complaints that they get; they're skeletal complications, musculoskeletal pain, visual disturbances, neurological disturbances, and a lot of -- that's just a few of the things that have been documented that can be an issue with the current available aromatase inhibitors that are out there in long-term use.

Chrysin is a way to have a more natural product out there that, to this date and from what we've seen in the studies that are out there now, has not really shown to have any of those issues in longer-term use.

Most of the time now, what you're seeing is true. We may not necessarily -- most of those studies have been done in women and breast cancer because they're the ones that are going to use aromatase inhibitors the longest.

But again now, more and more, we're seeing that they are used in men, not really for the

bodybuilding, but for areas of actually increasing testosterone levels with maybe not having to use as high of a dose because dose-related incidences of long-term use of high hormones can actually be an issue.

If we can lower the dose by allowing the dose to be more effective and decrease the potential for increased estrogen or other things that we might get from the hormone replacement that having an option that's an aromatase inhibitor that could be used long-term would be better than maybe having a lot of these side effects that we have from the ones that are currently out there.

DR. VENITZ: Dr. Vaida?

DR. VAIDA: Yes. It seems that a lot of the studies that you were showing, although they were in rats and animals, that was all with, what, oral therapy?

MR. WYNN: Those were all with oral therapy where they were actually utilizing, showing that if they were coming with the contact -- but yes, they were all oral. Let's just say yes.

DR. VAIDA: Thank you.

DR. VENITZ: Dr. Gulur?

MR. WYNN: But I think that, to answer more of that question, is what they're also stating in the findings that they did in the preliminary look at our nomination -- they said there was no safety or efficacy for oral or topical.

So they're actually stating that there's none out there at all, and actually, what we have shown is there is information out there on its safety and efficacy.

DR. VENITZ: Dr. Gulur?

DR. GULUR: The studies that you brought up are all on animals, rats and mice. Do we have studies, clinical trials on human beings, especially considering that you made the statement regarding the long-term side effects of existing FDA supplements? Are there further studies showing that chrysin, in long-term therapy, is safe in humans?

MR. WYNN: Currently, right now, there aren't any trials of chrysin that are available out

there. As far as historically, I know the presenter said that he doesn't really have any data on how long chrysin has been used.

I can tell you just from personal experience. I've been a pharmacist since '94 and I've seen it used since then. At the very least, it's been out there that long, probably longer than that and haven't really had any issues that I know of come up that have been submitted to the FDA or presented to me as a provider at the time. But currently right now, there are no clinical trials on chrysin that I know of.

DR. VENITZ: Go ahead.

DR. GULUR: Just one clarifying -- is there a formal mechanism for where you collect this data in patients that you compound on and do you collect whether there are adverse effects on these patients anywhere?

MR. WYNN: When I actually had my pharmacy, which I do not now, we actually did have a program that I had set up that basically we were calling and checking on patients.

It was a way for us to keep in contact to make sure that the patients were utilizing what we were making and compounding properly and at the same time gathering this kind of information.

If there was an issue, we wanted to know. I had my own program set up in my pharmacy that we did that with, and it was just part of our SOPs, and we actually called and checked.

DR. GULUR: All right. Thank you.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Yes, hi. I mean, do you have any data on either in humans or even in animals on levels achieved of this compound, any evidence that the levels you're achieving are able to inhibit aromatase, any evidence that the drug is actually producing a pharmacologic effect in animals or in humans? I mean, it's one thing to establish safety of something if it doesn't do anything.

MR. WYNN: Good point. Definitely, right now, I don't know -- I did not find a study on transdermal.

The only one that was submitted by the reviewer of our nomination was actually one where they actually used plant extract, which I didn't feel was maybe the proper way to look at how transdermal penetration would occur. Because if that's true, then the commercially available estrogen products we have, why don't we just use yen powder? I mean, we definitely use the constituent itself.

Currently, there's not information out there that's going to promote or dismiss its transdermal capabilities. I can say again, as personal experience, that the doctors were checking testosterone levels and looking at changes that were occurring while they were utilizing chrysin. But I would not have a true study.

DR. VENITZ: Let me ask you a follow-up question then. In your compounding experience, was it exclusively transdermal or did you also compound oral formulation?

MR. WYNN: Sure. It was exclusively transdermal. I had some physicians that would use

chrysin alone, and they would do that sometimes as patients get older when they didn't want to give a whole bunch of testosterone, their idea being that if they could get what we're already making, what little they're making to stay around a bit longer, they could get some additive effects of what they needed for those patients.

So I did see mostly all transdermal, and I did see it with some other steroid hormones and by itself.

DR. VENITZ: So it was all transdermal even though you had no evidence that it actually achieves levels that are better than the 400-milligram oral study that was reviewed that didn't show any effects on the --

MR. WYNN: These patients are actually under the care of a physician who was actively checking levels at the time. And if they weren't actually being effective to his needs, he would have stopped the therapy. So he was actually controlling -- he or she was looking at the levels and then assessing what they wanted to do at that point.

So I was not actively doing it, but the physician was in control, and watching levels, and making sure that they were getting a positive response.

DR. VENITZ: Okay. Thank you. Yes, Dr. Davidson?

MS. DAVIDSON: Dr. Wynn, can you characterize, either from your personal experience or as a supplier of the API, the number of patients that are receiving transdermal chrysin or the prescribers that are prescribing transdermal chrysin?

MR. WYNN: Sure. Hard to tell that. I honestly don't know. I'm not sure how many patients are actually currently actively being utilized. Like in my practice, let's say -- and this has been -- I've been out for a number of years, but at that time, maybe we had 15 percent that were actually utilizing chrysin. Not all physicians were doing that, but I had several that were utilizing its aspects for what they wanted.

MS. DAVIDSON: And can you help me

understand what 15 percent means in terms of numbers?

MR. WYNN: Sure. All right. So we were doing probably 300 a month; so 15 percent of that.

Committee Discussion and Vote

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

(No response.)

DR. VENITZ: Then thank you for your presentation.

We now have supposedly an open public hearing, but we have nobody signed up. We're going to continue our discussion and vote. We're now starting the official discussion on the topic of chrysin that we're going to vote on in a few minutes.

Any discussion? Dr. Davidson?

MS. DAVIDSON: I have an overarching question for FDA. It seems like there may be some potentially promising use for chrysin in terms of neuroprotection and maybe chemoprotection. I'm not sure I understand what that means other than

promoting apoptosis.

But my question is, could substances not placed on this list potentially be used in an investigational situation? Could they still be prepared for investigations under an IACUC, IRB, whatever?

MS. BORMEL: You're suggesting something could be looked at like chrysin under an IND? Yes, it could be looked up under an IND separate from consideration of the 503A bulks nomination process.

MS. DAVIDSON: I wasn't specifically thinking of an IND as we know it, which we'll learn a lot more about this afternoon, but an individual institutional researcher that may want to use it in a small human population for a prospective head-to-head comparison.

MS. BORMEL: Right. Usually, if a researcher is going to look at a particular drug, they would get an IND. We're talking about the IND process in order to do a research project. So yes, the researcher still could look at this particular drug under an IND.

DR. VENITZ: Any other questions? Yes, Dr. Pham?

DR. PHAM: I think I'm starting to get confused. If everyone else is clear on this, help me out here. But it seems like a lot of data that's being presented is speaking to the oral product, but the oral absorption is poor.

Yet at the same time, it seems that from a public access perspective, it seems most people will want the transdermal product, but we're not seeing a lot of data on transdermal.

I feel like there's a big disconnect, so I'm kind of getting a sense that what we want to potentially say is maybe there's a place for topical. Dr. DiGiovanna, help me out if you have some thoughts.

Maybe there's a place for topical, but the data doesn't support that. The data shows oral, but then there's not great information that oral gets absorbed, and it's potentially already accessible through dietary supplements and other things.

What is the sense then for -- is it even worth talking about just topical, knowing that oral is available through other mechanisms? But do we want something that doesn't actually have data supporting topical, even though it's actually potentially the way that it's used?

DR. DiGIOVANNA: I'm not sure if you're addressing that to me, but I'll take it on. So my perception of this is there's not a great deal of information, that it's poorly absorbed orally, and there's no information about the pharmacology of it when it's applied topically.

We don't know if it's absorbed well or at all. And without a clinical study to suggest that it does something, if you don't know that it's absorbed and you have no clinical evidence that it works, it makes it really difficult to make an assessment of its utility.

DR. VENITZ: And I would add to that, if you look at the doses that were used in those rat studies, if you scale them up to humans, they were like 2 to 7 grams per day.

To translate that into a dermal, the transdermal absorption would have to be very high, presumably at the doses that they're using because it is intended for the systemic effect.

On the other hand, I didn't hear in the FDA presentation nor in the nominator presentations any significant concerns about safety. We can argue whether the drug works or not or whether there's evidence to support that it might work after transdermal administration or not. But I haven't really heard anything related to safety issues. It could be a compounded placebo.

Yes, Dr. Vaida? I thought you raised your hand.

Okay. Any other comments?

(No response.)

DR. VENITZ: Do we want to proceed with the vote? Okay. Then let me go through my spiel.

The panel will be using an electronic voting system for this meeting. Each voting member has three voting 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 one product that just was presented.

All vote questions relate to whether the product should be included on the 503A bulk list. As always, after the completion of each vote, we will read the vote from the screen into the record and then hear individual comments from each member.

Ready to vote then? Can you put up the question?

So the voting question is FDA is proposing that chrysin not be placed on the list. Please vote yes, no, or abstain.

(Vote taken.)

DR. HONG: Question 1 on chrysin, we have 2 yeses, 9 nos, and zero abstain.

DR. VENITZ: Okay. Let's go around the table then, starting to my right.

Yes, Donna?

DR. WALL: I voted no because I just didn't really see a purpose in it. There's just so many

unanswered questions.

DR. CAROME: Mike Carome. I voted no. There's no evidence that, topically or orally taken, this has any pharmacological effect, no evidence clinically that it offers any benefits. We have no safety data, and there are FDA-approved products for treating cancer and for treating testosterone deficiency.

DR. VAIDA: Allen Vaida. I voted no basically for the same reasons. I don't see any clinical evidence for this drug.

DR. PHAM: Katherine Pham. I voted no. I think that the lack of adverse effects could potentially allude to safety, but I don't think that there's a consistent mechanism in place to catch that data in the community.

So balancing that with the fact that we have question on absorption, either orally or transdermally, I voted no.

MS. JUNGMAN: Elizabeth Jungman. I also voted no. The lack of efficacy and poor bioavailability were kind of the primary issues

there, coupled with the lack of safety information for long-term use.

Understanding that there are complaints about some of the FDA-approved alternatives, at least we have robust data about those.

DR. HOAG: I'm Steve Hoag. I voted on the question, which was "not," so I'm not sure if I -- because at the end, it was a little ambiguous.

But anyway, I would suggest that it not be on the list. In the future, I may consider that because if there's more data, it could be promising. But at the moment, it hasn't risen to that level for my evaluation.

MR. HUMPHREY: William Humphrey. I voted no for many of the same reasons already expressed. I didn't hear any evidence that it is absorbed topically and has any efficacy from that.

MS. DAVIDSON: Gigi Davidson. I struggled with this one. I was stricken by the 45 patients just in Dr. Wynn's practice that are still receiving this. And even though it is commercially available as a dietary supplement, that would not

be a form that could be used to prepare a transdermal dosage form.

I think that there's fairly confident knowledge that it doesn't cause the adverse effects that some of the FDA-approved alternatives are, so I voted yes for it to continue to be on the list and be used clinically to gather more data.

DR. VENITZ: I'm with Dr. Davidson. I had a struggle on this one, too, but ended up on the other side of the coin. I think the safety to me was reasonable to keep it or put it back on the list.

On the other hand, the total lack of any transdermal absorption data doesn't convince me that you're avoiding the first-pass effect that prevents its oral absorption in humans at very high doses.

If there had been any even tentative data suggesting that transdermal absorption actually occurs and it does avoid the first-pass effect, then it would be much more favorable because I think the compounding history that was outlined, to

me, sounded pretty impressive.

DR. GULUR: Padma Gulur. I voted no to placing this for similar reasons, which is a lack of data on how much is getting absorbed, if this drug is actually effective. It's true that perhaps there aren't any adverse event data, but that might be because the drug just isn't being absorbed. And while there appears to be some utilization in the population, again, lack of effectiveness or absorption data makes it hard to understand.

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

DR. VENITZ: Okay. Thank you. We are ahead of the schedule, so we're going to juggle a little bit. I think what we might have to is take a break now.

MS. BORMEL: Dr. Venitz, I just have a quick question.

DR. VENITZ: Yes. Go ahead.

MS. BORMEL: Is the vote going to be -- what is the official record of the vote?

DR. VENITZ: It is 9 to 2 -- with the

correction that Dr. Hoag made that he basically would be in the no category.

MS. BORMEL: Okay.

DR. VENITZ: So the official vote is 9 to 2, but it's --

MS. BORMEL: 10 to 1.

DR. VENITZ: -- supposed to be reflected 10 to 1, yes, for the record.

MS. BORMEL: Thank you.

DR. VENITZ: Any other comments or concerns about the vote?

(No response.)

DR. VENITZ: We have a scheduling issue now because we are ahead of the curve, and we have to keep our open public hearing at 10:35. What I would suggest is that we take a 10-minute break now, reconvene, and then we work our way through the lunch break, if that's acceptable?

(No response.)

DR. VENITZ: Okay. Then let's take a 10-minute break. It's now 9:37, so let's reconvene at 9:47, please.

(Whereupon, at 9:36 a.m., a recess was taken.)

DR. VENITZ: Welcome back. We are now moving to our second substance to review and that is cesium chloride. And as always, we are starting off with the FDA presentation, which Dr. Brave is going to provide us with again.

Dr. Brave?

Presentation - Michael Brave

DR. BRAVE: Good morning, again. I'd like to thank and acknowledge my colleagues listed here who helped me review this nomination. Cesium has been nominated for compounding as an alternate treatment to cancer.

It's unclear exactly what the nominator means in this case by the term "an alternate treatment to cancer." The proposed route of administration is intravenously. The references provided in the nomination contain only nonclinical information.

Cesium, an alkaline metal with chemical properties similar to lithium, potassium, and

sodium, is a trace element in human metabolism. The substance nominated for compounding should not be confused with radioisotopes of cesium that may be used for imaging studies or for radiation therapy.

Cesium is obtained by extraction from sea water. It can be easily characterized chemically. It is water soluble and stable in aqueous solution.

Nonclinical animal studies showed total body cesium under normal conditions to be approximately 1.5 milligrams. Normal plasma levels of cesium range from 0.00045 to 0.26 grams per gram wet weight.

Cesium chloride ingested by mouth is nearly a hundred percent absorbed in the small intestine. Cesium distribution is extensive with higher concentrations in the kidneys, skeletal muscle, liver, red blood cells, and brain.

The serum half-life of cesium is approximately 70 hours in men and 96 hours in women. Elimination is 85 percent urinary, 13 percent fecal, and 2 percent through sweat. The

renal mechanisms for excretion of cesium are thought to be similar to those with potassium.

A rationale for the use of cesium in the treatment of cancer was proposed in 1984 by Brewer who hypothesized that cesium-established alkaline conditions inside neoplastic cells leading to apoptosis.

However, the presence of cesium in a cell does not guarantee high intracellular pH, and there is no theoretical or clinical evidence to suggest that cancer cells are selectively vulnerable to cesium.

Evidence of clinical benefit from cesium in human cancer is limited to one case series published in 1984 by Sartori. That case series had major flaws, including its uncontrolled nature, retrospective design, and probable case selection bias.

Studies in animals identified the central nervous system and cardiovascular system as targets of toxicity. Nonclinical studies also show the potential for genotoxicity and embryo toxicity.

Cesium blocks potassium rectifier channels on atrial and ventricular myocytes resulting in prolongation of the QT interval, which can lead to fatal arrhythmias.

Numerous case reports describe serious toxicities resulting from cesium chloride ingested as an alternative treatment for cancer, including hypokalemia, seizures, ventricular arrhythmias, syncope, and death.

Often arrhythmias occur after weeks to months of therapy with cesium, which is not surprising given the long half-life of cesium. It takes approximately 200 days of daily dosing to reach steady state.

Published literature indicates that cesium chloride used in the treatment of cancer has been taking place since at least the 1980s. Currently, oral cesium chloride is advertised by a number of compounding pharmacies.

In summary, while cesium chloride can be characterized using standard chemical techniques and is stable in aqueous solution, there are

serious safety concerns related to its use.

Studies in mice showed cardiac and central nervous system toxicity, as well as reproductive effects. Clinically, reports of serious toxicity following cesium chloride use for the treatment of cancer have included hypokalemia, seizures, ventricular arrhythmias, syncope, and death.

Cesium chloride has not been shown to be efficacious for the prevention or treatment of any form of cancer, whereas many FDA-approved treatments for cancer do have established records of safety and efficacy.

Finally, we found insufficient information to evaluate the historical use of cesium chloride in pharmacy compounding. A search of the internet indicates compounding with cesium chloride takes place; although the extent and indications for which this compounding is done are unclear.

Based on a balancing of the four evaluation criteria articulated in the Federal Register, we find that cesium chloride is not a suitable substance for compounding under 503A of the Food,

Drug, and Cosmetic Act.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Brave.

Any clarifying questions by the committee?

Dr. Carome?

DR. CAROME: I just want to ask, would it be fair to say that FDA has concluded that cesium chloride raises significant safety concerns?

DR. BRAVE: Would it be -- could you repeat the question?

DR. CAROME: Would it be fair to say that FDA has concluded that this drug substance raises serious safety risk concerns?

DR. BRAVE: Yes.

DR. VENITZ: Dr. Hoag?

DR. HOAG: Just a point of clarification, is this oral cesium chloride, IV, or all?

DR. BRAVE: It's IV. The proposed route of administration is IV.

DR. VENITZ: Do we know any more about the compounding history, about its use?

DR. BRAVE: That information is not

submitted with the nomination, so we have no way to know that.

DR. VENITZ: Okay.

Any other clarifying questions?

(No response.)

DR. VENITZ: Thank you, Dr. Brave.

That brings us to the nominator. We have one presentation on cesium chloride, Dr. Anderson from the American Association of Naturopathic Physicians, AANP.

Presentation - Paul Anderson

DR. ANDERSON: Good morning, and thank you. Of the three that I am testifying on today, cesium was not one I was involved in the nomination process for. So I'm giving background information, and I'll try and answer questions the best I can.

I do want to make a note, because in all of my presentations, I will reference research that I am involved in and in an ongoing basis, which some of these of substances have been used.

Some of the data is published in case reports, some is not, and I will speak to that as

we go through.

The first was an NIH-funded study, '09 to '14, in collaboration with the Seattle Cancer Care Alliance essentially and the BIORC clinics, and then the current ongoing multicenter trials, the CUSIOS trial.

To give background to where my testimony will come from in the first two drugs that we're going to talk about, but cesium specifically, it is in specifically advanced cancer in patients who have failed all other therapy. That will be what I will be speaking to.

As far as efficacy, the Sartori paper was very well-characterized earlier by our colleagues so I will not go into that, except to say that this is where the idea to use cesium chloride appears to have arisen. It, I believe, had some use in Europe prior to the 1980s which also dates back.

As far as the compounding history, I don't have a slide specifically for that, but that is of note. I am aware of cesium chloride being compounded by registered compounding pharmacies,

both orally and for parenteral use at least to 1997, possibly before that, probably before that.

The safety, in my mind, having to review protocols and look at protocols, is probably the most paramount issue with cesium chloride. In looking at one of the studies that was brought up and then a couple of others that were not, the first is just a statement from Melnikov, et al. in 2010 about the safety of cesium in its relatively mild toxicity.

Like most all substances, including minerals, the toxicity is highly dose-based, and administration-based, and also based in monitoring, appropriate monitoring. The three primary modern sources for the adverse events associated with cesium chloride in four. And all four of them that are stated in these three have one critical factor in common.

These two essentially were patients from '03 and '08 that were reported, and this is a total of three cases where they had cardiac anomalies. This was mentioned earlier by our colleague. And they

were due to dose irregularities or overdosing with cesium chloride.

Then the more recent event, which was a fatality published in 2013, and just an excerpt from the abstract showing that this was actually upon advice from a nutritionist, the husband took an oral solution and injected 9 mLs into the tumor.

So this particular patient then went into complete cardiac shock and passed away at the emergency department. Those are the four.

When I read the papers on the safety issues, at least these more modern ones, the most glaring issue that came up to me -- because I have experienced, as you'll see, at least supervising and referring the use of cesium chloride parenterally and orally in a large number of cases and we have not seen these sort of effects as that none of these people were under the care of a qualified physician during the use of the cesium chloride.

They were obtaining it as a dietary supplement, and they were using it with either no

guidance or very poor guidance. I think that that is of note.

Alternatives, when you are looking at -- if we limit, as I said in the beginning, the discussion to advanced cancers that have failed therapy, alternatives is a relative term.

There are many, many therapies for various cancers that have various levels of safety, efficacy, et cetera. We all know that.

When we get to the point of palliative oncology and/or stabilizing unstable disease, we get to less and less options, and sometimes, as you'll see later, we have no options.

In the sense that we're looking at trying to palliate in advanced cancer where there is no more opportunity for therapy, what we have seen and are doing ongoing investigation is that cesium does appear to hold a place in the palliative setting.

We do see stabilization of advancement of disease and palliation of things such as pain and other quality of life measurements.

We'll wrap up. My personal experience with

cesium chloride has been in the research setting and has been in these two trials. In the setting, the physician collaborators that have worked either with or under me have used many, many doses, thousands of doses actually without any high-grade adverse events, no hypokalemia, no cardiac irregularities, et cetera.

I believe that that is because that they are monitoring the patients very closely, and they are also taking prophylactic measures against such things.

A point I would like to make is that because the safety profile, in my mind, at least from what I have seen from all of these doses, is based on the administration, and monitoring, and management by a qualified physician, it would be my opinion that keeping the drug available through registered compounding pharmacies would limit its use to prescribing physicians only because the adverse events that we've talked about happened under the care of non-licensed or unqualified physicians. I believe that this would be a way to regulate and

monitor those events. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Anderson.

Any clarifying questions by the committee?

Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. You showed some data from a study that indicated the term of 50 percent recovery of patients with untreatable cancers.

Recovery isn't a usual term I'm familiar with in oncology studies. Usually, they talk about objective measurements somehow. Do you have any information on how that was measured?

DR. ANDERSON: Yes. I believe -- is it Dr. Brave who gave the first presentation, and brought that same study up, and mention that that was one of the issues with the study?

So I was not really using it to justify the use discretely. I was just saying that that is the one that we have as flawed as it is, yes.

DR. VENITZ: What doses do you typically use? You mentioned that the toxicities, as far as

you're concerned, are very much dose-dependent. What doses -- how many milliequivalents do you use?

DR. ANDERSON: The groups that are using the cesium orally and/or in parenteral use are in our off-sites. Because I do not directly manage their patients, I would not want to make a guess at what doses they're using. We have it in monographs though.

DR. VENITZ: Thank you.

Dr. Gulur?

DR. GULUR: Thank you for your presentation. My question is with regards to your use of this currently for research. Did you not have to do an IND in order to conduct the research with this substance?

DR. ANDERSON: Very good question. The way that the IRB was convened and the language that they used was that, as long as the substance was within the scope of practice of the practitioners employing it, and that there was proper informed consent, and that it was compounded within the guidelines of the FDA, it could be employed in

advanced cancer.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Given that you're involved in these studies, and that this is a substance that presents at least some significant safety concerns, and is used in very sick patients, I was wondering if you could help me understand the argument for using it in a one-off basis obtained from compounding pharmacists as opposed to as part of a clinical trial protocol where you would at least have review of that protocol and you'd be collecting the results for use potentially for future patients.

DR. ANDERSON: Yes. Good question. Part of the purpose behind the first trial that we did in cooperation with NIH was to essentially have a more open source to therapies that may or may not work over the time of the study but that we could demonstrate that they could be administered safely.

The point at the end of that study was then to move forward any of the substances that did show reasonable safety and purported efficacy and then

move them to just what you were talking about.

One of the real rubber-meets-the-road issues is certainly finding a funding source to do a single-agent trial such as what you were talking about without any data to back it up.

Our purpose in doing that -- and as you'll see with dichloroacetate, et cetera, our purpose in doing these was to see, A, if anything actually did happen that we could measure, B, if we had some level of safety and we could come up with protocols that made sense. Then we could move on to proposing a study.

DR. VENITZ: Dr. Carome?

DR. CAROME: Can you describe in more detail the clinical trial you're talking about? Is this a clinical trial that is testing only cesium chloride or multiple different agents?

Are there control groups? Are there objective criteria for enrollment, objective criteria for measuring outcomes? Is NIH funding all of this research? Are the trials registered on ClinicalTrials.gov?

I'd like to know from FDA whether this is a type of research that would require an IND.

DR. ANDERSON: Good questions. Yes. Well, there's two different trials that were mentioned. The first, which is closed but is in statistical analysis, was a prospective study.

The outcomes were -- initially in that first study, the outcomes were survival, and the survivals were matched with our cohort within the Seattle Cancer Care Alliance who were the same demographic, same cancer but not enrolled in the alternative therapies portion.

At the end, the survival of group A versus group B was the final clinical measurement. The use of therapies within the integrative oncology arm was what I described earlier, which is it was not one particular agent. It was a multiple menu of agents, and they were chosen by the supervising physicians as to potential for efficacy.

All of these had some or maybe very little data to support their use in the front end, so this was trying to establish that as they went through.

The endpoint, in that particular study, was survival.

In the second one, the CUSIOS one that's mentioned, half of the centers are actually in Canada, and the other half are in the U.S. The endpoints there are both survival of the particular cancers, as well as quality of life measurements.

DR. VENITZ: Any further questions?

(No response.)

DR. VENITZ: Okay, Dr. Anderson. Thank you.

DR. ANDERSON: Thank you.

DR. VENITZ: That gets us into --

DR. DOHM: Can I just interject? I think there was -- also part of the question that was posed to FDA about whether or not an IND would be required in this scenario.

I'd just like to say that it certainly sounds like the IND requirements would be applicable here, although there are certain exceptions. So we would need to have a full kind of suite of information about it in order to better assess whether or not it would be appropriate to

have an IND in this scenario.

Open Public Hearing

DR. VENITZ: Okay. Thank you, Dr. Dohm.

That gets us into the first open public hearing session. So let me read the official announcement.

We will now proceed to 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 written or oral statements 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 a compounding pharmacy of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, the 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. With that said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to

carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation.

I'm asking now our first OPH speaker, Dr. Hauser, to step forward and present.

DR. HAUSER: Good morning. Thank you for allowing me this opportunity to share Community Pharmacy's perspective regarding the work of the Pharmacy Compounding Advisory Committee.

I'm Ronna Hauser, vice-president of pharmacy affairs at the National Community Pharmacists Association, and I have no financial relationships to disclose.

NCPA represents America's community pharmacists, including the owners of nearly 23,000 independent community pharmacies. According to a member survey, approximately 88 percent of our members provide some type of compounding service, but over 95 percent of respondents stated they do not plan to register as a 503B outsourcing facility.

Therefore, the vast majority of our members will be held to the laws and regulations of Section 503A of the Food, Drug, and Cosmetic Act.

As the FDA and PCAC members continue to consider which drugs nominated will be considered for inclusion on the 503A positive list, among other responsibilities, NCPA is committed to working with the FDA and stakeholders on these critical issues.

However, we do have concerns with the creation, oversight, and operation of the PCAC and associated processes. Among these concerns are the following:

Number 1, inadequate member selection and renewal processes. NCPA remains concerned that none of our nominees to the PCAC were ever contacted. Unfortunately, there is currently not one voting member of the PCAC who compounds for human use on a daily basis.

NCPA finds this fact astounding considering the community is making recommendations that can vastly impact the practice of compounding. The

previous PCAC had at least three pharmacists with current experience and expertise in compounding, one of which specialized in sterile compounding.

The FDA should reopen the nomination process for committee members in order to have at least one practicing human compounder on the committee as a voting member.

Number 2, FDA's insistence that any bulk drug substance not voted under the positive list can easily be obtained via the investigational new drug process. In reality, this is a cumbersome, timely, and expensive process especially for community healthcare practitioners who have previously presented their real-life concerns with the IND process to the committee.

Number 3, unequal time allotted for nominators to defend substances and respond to committee questions. Throughout this entire process, each nominated substance is given a total of 10 minutes to be defended by the nominating organizations.

Oftentimes, nominators will have to split

this time up. All the while, the FDA has unlimited to present their review and opinions related to the nominated substances.

In addition, nominators have a limited timeframe to organize their presentations, normally less than three weeks where FDA has more time, likely months, to prepare.

Number 4, FDA's indication that it does not consider USP monographs for dietary supplements to be applicable USP or NF monographs, therefore limiting compounding to only USP drug monographs when no basis exists for FDA to exclude USP or NF monographs for dietary supplements.

This is a great trouble to NCPA as it defies logic that these substances can be easily obtained by the public at any Costco, Walmart, or CVS, for example, but in the hands of healthcare practitioners are not to be trusted.

The practice of compounding is built on the patient/physician/pharmacist triad, and there's no better way to oversee the use of these preparations than through this relationship.

Number 5, a confusing nominating and review process that leads many unanswered questions for healthcare practitioners and patients who rely on compounds, NCPA contends that it was premature for the FDA to have solicited nominations for the 503A list, as well as selected six products to consider at the first PCAC meeting before developing and agreeing on criteria used to develop the list.

In addition, when nominating, we were asked for all possible uses, not the most likely. We are also concerned that the FDA has separated substances in the recently released 503A bulk drug substances interim policy based on nothing more than if the agency considers that adequate information to evaluate the substance was included as part of the nomination process.

Not being able to compound with these substances included on FDA's 503A List 3 will cause impaired patient access and is causing confusion, not to mention that many of the substances included on List 3 are by FDA's own definition, not active pharmaceutical ingredients that should even be

under discussion.

I would also like to address a comment that has been made on multiple occasions during previous PCAC meetings. That is the notion that if the FDA places a nominated substance on the 503A list, then it can be marketed with drug claims for any use.

Marketing unsubstantiated claims such as this are illegal, and if FDA or PCAC members have concerns about claims, then appropriate action and education should be undertaken.

Lastly, I would like to voice NCPA's support for the nominated bulk drug substances that the committee is discussing at this meeting. NCPA nominated two of the substances under discussion, chrysin and tea tree oil. And I fully support my colleagues here today speaking to their merits.

The intent of the committee was to increase appropriate access to bulk drug substances without a USP/NF monograph or from an FDA-approved product. Unfortunately, quite the opposite is occurring.

In summary, NCPA is committed to working with the FDA, the committee, and other stakeholders

regarding these important matters. We appreciate your consideration of our remarks today, and thank you for allowing me the time to present.

DR. VENITZ: Thank you, Dr. Hauser.

Any questions by any of the committee members for Dr. Hauser?

(No response.)

DR. VENITZ: Okay. Thank you again.

DR. HAUSER: Okay. Thank you.

Committee Discussion and Vote

DR. VENITZ: That concludes our open public hearing portion, and we won't take any more comments for right now.

We're now proceeding with our discussion and ultimate vote on our second product, cesium chloride. Any comments, any discussion items?

Mr. Mixon?

MR. MIXON: I just wanted to make a comment. I serve pharmacies who are seeking accreditation or reaccreditation for the PCAB designation, and I have yet to come across any pharmacy, nor do I know of any pharmacy that -- other than what are listed

in some of the supporting materials that compound with this drug.

I just want the committee to know that this is not something that every compounding pharmacist does.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. This substance is a little bit different than the others, I think, that we've discussed in that its indication seems to be for patients who are at end-of-life scenarios because of malignancy.

It occurs to me that these patients are a very vulnerable group that are easily manipulated by anything that offers them hope. I think in that scenario, my perception is that potentially toxic compounds really need to be studied in a controlled environment under an IND to determine if there's any evidence that they offer benefit comparable to the toxicity that they offer. This particular compound raises some concerns to me that the others didn't.

DR. VENITZ: Any other comments?

The only thing to follow-up that I'd like to contribute, the dose-dependence or the dose-related side effects, especially the Torsades de pointes, is pretty obvious.

Unless there are clinical studies or a study like interventions that allow us to really assess at what doses you can avoid, even if there were no benefit, there is no way that a drug that can be given safely -- not a drug; a product that can be given safely and effectively.

So even if you state the point that the efficacy is not demonstrated, it has a major safety issue, and safe doses have not been established, forget the fact that we know nothing about effective doses.

No more comments? Yes, Dr. Hoag?

DR. HOAG: This is a comment. I also worry a little bit about where you get this material. The FDA said that it's easily assayed, but that's only if you're set up to do those types of assays. It requires often like specialized equipment and things which I bet a lot of people don't have. So

the impurity and the impurity profiles in there would be something to consider. Where would you source this material from?

DR. VENITZ: Okay. Let's proceed with our vote. Let me go through the preliminaries again.

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 this 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.

Then the process itself, 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.

Please go ahead and proceed with the vote. No means you are not putting it on the 503A bulk list.

(Vote taken.)

DR. HONG: Question 2, we have zero yeses, 11 nos, and zero abstain.

DR. VENITZ: Okay. Let's go through the individual comments starting with Dr. DiGiovanna.

DR. DiGIOVANNA: I voted no because I think there's a great concern about the toxicity, the length of the half-life of excretion of the compounded, the lack of any efficacy, and the potential vulnerability of the population where it's intended.

DR. HONG: Could you state your name for the record, please?

DR. DiGIOVANNA: John DiGiovanna.

DR. VENITZ: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no for similar reasons as stated by Dr. DiGiovanna. I think this is definitely a drug that should go through the IND process. It should be registered. We should know what the adverse events are so that the population can be appropriately informed.

DR. VENITZ: Jurgen Venitz. Ditto.

MS. DAVIDSON: Gigi Davidson. I voted no

because it has a very strong safety signal, and I was also impressed by Dr. DiGiovanna's comments about this vulnerable population. And I think it should be used within an IND situation for that reason.

MR. HUMPHREY: William Humphrey. I voted no for many of the same reasons. The supporting information that we heard this morning was it sounded like either phase 1 or phase 2 clinical trial for a non-approved drug, and in which case would require an IND, I think.

DR. HOAG: Steve Hoag. I voted no for all the reasons previously stated.

MS. JUNGMAN: Elizabeth Jungman. I also voted no given the safety profile of the drug and the vulnerability of the patient population. I think it should be used in a more controlled environment.

DR. PHAM: Katherine Pham. I voted no due to the major dose-dependent toxicity concerns, especially Torsades.

DR. VAIDA: Allen Vaida. I voted no for all

the reasons that have already been said. Also, I had the real concern with the four cases that were not under qualified practitioners, and I don't really agree that putting it on the list would actually help that.

DR. CAROME: Mike Carome. I voted no for many of the reasons stated. I mean, the drug clearly has significant toxicity, particularly cardiac toxicity that has biologic mechanism for that toxicity. There's no reasonable evidence that offers any clinical benefit.

I actually would urge the FDA to immediately place this drug substance on the interim 503A Category 2 list of bulk drug substances that raise significant safety risks that may not be compounded, pending final rulemaking.

DR. WALL: This is Donna Wall. I voted no for all of the reasons stated.

DR. VENITZ: Thank you. Moving right along to our third bulk substance, sodium dichloroacetate, and we will have Dr. Brave again present the FDA's summary.

Presentation - Michael Brave

DR. BRAVE: Hello. I also reviewed the nomination for sodium dichloroacetate, and I'd like to thank the colleagues who helped me review this application and the same colleagues that helped me review the other two applications.

Dichloroacetate has been nominated for the list of substances that can be compounded. The proposed indication is for the quote, "adjunct treatment of cancer." We are uncertain what the adjunct treatment of cancer would mean, whether it would mean in combination with other chemotherapeutic agents, for example, or as a single agent.

The proposed routes of administration are orally and intravenously. The references provided in the nomination include only nonclinical information. Dichloroacetate is available as a dietary ingredient in dietary supplements.

Chemically, dichloroacetate is a small molecule synthesized from acetic acid, and it can be easily characterized. It is stable in oral

dosage forms at low temperatures but is unlikely to be stable as an injectable solution.

This slide and the next two slides discuss the theoretical rationale for the use of dichloroacetate as anticancer therapy.

Cancer cells exhibit a metabolic shift from glucose oxidation to glycolysis compared with nonmalignant cells. This phenomenon, known as the Warburg effect, is thought to reflect mitochondrial injury and alternate isoforms of glycolytic enzymes in cancer cells.

Glycolytic enzymes in the cytosol of cell metabolize glucose to pyruvate, which then enters the mitochondrion, where pyruvate dehydrogenase catalyzes its oxidative phosphorylation to acetyl-CoA.

Pyruvate dehydrogenase kinase inactivates pyruvate dehydrogenase by phosphorylation. By downregulating the activity of pyruvate dehydrogenase, pyruvate dehydrogenase kinase decreases the oxidation of pyruvate in mitochondria and increases the conversion of pyruvate to lactate

in the cytosol.

The opposite action of pyruvate dehydrogenase kinase, namely the dephosphorylation and activation of pyruvate dehydrogenase, is catalyzed by pyruvate dehydrogenase phosphatase.

Dichloroacetate is a pyruvate analogue which inhibits pyruvate dehydrogenase kinase and thus facilitates entry of pyruvate into the mitochondrial tricarboxylic acid cycle. This inhibition is hypothesized to translate into anticancer activity.

The information on this slide pertains to the sodium salt of dichloroacetate but is likely relevant to other salts as well. Dichloroacetate bioavailability in healthy human volunteers varied widely, from 27 to 100 percent.

Dichloroacetate is dehalogenated by an enzyme abbreviated as GSTz1 MAAI in the liver to monochloroacetate and glyoxylate. There are four human polymorphisms of GSTz1 MAAI, one of which has a 10-fold higher binding affinity for dichloroacetate than the others.

After single infusions in healthy volunteers, peak serum concentrations of dichloroacetate were dose proportional up to 30 milligrams per kilogram after which clearance decreased, likely due to inhibition of GSTz1 MAAI by dichloroacetate leading to drug accumulation. Plasma dichloroacetate clearance is markedly decreased in patients with cirrhosis.

Dichloroacetate is a byproduct of water that has been disinfected with chlorine. Dichloroacetate is also a metabolite of the environmental contaminant, trichloroethylene.

Because of its presence in the environment, the U.S. Environmental Protection Agency conducted carcinogenicity studies in mice, and these showed dichloroacetate to be a hepatic carcinogen.

The safety of dichloroacetate, based on both nonclinical and clinical studies, is of concern. Nonclinical studies showed dichloroacetate to be potentially toxic to multiple organs, as well as carcinogenic. It also decreased fertility in rats.

In clinical studies, toxicity primarily

involved the central nervous system. A final safety concern is that dichloroacetate exhibits significant interindividual variation in absorption and excretion and thus accumulates over time, complicating both dosing and the management of any toxic effects. FDA is aware of one study being closed due to safety concerns and patient deaths.

Three phase 1 clinical trials evaluating dichloroacetate have been published and are summarized on this slide. Kaufmann randomized 30 patients with mitochondrial encephalopathy lactic acid and stroke-like episodes, a condition known as MELAS to dichloroacetate 25 milligrams per day versus placebo.

The trial had a crossover design and the primary outcome measure was an assessment of neurologic, neurophysiological, and daily living function. The trial was terminated early because of a high rate of patient discontinuation due to sensory and peripheral neuropathy.

Chu performed a dose escalation trial of dichloroacetate in 24 patients with advanced solid

tumors. The starting dose was 6.25 milligrams BID, and the highest dose administered was 12.5 milligrams BID. Toxicities included fatigue, nausea, vomiting, diarrhea, and neuropathy. The recommended phase 2 dose was 6.25 milligrams twice daily.

Dunbar studied dichloroacetate in 15 adults with recurrent high-grade glioma or brain metastases from a primary cancer outside the central nervous system.

Dosing was based on haplotyte variation in the GSTz1 MAAI alleles. Two patients experienced paresthesias requiring dose modification.

In ongoing and published clinical trials of dichloroacetate, no tumor responses have been reported to date. FDA-approved products are available for the treatment of many forms of cancer.

Insufficient information is available to determine how long dichloroacetate has been used in compounding.

In summary, dichloroacetate is chemically an

easily characterized small molecule that is stable in solid forms suitable for oral administration only at lower temperatures and is unlikely to be stable in an injectable form.

Safety concerns reported in clinical trials of dichloroacetate include peripheral neuropathy and gastrointestinal symptoms. Dichloroacetate exhibits significant interindividual variation, and absorption, and excretion, and accumulates over time.

In published clinical trials of dichloroacetate in patients with cancer, no objective tumor responses were reported. We did not find evidence of ongoing compounding of dichloroacetate other than for investigational use.

Based on a balancing of the four criteria articulated in the Federal Register, we find that dichloroacetate is not a suitable substance for compounding under Section 503A of the Food, Drug and Cosmetic Act.

Clarifying Questions from the Committee

DR. VENITZ: Thank you.

Any questions? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. You showed an evaluation of safety from three clinical trials. The efficacy of all of those trials is not given. Were there no responders or how was that assessed?

DR. BRAVE: That's correct. There were no clinical responders, and the trials were early-phase trials that were not designed to assess efficacy. They were designed to find the dose and establish and collect preliminary safety signals.

DR. VENITZ: Then can I follow up on the dose? In those three studies that Dr. DiGiovanna was referring to, you have doses ranging from 25 milligrams per kilogram to 6.25 milligrams. What was the rationale? I mean those are huge differences between doses. What was the rationale as far as you can tell?

DR. BRAVE: I don't know. They were typically in dose-finding studies. By nature of the design of the study, the dose varies widely. I mean, a wide range of doses is studied.

DR. VENITZ: But you also have a pharmacokinetic study on one of your previous slides where they gave 30 milligrams per kilogram infusions. So is there any rationale, anything that you could decipher from the literature how those doses were selected?

DR. BRAVE: No.

DR. VENITZ: Okay. Thank you.

Dr. Vaida?

DR. VAIDA: You just asked my question. Thank you.

DR. VENITZ: Dr. Carome?

DR. CAROME: I have the same question I asked about the last drug. Does the safety data that you reviewed raise significant safety risk concerns?

DR. BRAVE: Yes, it does.

DR. VENITZ: Yes, Dr. Wall?

DR. WALL: You spoke that it's unlikely to be stable as an injectable solution. What happens when it becomes unstable?

DR. BRAVE: I'd have to defer to my

chemistry colleagues for that.

DR. VENITZ: Please introduce yourself for the record.

DR. ZHANG: My name is Ben Zhang. In this scenario, in aqueous solutions, it's likely to hydrolyze and degradation to acetic acid and other degradants.

DR. VENITZ: Thank you. Any other clarifying questions for Dr. Brave?

(No response.)

DR. VENITZ: I see none. Thank you, Dr. Brave.

Then let's proceed with the nominator's presentation. We have one presentation on sodium dichloroacetate and that is Dr. Anderson, please.

Presentation - Paul Anderson

DR. ANDERSON: Thank you again. Current use, some of these were already mentioned.

I did want to bring up that, in addition to the dose escalation and dosing studies mentioned, between 2010 and 2016, there are human case reports and trials that I will just show the citations for

and we can look at them briefly.

The newest is this one from Lemmo, et al., and it's a case study, prolonged survival. The next is from Chu, a 2015 dose-escalation study, then Dunbar. The next is Khan, and this is a three-case series that showed stability of advanced disease in advanced cancer. The next is Strum, and this one, I believe, was mentioned earlier, but it was talking about complete response with NHL.

Another one from similar authors was in a different patient after progression with the standard of care. The next is another one from Khan, a colleague in Toronto using DCA for remission in metastatic renal squamous cell.

Then going backwards in time, the first one that Khan published was use of oral DCA in the palliation of pain arising from differentiated carcinoma. Then we have another NHL and then thyroid carcinoma. So those are human case reports. They're not large scale trials, but they are published.

I have some other experience that I'll share

at the end. The other is papers that show recent use for the scientific basis of DCA as having a potential unique role in the therapy of advanced cancer.

Also, as was mentioned earlier, it has been studied some because of its mechanism of action in metabolic illness as well. These are some current research looking more into the basic science of the drug.

With regard to safety -- this was very well talked about already by Dr. Brave -- the biggest concern really has been peripheral neuropathy and that is believed to be related to the metabolism through the GST-zeta pathway.

The potential for this was seen early. The other paper that neither of us mentioned was a case series from Michaelis which is where some of the earlier ideas about dosing came from, and I apologize for not putting that one in.

That was from, I believe, McGill, where they looked at GBM patients with DCA. They did see in that particular study the most common reason for

complaint was peripheral neuropathy.

That particular paper led our group to develop protocols that would -- in the beginning, they were theoretical as far as protecting the peripheral nervous system during the treatment with dichloroacetate.

What we found was that if we paired the dichloroacetate therapy along with neuroprotective nutrients that we did not experience -- patients did not experience peripheral neuropathy.

At this point, my group has administered over 10,000 doses of dichloroacetate. Those have been both oral and intravenous, and I'll talk about that coming up a little bit later.

Additionally, our Canadian research colleagues have administered the same amount, and we've had no high-grade adverse events. In our particular clinical area in the U.S., we have not had any peripheral neuropathy by using the neuropathy abatement protocol. In Canada, we don't have updated data, but they have very, very low incidence at this point.

Alternatives, again, in this case, we're looking at much like the cases that I showed the citations for earlier. In this case, we're looking at advanced cancers usually that have failed all standard therapy.

There is, as yet part of our group, an ongoing case series that is not published because it is still ongoing. The criteria are that the patient has to have failed all therapy, and they have to be cleared by their oncologist as failed therapy and no evidence of current standard of care that would work.

In that particular case series, it is not limited to one cancer type. It is limited to complete failure of therapy, and so I'll talk about those coming up.

The problem that we see is, with an alternative to dichloroacetate, there really are very few things that work like it does; 3 bromopyruvate and 2 deoxyglucose, two experimental agents work similarly but not the same. So as far as a mechanistic alternative, it

does not exist.

Although this was disagreed with earlier, I'll make the point that I believe this should be administered only by trained and qualified practitioners because there are, like all drugs, safety issues with it.

I believe that inclusion keeps it in that ballpark, as opposed to people sourcing it from the internet, et cetera.

In the cases that we have so far, in the non-responder groups, what we look at then other than survival, as I mentioned earlier in those groups, are whether they get progression of disease at the same rate or similar rate to when they fail their standard therapy. So these are patients who come and fail standard therapy.

There are too many for me to recount, and I know I only had 10 minutes, so I didn't bring summary slides on each patient. But essentially, our metrics with those patients are whatever objective data that they had that we were following to follow their evidence of disease or progression.

And it was usually a combination of imaging, sometimes laboratory markers such as peripheral blast, and blast crises, and other things such as protein spikes and multiple myeloma.

In a great deal of the cases, so far what we are seeing is that we have had arrest of progression or, in some cases, regression of disease on imaging as we move forward. In the first trial, this was developed as a salvage therapy, so the patient had to, as I said, fail all standard of care. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Anderson.

Any questions? Dr. Wall?

DR. WALL: I have three questions. One, you talked about appropriate dose. How do you determine the appropriate dose? What is it that you were looking at to get to an appropriate dose?

You said then you used over 10,000 doses. How many doses to a therapy, for a person's therapy? I mean, is it like for a month? Is it forever and ever? What determines that therapy?

And then after those, I'll ask the last one.

DR. ANDERSON: Okay. Thank you. So to the first question, early when we were determining dose, we had just, at the time, the Michaelis paper, which predates the papers that were presented earlier.

Because it was done in a human cohort with GBMs, we based our initial dosing upon that and then in collaboration with our colleagues in Canada, who are also using the dichloroacetate.

The dose ranges were slightly different from the other papers that were shown earlier. The oral dosing was between 15 and 25 milligrams per kilogram BID on a rotating schedule. The rotating schedule was for 14 days on and 7 days off to avoid bioaccumulation.

In the intravenous form, actually, the dosing was higher, but the frequency was lower. In the intravenous form, the dosing was between 50 and 80 milligrams per kilogram, and that was done twice a week for 2 weeks on and 4 weeks off, so the dosing was quite different than the oral dosing.

As I said, the prophylactic measurements for preventing the peripheral neuropathy, et cetera, were postulated in the beginning, but we didn't do any of this without doing that. We have not experienced the peripheral neuropathy.

As far as duration of treatment, in the group that is managed through our center -- and I say that because the other centers have different groups going on -- most of ours are with the salvage therapy, so they failed all other types of treatment. In most of the cases, it has been ongoing dosing on those rotations over the course of the remainder of the person's life.

The third?

DR. WALL: The third question is we've heard that it is unstable. It breaks down to acetic acid. How do you know that the IV product you are giving them is not broken down?

DR. ANDERSON: Yes, that's an excellent question. We have worked with three different sterile compounding pharmacies that have done assays.

As part of our protocol, we use the pharmacy that is in closest proximity to us which is in the same city for all of our product, and we have a very short use date, which fits the stability that was measured.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Yes. I just want to preface that I'm speaking here as part of regulated industry.

It sounds to me that what you're describing here is an experimental compound. I'm very comfortable with you conducting human experiments with an experimental drug under an IND with proper informed consent.

That's really the construct that we all live in in regulated industry. I can't take a compound and just do experimentation on people with a compound that I might find on a shelf. I have to get an IND. We have to identify the potential risks. We have to inform patients of those potential risks.

It's a regulated environment when we do

these experiments. We have to inform the FDA about safety matters that come up. We have to first ask the FDA's permission essentially under an IND to do these studies. Of course, we have to -- all of these studies are also under the auspices of IRBs.

So I have no problem with your doing that, and I think that that's what you've described this molecule is.

Certainly, the other problem I would just point out is if we have molecules like this and we put them on a list, that basically says that we have two standards for molecules that can be used in human experimentation.

Really, as an industry, I think that's not the right way to go forward.

DR. VENITZ: Do you want to comment?

DR. ANDERSON: Just to the point, we did have IRB approval and complete informed consent.

DR. VENITZ: Dr. Carome?

DR. CAROME: You had mentioned some degree of NIH involvement or support for the two studies you mentioned, CUSIOS, that's the ongoing one, I

guess. Is that true? Is that NIH funding?

DR. ANDERSON: The two are two different funding streams. The NIH was involved in the first one, and the CUSIOS is a Canadian-funded study, so yes.

DR. VENITZ: Dr. Pham?

DR. PHAM: So I feel like this could be similar to the quinacrine conversation we've had previously. Are you familiar with the treatment IND or intermediate-size population IND options?

DR. ANDERSON: I couldn't hear the first half of what you said, sorry.

DR. PHAM: Sorry. I will speak into this. I just think that in a former PCAC meeting that I'm not sure you would have been aware of, there was a similar conversation, I think, related to going beyond expanded access or single-patient, the intermediate-size, or the treatment IND option.

I wasn't sure if your group was familiar with that or if there were other oncology groups that could potentially go in together on something like a treatment IND?

DR. ANDERSON: No, we were not aware of that intermediate, yes. I would like to --

DR. VENITZ: Can I follow up on Dr. Braunstein's question? In one of your earlier, I think, first two or three slides, you reviewed clinical studies. Right?

DR. ANDERSON: Yes.

DR. VENITZ: Can you go back to those slides?

DR. ANDERSON: Sure.

DR. VENITZ: Because I was wondering, were those phase 1 studies? Just looking at the title, they appear to be. If so, were they done in the United States or with or without FDA oversight right here?

DR. ANDERSON: Yes. So the first one is from Canada, and this is a case report. The second one, I believe, is in the U.S. as an open-label single-arm that I believe was done with FDA oversight. The third one, I am unsure where that originated.

DR. VENITZ: Okay. I think those were the

ones that I was -- yes.

DR. ANDERSON: Those were the ones that you were -- yes.

DR. VENITZ: So two of those are labeled as phase 1 studies. How can you do a phase 1 study without an IND? I think that's what your comment was, and I had the same question.

DR. ANDERSON: I believe that both of them did. So I was not involved in neither one of these, but --

DR. VENITZ: So this compound has -- somebody has an IND on this compound --

DR. ANDERSON: I believe so.

DR. VENITZ: -- an investigational IND?

DR. ANDERSON: Right.

DR. VENITZ: So let me then turn around and look at my FDA colleagues. How does that affect then putting it or not putting it on the 503A list? It's not an approved product, but it's a product that is being studied under an IND.

DR. DiGIOVANNA: Yes. This is John DiGiovanna. The Chu study apparently was done at

the University of Alberta, Department of Medical Oncology. That's one of the studies that was mentioned.

As the FDA presentation suggested, they did not find any responses, but the end of their abstract for their publication says, "Toxicities will require careful monitoring in future trials." So they did have, as the FDA presented, some various toxicity issues.

So I think some of what's been presented have been studies done in different places that have been published. And those, I think are the three that the FDA presented. Some of these others may just be case reports.

DR. VENITZ: But what about the fact that there are studies going on, phase 1 studies going on with an IND on this product while we are considering it as putting or not putting on the 503A list?

MS. BORMEL: That's an entirely separate point. If something is nominated for the 503A bulks list and the committee recommends and the FDA

ultimately puts it on the list, that could be used irrespective of whether there's an IND. I mean, anybody could -- any compounder could use it.

Under the IND, there are safeguards in place. There's informed consent; there's the IRB; there's different other standards that have to be met in order for that product to be used.

I mean, they're very separate concepts. There are no safeguards. They are not the same safeguards that are present under an IND under a drug that's put on a 503A bulk list.

DR. VENITZ: Thank you. I think we had another question. Dr. Carome?

DR. CAROME: Mike Carome, again. In looking at the description of the CUSIOS study on ClinicalTrials.gov, it characterized it as a prospective observational study.

The way that I read the description, it sounds like the interventions that are given to the patients who are in the study are sort of just chosen by the practitioner. It doesn't appear to me any standardization of the agent selected, the

dosing, the duration. Am I reading this accurately?

DR. ANDERSON: Partially. The prospective nature is supposed to allow each of the seven centers to treat the patients as they come in, as they normally would in an integrative oncology setting. Under that banner then are whatever therapies they would be using prior to that or know of prior to that that they would have employed in a non-study setting with their patients.

You would potentially have a patient with the first type of cancer who would have a protocol driven, so there would be dose duration. All of that would be preset, but it would be chosen by the clinician group at that particular site. Then they would be followed.

Then the second patient, if the clinician group decided that that particular therapy group that the first patient got was not appropriate, the second patient would get different therapy. It's following them in survival over that time with known therapies.

DR. VENITZ: Okay. Any other clarifying questions for Dr. Anderson? Yes, Ms. Davidson?

MS. DAVIDSON: I believe Dr. Brave characterized this as an EPA-established carcinogen. In the 10,000 doses you've worked with over the years, did you have a protocol for handling for the preparers of the drug or do you have any concerns about worker exposure to this chemical?

DR. ANDERSON: Good question. As far as the preparers and those compounding the intravenous product which would be the ones that would be exposed in our center -- those compounding the oral product would be exposed at the pharmacy level -- we use the safety protocols for personnel that the pharmacy developed and use the same ones in the center for those who are handling it for IV use.

Was there a second question? Sorry.

MS. DAVIDSON: Just to clarify that your workers knew that it was an established carcinogen when they were handling it.

DR. ANDERSON: Right. Yes. Yes.

DR. VENITZ: Dr. Gulur?

DR. GULUR: You mentioned that you do have an informed consent process. What do you consent -- what do you make your patients aware of with regard to this drug, and what alternative strategies are offered to that patient?

DR. ANDERSON: In the case of our center where the only group that were allowed to be availed of the drug were non-responders, complete nonresponders, the alternative was essentially other palliative care, and they were consented.

They were consented. They were consented on a number of levels, but they were consented specifically for the dichloroacetate as to the propensity for peripheral neuropathy, et cetera, so the standard things that are in the data that was shown earlier by my colleague. They were made aware of all of that, and there were about four layers of informed consent before they got to drug consent.

Committee Discussion and Vote

DR. VENITZ: Thank you, Dr. Anderson.

Now, we have on our schedule another open hearing, but we don't have any speakers, so we're going to move right into our discussion. So I'm opening the floor for any comments, discussions, contribution. Dr. Braunstein?

DR. BRAUNSTEIN: I just want to point out to the committee, I mean, I can speak from personal history that in industry, we develop drugs.

Early in development, especially in drugs in cancer patients for cancer, we do studies in patients, I guess, similar to the kinds that we're hearing here. These are patients who failed all other treatments. Each one is a heartbreaking case, of course, is a heartbreaking story. And we do these initial studies under an IND with informed consent, and under FDA oversight, and IRB oversight.

Every now and then, you find a drug that after studying the drug in maybe, I don't know, 25, 30 people, maybe a handful of them might respond. Even before we do this, we have a lot of data in animals that would support trying this new agent in

people.

If we get some data in a couple of patients, maybe, maybe we'll go on to phase 2 and try and demonstrate that, but we wouldn't come to FDA or to a committee like this and ask for license to start selling the drug to patients.

I mean it's not from -- and if we start allowing that, then we really have a system that's broken because it exposes patients to basically an unregulated substance on the one hand.

The patients aren't necessarily sophisticated enough to distinguish between what is a regulated substance and this type of an unregulated substance.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. I think you raise an important issue which -- I believe over the prior meetings, the FDA has been attempting to educate the committee and those of us that by placing these various medications on the list to be able to be compounded or not be able to be compounded, what happens subsequently may be

beyond our expectation.

I think, as you are implying, it's a value for us to consider; for example, populations who may be wanting medications for untreatable conditions or conditions with an unexpected soon mortality, where if the medications are potentially dangerous, it poses a risk.

I think in those situations, we need to be cognizant that studying those medications under an IND permits their efficacy to be identified and their toxicities to be characterized. And I think that's something we need to be cognizant about.

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

DR. WALL: What we keep running into is that -- the origins of medicine was that it was all compounded, it was all experimental, it was tried, and see what's going to happen.

The question is, has science moved to the point of where we -- and actually, safety moved to the point where we need to totally stop that practice or is there still a need for that practice in certain circumstances? I think that's a

question I keep running up into.

When it comes to this product, we're dealing with this really vulnerable population. I really think it needs to be studied. These are generally, at least in my mind, not emergencies. You watch that they've been failing, and you plan, and you work on what needs to happen.

You create those protocols, which are prolific in the cancer communities, to deal with it. But I really think with are running into this conflict of cultures almost, in a way, of what we have done which has not been bad, and it has brought us to where we are to where we need to go.

DR. VENITZ: Dr. Pham?

DR. PHAM: I think that goes back to why I previously asked the question about the treatment IND or the intermediate size because, previously, in discussions, we've also talked about the challenges and resources needed for the single patient or previously known as compassionate-use IND or expanded access IND. We're going to hear more about that.

I still think that there needs to be a lot broader education about what this intermediate-size one is, this treatment IND, because quinacrine -- previously, we talked about there being a group, more than just one specific practitioner group, that had vested interest in seeing that product still available.

Going back to some of these phase 1, phase 2 studies and dose-finding, if we can get those that have vested interests to study it as one specific dose and route of administration and have that group be able to standardize in the treatment IND, you will generate the standard protocol that then increases the available information for that specific dose, that specific frequency, that specific route of administration, and all the safety and efficacy that goes with that protocol.

I think it goes to the point you were saying, that if we keep encouraging this access to the treatment IND programs, hopefully, it will generate the information that Dr. DiGiovanna says is lacking for this vulnerable population.

But it creates a way to actually standardize it and have like this community of collaboration across the different groups. Like in this specific case, it will obviously come from the oncology practitioners. They all are going to be looking at it for this patient population, but hopefully even a specific indication.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: I just want to state on the record that this is very different than quinacrine. Quinacrine is a substance that has been widely used. It's considered a standard of care.

It's a substance whose safety is well-characterized. Actually, it was an approved drug for many years.

This is an experimental drug, essentially, about which we know very little. So this would not, in my mind -- I mean, we'll let the FDA talk about it, but in my thinking about it, this is not an expanded access type of drug.

An expanded access type of drug is for drugs where there's reasonably good evidence for safety

and efficacy, perhaps the need to have some kind of informed consent because there are some risks that's not -- no drug is completely safe. I think that was the FDA's position before and that makes sense. But this is in my mind a very different situation.

DR. VENITZ: Dr. Pham?

DR. PHAM: I think I appreciate that that this obviously is of much more limited use and more experimental. I feel like it's the compromise to saying making it accessible in the 503A list is obviously going to be a higher issue for access and safety, whereas if there is a mechanism for those that want to still be able to study it in a cohort, at least it's available through a different mechanism than placing it on the list.

I agree with you that I think it's not as widely used and does not have the history established data that quinacrine did, but in terms of using it as the intermediate-size population, you're allowing it to being used more than just the single-patient emergent IND program.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. I think if you were going to engage in studies under an IND for this product, I think you'd want to do studies that are more rigorous than the ones I've heard described that are currently being conducted.

DR. VENITZ: Any further comments? So are you ready to proceed? Dr. Jungman?

MS. JUNGMAN: I'm just going to jump in just for a second. What I think is the theme of this conversation is that we want to be careful that we're not undermining the FDA approval process. We are constantly bemoaning on this committee the lack of data that we're having to work with.

I think this is a good example of a substance where we really want to see not just the patient protections, which are, of course, important of the IND and the informed consent, but also that ability to standardize protocols and to gather good data.

DR. VENITZ: Anybody else?

(No response.)

DR. VENITZ: Okay. Then let's proceed with the vote. If you vote no, you're 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.

What we are voting right now, as you can see on the screen, whether dichloroacetate should be placed on the list, yes or no?

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

(Vote taken.)

DR. HONG: Question 3, zero yes, 11 nos, and zero abstain.

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

DR. WALL: Donna Wall. I voted no because I think it really needs to be under a study. We are,

again, dealing with an extremely vulnerable population. I believe there is time that it should be studied and patients know that they are getting good effective medicine.

DR. CAROME: Mike Carome. I voted no. I think there are serious significant safety risks with this drug. There's a complete lack of evidence that it's effective.

Like the last one, I would urge the FDA to, again, immediately place this drug on the Category 2 list of drugs under the interim guidance and not allow it to be compounded because it raises significant safety risks.

DR. VAIDA: Allen Vaida. I voted no for the same reasons. Basically, for the discussion that we did have, this is a drug that needs well-controlled trials.

DR. PHAM: Katherine Pham. I voted no. I was concerned by the instability as an injectable product and also the toxicities with the oral product, particularly the peripheral neuropathy, the fact that a safe and effective dose has not yet

been determined but potentially IND options could help provide some more of that data.

MS. JUNGMAN: Elizabeth Jungman. I voted no because of the significance of the safety concerns, the lack of effectiveness data, and the vulnerability of the population.

DR. HOAG: Steve Hoag. I voted no, and I was worried about the formulations, the stability, the safety. And I agree with many of the comments said previously.

MR. HUMPHREY: William Humphrey. I voted not for many of the same reasons. I'm also concerned about the fact that it has to be genetically dosed. And I'm not sure if we put it on this list that everyone that would use it would have that capacity.

MS. DAVIDSON: Gigi Davidson. I voted no for many of the reasons stated and additionally because of concerns about worker exposure to a potential carcinogen.

DR. VENITZ: Jurgen Venitz. I voted no for basically the same reasons that have already been

stated.

DR. GULUR: Padma Gulur. I voted no for the same reasons, stability data, safety, effectiveness, and would support the comment earlier regarding the scientific rigor in any study design, and the need for established protocols.

DR. DiGIOVANNA: I'm John DiGiovanna. I voted no for all the reasons that have been mentioned.

Adjournment

DR. VENITZ: Thank you. That concludes our discussion of dichloroacetate. We are now going to take an early break. No nap time because we won't get together again until 1:00, so let me read you the official language.

We will now break for lunch, and we will reconvene again in this room at 1:00 p.m. Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break.

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

lunch amongst yourselves, FDA, or with any member of the audience. Thank you, and see you at 1:00.

(Whereupon, at 11:17 a.m., the morning session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Thursday, June 23, 2016

1:00 p.m. to 5:08 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

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Padma Gulur, MD

Professor, Department of Anesthesiology and

Perioperative Care

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Allen J. Vaida, BSc, PharmD, FASHP
Executive Vice President
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Horsham, Pennsylvania

Jurgen Venitz, MD, PhD

(Chairperson)

Associate Professor, Virginia Commonwealth University

School of Pharmacy, Department of Pharmaceutics

Richmond, Virginia

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING DRUGS ADVISORY COMMITTEE

INDUSTRY REPRESENTATIVE 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)

Jeffrey Brent, MD, PhD

(Participation in DMPS discussion)

Distinguished Clinical Professor of Medicine

University of Colorado School of Medicine and

Colorado School of Public Health

Denver, Colorado

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

(1:00 p.m.)

DR. VENITZ: Let's reconvene our meeting, please. Welcome to the afternoon session of the PCAC. We're now going to take a little detour, getting information on expanded access programs. We'll have Dr. Jarow present on expanded access to investigation of new drugs.

Dr. Jarow?

Presentation – Jonathan Jarow

DR. JAROW: Good afternoon, everyone. I'm back, for those of you who were at the last Compounding Advisory Committee meeting.

It was felt, after the last session and the questions that came up, that it'd be worthwhile to give an expanded-access IND-for-dummies talk to answer a lot of the outstanding questions that exist.

Although I wasn't here this morning, I was at another meeting, I understand that a lot of these issues came up again today.

So here's a summary of potential questions

that people might ask about this process, and I'll give you the short answers here. And then hopefully, you have a copy of my slides because, at the end, there's two slides with resources that you go to for much more in-depth information.

But question number 1, is there a model for expanded access to an unapproved drug or a formerly compounded drug? And the answer is yes.

The best, the only existent model for something like that right now is domperidone, which recent had the protocol and materials posted online for people to access, but that's in single-patient INDs.

I don't think that's necessarily the best model for all situations. And the one that I'm going to put forward today is something called an intermediate-sized access IND. So yes, there is a model.

Can the sponsor charge patients for the costs incurred, as well as the drug? And the answer is yes. Can administrative costs be passed on? The answer to that is yes.

Who can serve as the sponsor of the IND? It could be a manufacturer. It could be individual physicians or other groups, and we'll get into some details later on.

How is the drug dispensed? The sponsor dispenses the drug directly or through an investigator.

Are multiple courses of treatment possible? The answer to this is also yes, provided applicable requirements are met. This would be part of the protocol.

I learned through practice talk internally at FDA -- for those of you who have participated in or run a multicenter clinical trial, this is simple stuff, very routine and easy.

For those of you who never done this, it probably seems very opaque and problematic. I'm going to try and clarify this, but I'll also want to say -- and it's going to come up again -- talk to us. Talk to us. We are here to help.

So what are the eligibility criteria for an expanded access protocol? One, the indication has

to be a serious or immediately life-threatening condition. There has to be no comparable or satisfactory alternative therapy.

The potential patient benefit justifies the potential risk, and the risks are not unreasonable in the context of the disease or condition to be treated, and it's providing the drug will not interfere with ongoing clinical investigations that could support marketing approval of the expanded access use of that drug.

There are multiple types of expanded access. Expanded access is basically access to an unapproved drug, which we're going to call an investigational drug, outside of the clinical trial setting.

This is not for research, although frequently the information gathered from expanded access protocols may be used as part of an application. But in general, the intention is, in expanded access, to treat patients.

It could be submitted as a freestanding IND or a protocol under an existing IND. They come in

three flavors; single-patient, which would include both emergency and non-emergency use, intermediate size patient population, and a treatment protocol or IND, which is for more widespread use.

For an intermediate-sized access IND, the application must state whether the drug is being developed for marketing.

The treatment protocols for INDs are typically those drugs where there's an application about to be submitted to the FDA. It's in the final phase of development and it's usually used to bridge the gap between completion of phase 3 trials and marketing approval.

An advantage of the intermediate-sized access IND is that many healthcare providers treating patients with investigational drug under a single IND sharing an IRB, a protocol, and a consent form.

There would be a single sponsor of this IND, and then there would be subinvestigators, which would be the healthcare providers that had individual or more than individual patients that

they were treating with the drug.

The key components to putting together an IND application is identify a sponsor and principal investigator, and they can be the same person; write a protocol and informed consent; create an investigator brochure, so you need labeling for the drug product, and there's guidance on how to do that on ICH E6; and identify a manufacturer.

One of the key components of this -- and we're going to have a switch in terms for you here at the compounding AC -- is that if it was a formerly compounded drug and you're in an IND setting, you are no longer compounding the drug.

The organization or manufacturer that's making the drug is called a manufacturer now, not a compounder, but it can be one and the same.

If you need help getting started with this because this is all unfamiliar stuff, you need to contact the review division in the Office of New Drugs that will be receiving the application. The division within the Office of New Drugs is identified based on the indication.

For example, if it was an indication for reproductive stuff, it would go to what's called DBRUP, Bone, Reproductive, and Urologic Products. If it was for lupus, or arthritis, or something like that, it would go to DPARP, which is the division that reviews rheumatology.

You may not know which division or the telephone number of that division to contact if you've never been through this process before, so there are other avenues to gain access.

One is to contact the Division of Drug Information in CDER, and I've provided their phone numbers and email address. If you're a physician in the office and you call, you're likely to get an answering machine, and they actually -- I did an experiment -- call back pretty promptly, but you'll probably be on to your next patient and not be at the phone, so it'd probably be wisest to email.

The other option is to call the Office of Health and Constituent Affairs. We have a representative here in the room from that office, and they are extremely helpful.

We also recommend, in any of these communications if possible, that you copy the CDER compounding team who can also help facilitate your navigation throughout the bureaucratic structure of FDA.

One of the things you're going to want to do, and you can do this more than once, is have something called a pre-IND meeting with the people in the review division.

This is not required, but it is extremely helpful, particularly if you're never done this before and so it's strongly recommended.

You will need to submit some stuff in advance to the meeting. You would need background information on what your plan is and then specific questions, and these could be about the chemistry and manufacturing controls, what kind of documentation you need regarding the safety of that drug, and whether your protocol looks good or has any deficiencies in it.

This meeting can take place face-to-face, by telephone or written responses only. I would

strongly suggest that you take one of the first two options. Written responses only are great if you know what you're doing, and you have a specific question, and you'll understand the answer in FDA jargon. However, if you need a lot of back and forth, a face-to-face meeting or teleconference is much better.

So what goes into an IND submission? You need to have a qualified investigator, and that includes the subinvestigators. That's done by submitting their curriculum vitae or resume.

You need product information. If you're having a single manufacturing site, it would just be for that site. If you have multiple, it would be for multiple sites.

It would require information regarding purity, strength, quality, stability, and how you're going to distribute the drug product.

You need information regarding safety. And formerly, frequently for a new molecular entity, that's all nonclinical research. Clinical information trumps nonclinical and so for a

formerly compounded drug, you will have literature that you could point to and provide a great deal of safety information.

You also need some efficacy for the rationale for the intended use of the drug and at least preliminary clinical evidence of effectiveness.

For instance, quinacrine, which was discussed at the last advisory committee, you would have the literature, again, to point to in terms of efficacy and safety.

Then you need a protocol. Now, for a regular IND, for non-expanded access, this is a research protocol. We're going to take 300 patients. We're going to randomize them 1 to 1 to a drug and a placebo. We're going to have these office visits to monitor them. We're going to give them this dose. We have these monitoring plans in place. We'll be checking their hemoglobin and liver function tests every three months or whatever, the whole plan.

You do the same thing for an

intermediate-sized treatment protocol, except there wouldn't be the randomization, et cetera. You would describe, in this protocol, how each of the subinvestigators should manage their patients that are on this drug. It would be basically a best practice, a guideline basically, on how to manage that disease with this drug.

It would have the proposed method of administration of the drug, the dose, the duration, eligibility criteria, clinical procedures, and monitoring to evaluate effects and minimize risk.

Informed consent with IRB approval would be required, a statement about product development, so that's the one I referred to earlier. You could essentially say it is not being developed. And then the investigator brochure, which I referred to earlier as well -- and you can get guidance on how to prepare one of those from ICH E6.

With an IND comes some regulatory responsibilities. Number one, you cannot begin treatment of patients for 30 days unless you receive notification from FDA sooner than that.

If you receive no notification that it's on hold, you can proceed at 30 days even if you have not heard back from FDA. You also need IRB approval, of course.

During the course of the treatment of these patients, IND safety reports should be submitted if there are any serious unexpected, suspected adverse reactions and annual reports as well.

You will have to notify FDA of any new subinvestigators that are added on. So as a doctor in another location learns about this intermediate-sized protocol and contacts the principal investigator and says, I have a patient I'd like to treat, and they meet the criteria, they can be added on as a subinvestigator. You would then have to submit their CV to the FDA.

You also have to notify FDA of any product manufacturing or changes in distribution. In addition, if you're charging, there is an annual renewal of charging authorization.

What are the rules on charging? They are different for the different types of expanded

access INDs. There's a guidance that was recently published on this, so you could refer to that. Again, that's in the back of your slides.

You have to, one, provide reasonable assurance to FDA that charging will not interfere with drug development and so again, if you're saying it's not being developed, that's an easy thing to satisfy; provide documentation of the calculated amount that you're charging the patient; and provide a statement from an independent certified public accountant that they've reviewed this and approved the calculation.

You can recover direct drug costs and so that has implication as to who the sponsor is. If the sponsor is the manufacturer, you can recoup the direct costs of making the drug. If someone else is the sponsor, then they recoup the cost of purchasing the drug.

You can recover costs of monitoring, IND reporting requirements, and other administrative costs directly associated with expanded access use.

You can also hire a third-party

administrator or CROs, as we affectionately call them, to recover fees. They could hire them and then recover the fees that were involved with that.

So these are the resources that I kept on mentioning as to where you can find these forms and these guidances. And thank you. I think we now open it up for clarifying questions if I'm not mistaken.

Clarifying Questions from the Committee

DR. VENITZ: Yes. Thank you, Dr. Jarow.

Any clarifying questions? Dr. Braunstein?

DR. BRAUNSTEIN: Hi. Ned Braunstein, I'm the industry rep, and thanks for the talk. This is stuff we do all the time in industry, but some people around the table don't do all this. It's good to have this.

I have one question though. For the nonprofessionals who are going to be interacting, will you accept paper INDs, or does everything have to be electronic?

DR. JAROW: Emily, do you know when that goes into effect that everything has to be

electronic? It currently isn't, I don't think.

MS. GEBBIA: Yes. I don't know off the top of my head. I don't know, Rich, if you know when the electronic requirements go into effect. We can look into that, and it would be certainly something that could be raised when you contact FDA for a pre-IND meeting.

DR. JAROW: Pre-IND meeting, yes, absolutely. Right now, I don't think it's a requirement. It's much preferred by the review division. So if you want a happy review division, please send it electronically.

Any other questions? Yes?

DR. DiGIOVANNA: Yes, John DiGiovanna. It's very helpful to see all of this. However, to an individual investigator, it appears equivalent to establishing a pharmaceutical company.

Going through my quick review of the -- I guess what caught my eye first was the investigator brochure which sounds like the IRS 1040 form, which begins to get quite, quite large when one adds additional things to it.

This ICH E6 is, again, 63 pages of, I guess, rules about how to do this. So what goes into an investigator brochure? I could envision a small group coming together, and finding an IRB, and then a public accountant, and various other specifics that might need to be done.

But that seems to require a lot of information about the compound and other things, so how laborious is that?

DR. JAROW: Exactly. This is why I would strongly urge where you anticipate it's going to be more than a single patient or two or three patients to go the intermediate-size expanded access protocol or IND.

The reason is you only have to do it once. Each physician in different parts of the country wouldn't have to reinvent the wheel, if you will. But it does require, as you point out, two areas of expertise.

One is going to be the manufacturing side, so a current compounder of the drug would likely have all of that information. And then it's also

going to require someone with expertise in that specific disease that's being treated, preferably someone who has some background in clinical trial design and research. Because, for someone with that background, this stuff is not a huge hurdle.

For your average treating physician located in the middle of Nebraska, let's say -- I don't want to pick on Nebraska -- middle of Maryland, this would be a huge hurdle, and they would look at this and say, "I can't do this."

But for someone who's done it multiple times already or been involved in it as a site investigator, this is all pretty familiar stuff, as the industry rep will share with you. But it is intimidating at first.

The guidance that you referred to is 63 pages, but that's not on doing the investigative brochure. That's good clinical practice, which has a lot of stuff in there unrelated to this specific issue.

Having said that, it's just like product labeling. If you looked at -- a package insert, I

think, is the common term for this. It basically contains those key components. What's the indication? What's the safety profile? What's the efficacy data?

It's going to be a lot of this stuff that you're putting into the protocol itself to get the IND opened up. It's not as bad as it sounds, but again, I fully agree with you. For someone who's never done this before, it would seem impossible.

That's why I would not encourage people to do single-patient INDs for this unless they really are just going to treat a single patient, but this would be a mechanism to get it done.

Then once you let the community -- let's say we're talking about quinacrine and lupus. You let the community know that this is out there, and there are ways that you can do that. Then you can have them just join.

DR. DiGIOVANNA: So what you're suggesting then, with respect to quinacrine, is that if there was an organization who is interested in setting up an infrastructure, that that organization could

either be an individual investigator, or perhaps a patient advocacy group, or perhaps a manufacturer of some sort, a compounding pharmacist who then could bring together the expertise to develop the protocol, the investigator brochure, the consent form, the IRB, the other issues, the other necessities that were involve.

If there were costs that were incurred for that, they could be covered, and the medication then could be available to physicians broadly across the US who submit the proper documentation, CV or whatever, to make them quote, unquote, "investigators" in this enterprise.

Then they would not have to have their own IRB; they would use their quote/unquote "central IRB" and consent form, and the drug could then be manufactured, made available if it was intended to do so for only the costs that were necessarily incurred in creating this whole enterprise, and that this didn't have to be done multiple times.

It may have to require each investigator to submit information about toxicities or adverse

events to the one investigator, but it in essence could be done once by a small group and then made available with controls of the toxicities and adverse events submitted back to the FDA.

DR. JAROW: Right. And just to take it a step further -- the industry rep will be familiar with this -- there are large companies like Pfizer -- I don't know your company -- that have all the in-house resources.

Then there are small companies that actually contract a CRO to do all the steps you're talking about; write the investigator brochure, write the protocol, write the informed consent. So they can -- the sponsor can delegate these responsibilities to a third party.

Emily, did you want to clarify anything?

MS. GEBBIA: I just wanted to make one quick point about the individual-patient expanded access. Dr. Jarow is right that it can be burdensome if, each time, you're recreating the wheel.

We've been working really hard to be responsive to people's request for information

about the use. And as he mentioned at the beginning of his presentation, for example for domperidone, there's a packet available online so individual physicians who want to get access to that information can do it and get the proper paperwork.

Once there's an infrastructure in place and under the right circumstances, it's not necessarily having to recreate the wheel each time.

DR. VENITZ: Mr. Mixon?

MR. MIXON: I just wanted to clarify, did you say that a compounder could be the manufacturer?

DR. JAROW: So now, what we would -- everything would be -- so now, a healthcare provider is no longer called that. They're called a subinvestigator. Potentially a compounder is no longer called that. They're not compounding under 503A if it's a drug that's not compounded anymore. So now you're a manufacturer and so that would be the situation.

MR. MIXON: Subject to CGMP?

DR. JAROW: Yes. So you would be subject to CGMP.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Also, to help some of the people, I thought I would like to clarify some things to help with the discussion.

In theory -- and if you could help me on this -- I think, like, a foundation could be the sponsor. And they could designate a CRO to be their agent. Right? And the CRO could then handle all the safety reporting. Right? So that way, an investigator in this case or one of the docs who has a patient would send the information to the CRO.

They'd make sure that it gets handled to FDA on time so that -- like, the Lupus Foundation is not worried about that, right, because that's not their -- you can imagine how some of this stuff could be daunting to a foundation. So a lot of this stuff could be worked out.

Then it's my understanding the sponsor could -- as part of the cost of the drug, these

administrative costs could be included, along with the cost of procuring the drug could be included as the cost to the patient. You'd have to figure out -- you'd need an accountant obviously to figure out how to do this right; would that be all correct.

DR. JAROW: Yes. And I've noticed the reaction in the audience, not by you, at the mention of CGMP. So I also gave a resource, so what would be required would be statutory CGMP, not regulatory CGMP. And that may be a foreign language to you, but the guidance for phase 1 research studies which is the statutory CGMP, will be, is provided.

That's primarily risk-based and it depends upon partly formulation, the vulnerable populations, contaminants. A lot of the requirements potentially could be handled with literature. There's a significant amount of flexibility there as well, but there would be CGMP requirements for an investigational drug under an IND.

DR. BRAUNSTEIN: Sorry. I was asked to explain what is a CRO, a contract research organization. There are lots of these companies and they sell their services.

DR. JAROW: Yes. Right.

DR. BRAUNSTEIN: One other thing just to clarify, you could have more than one manufacturer in the IND, as long as they agreed to some common standards; is that correct?

DR. JAROW: Yes, exactly. They would have to meet the same CGMPs.

DR. VENITZ: Any other clarifying questions?

Dr. Hoag?

DR. HOAG: Could you repeat that again about the regulatory and statutory CGMPs?

DR. JAROW: I'm not an expert on CGMPs, but you can go to the guidance. The regulatory CGMPs are quite extensive, and those are required as you get to phase 3 in IND product development and, of course, are required for marketed drugs.

The statutory CMGs [sic] are less stringent, let's say, or they're different, and you

can -- someone wants to answer it?

Sarah, you want to help bail me out on this?

DR. ROTHMAN: Yes, sure. I'm Sarah Rothman. I'm in CDER, Office of Compliance, in OUDLC. Statutory requirements for GMPs are in Section 501A(2)(b) of the statute, and that's the statutory authority for all of our CGMP regulations that apply to conventional manufacturers, parts 210 and 211.

For anyone conducting a phase 1 study, we understand that it might be smaller scale. You might not have sophisticated manufacturing controls at this point where you're making larger batches of drugs.

We have a regulation. It's 210.2(c), 21 CFR 210.2(c) that says that statutory CGMP requirements apply to phase 1 studies, so you have to comply with CGMP requirements. But the CGMP regulations and parts 210 and 211 do not apply with certain exemptions.

We have a guidance that describes how you can comply with statutory CGMP requirements, and

it's not what you would see in the regulations in parts 210 and 211.

They're much more flexible. They take into account that you might be doing smaller-scale production at this point. And really, if you look through the guidance, it's not what you would see in the regulations.

DR. VENITZ: Thank you.

Dr. Wall? Last question.

DR. WALL: This is my real stupidity showing, but what's the difference between expanded access IND and a regular one?

DR. JAROW: A regular IND is meant for research whereas expanded access is designed for treatment. There are unique settings in which the information needed to approve a drug comes out of expanded access experience. But in general, it's aimed at treating patients and hence the requirements that I described which would not exist for a regular IND.

It doesn't have to be a life-threatening or a serious illness for a regular IND. It doesn't

have to be no-alternative therapies for a regular IND. Those are the differences.

There will be restrictions. So if you have a formerly compounded drug that's not treating a serious or a life-threatening condition, this is not an avenue for that. It would not be eligible.

DR. VENITZ: Okay. Thank you, Dr. Jarow. We appreciate that, and I'm pretty sure we'll see you again.

Now, let's move on to our next order of business in continuing our review of bulk substances, pyruvic acid. The FDA presentation will be given by Dr. Carr. She's a medical officer in the Division of Dermatology and Dental Products.

Presentation - Brenda Carr

DR. CARR: Good afternoon. As stated, I'm Brenda Carr. For the next several minutes, we're going to be discussing pyruvic acid.

I was the clinical reviewer for this substance. Other members of the review team were Ben Zhang, Carmen Booker, Doanh Tran.

Pyruvic acid, 40 to 50 percent, has been

nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for the topical use and the treatment of acne, melasma, and warts.

The next couple of slides will spend time on the physical and chemical characterization of pyruvic acid. Its chemical structure is depicted on this slide.

The substance is soluble in water. It can undergo decarboxylation reactions under both basic and neutral conditions, and it's also sensitive to sunlight. It's unlikely to be stable in ambient environments, and structurally, it's well-characterized.

This reaction presents a current synthetic method. In regard to likely impurities, there would be trace amounts of the starting materials and byproducts, specifically acetic acid and lipoic acid.

In conclusion, pyruvic acid is a well-characterized small molecule. In the proposed

dosage form, it's unlikely to be stable without proper storage, specifically careful sealing, isolation from moisture, and being kept away from light.

We'll move on to discuss the nonclinical assessment of pyruvic acid. It's an intermediate compound created in the metabolism of carbohydrates, proteins, and fats. Its main metabolite is pyruvate, which is a product of glycolysis.

Very few repeat-dose studies have been conducted with pyruvic acid. However, acute studies show that it causes irritation to the skin or corrosion and eye damage.

There's no nonclinical data to evaluate the chronic dermal toxicity of pyruvic acid. There's no information available pertaining to mutagenicity.

Pertaining to developmental and reproductive toxicity, one study found that pyruvate is metabolized during organogenesis and that interruption of this process could lead to neural

tube defects, as well as other developmental toxicities. There is no nonclinical data to evaluate the developmental and reproductive toxicity of this substance.

There's no information available on carcinogenicity. There's no nonclinical data to evaluate the dermal carcinogenicity of pyruvic acid.

Now, we'll move on to the clinical assessment of pyruvic acid, and we'll begin this section of the talk by presenting the safety information.

We found reports of irritation, erythema, stinging, burning, that erythema was reported to persist anywhere from minutes to hours. Stinging and burning were said to be readily relieved by neutralization with sodium bicarbonate solution.

We also found reports of pain. And in the setting of common warts, the discomfort is said to be a possible indicator of the desired destructive treatment effect. We also found reports of scarring, pigmentation, and crust.

Pyruvic acid may emit pungent vapors that are irritating to the upper respiratory mucosa. In the absence of cautionary measures such as adequate ventilation, these vapors could pose risks to patients, providers, and assisting staff.

We found no pharmacokinetic information, and we found no information on long-term outcomes. However, as stated, scarring was reported as a risk, and scars are permanent.

We'll transition now to discuss the efficacy information that we found. Tosson and colleagues evaluated pyruvic acid in all three nominated conditions, especially acne, melasma, and common warts.

Acne and melasma subjects were treated with a 40 to 50 percent pyruvic acid pill every 2 weeks for 1 to 3 months. Warts were treated with 70 percent pyruvic acid paint which was applied twice daily for 2 to 3 weeks.

This group reported, for their acne subjects, complete disappearance of lesions in 33 percent, disappearance of greater than

75 percent of lesions in 20 percent.

For melasma subjects, improvement of greater than 50 percent was reported in 20 percent of subjects and improvement of 25 to 50 percent in 33 percent.

A warts total clearing was reported for 80 percent of subjects and improvement which was not otherwise defined was reported in 20 percent.

Cotellessa's group conducted an open-label study of 50 subjects with papulopustular acne. This group treated subjects with 40 to 50 percent pyruvic acid every two weeks for 3 to 4 months. They reported clinical disappearance of lesions in 40 percent, improvement of lesions without complete disappearance in 50 percent, and no improvement in 10 percent of subjects.

Ardigo and colleagues conducted a pilot study using reflectance confocal microscopy wherein they evaluated pigment distribution in melasma subjects.

In some of these subjects, 7 specifically, they evaluated treatment response. Subjects were

treated with six cycles of a peeling with 50 percent pyruvic acid daily for 2 weeks, and this was followed by a topical application of a Kligman's formula containing 2 percent hydroquinone which was applied daily for a total treatment duration of 5 months.

Outcomes were largely reported in histological terms and included a major reduction in pigment at keratinocytes in the epidermis in two subjects, and three subjects were found on microscopy to have trace pigment.

Berardesca's group evaluated 50 percent pyruvic acid formulation in subjects with photo damage, superficial scarring, or melasma. These authors did not specify how many subjects were affected by each condition.

Subjects received four peeling sessions, each of which was 2 to 5 minutes in duration, and the peels were done once every 2 weeks. The peels were neutralized with a 10-percent sodium-bicarbonate-in-water solution.

They reported treatment outcomes which

included a significant reduction in the degree of pigmentation in patients with melasma.

The last review charts 56 patients with common warts treated with either a 70-percent pyruvic acid or a combination of 70-percent pyruvic acid with 8.5-percent 5 fluorouracil.

Seventy-five percent of the patients used the prescribed product for 1 to 4 weeks, and the remaining patients used the product for 1 to 2 months.

This is the table of results from the Halasz publication, and we'll focus on the cleared column where "cleared" was defined as all warts resolved. Fifty-eight percent of subjects who received a combination product cleared, and 78 percent of subjects who received the pyruvic acid-only formulation cleared.

Shahmoradi's group conducted a randomized controlled trial in 60 subjects who had at least two plantar warts. They treated subjects with the 70-percent pyruvic acid or a 16-percent salicylic acid solution twice daily for 4 weeks.

They reported that the number and the size of warts were decreased in both groups, but they found no difference in efficacy between the products.

We'll now just touch or present the approved therapies for the nominated conditions. Approved therapies for acne vulgaris fall into several categories; antibiotics which are available for topical and systemic administration, bacteriostatics, topical retinoids, combination products, hormonal products, and others such as azelaic acid which is a dicarboxylic acid.

For melasma, a combination cream is available. It includes the active ingredients of fluocinolone acetonide, hydroquinone, and tretinoin.

For warts, approved prescription therapies are available only for genital warts. However, over-the-counter therapies are available for non-genital warts.

Pertaining to historical use, pyruvic acid has been used in pharmacy compound for at least

three decades. Other dermatologic conditions for which it's been used include seborrheic keratosis, actinic keratosis, and photoaging. While the precise extent of use could not be determined, it appears to be worldwide.

In conclusion, pyruvic acid is well-characterized both physically and chemically. Reported adverse reactions generally appear to be local, temporary in duration, non-serious in nature, and readily manageable.

We found no information suggesting undue concerns regarding respiratory exposure to vapors. Although limited, available information did not raise any major safety concerns associated with the use of pyruvic acid.

The available information indicates that the substance may have efficacy in the treatment of acne, melasma, and warts, the nominated indications.

Finally, pyruvic acid has been used in pharmacy compounding for at least 30 years and its use appears to be worldwide.

Based on our review, we recommend that pyruvic acid for topical use be included on the list of bulk drug substances that can be used in compounding under Section 503A of the federal FD&C Act. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Carr.

Any clarifying questions?

(No response.)

DR. VENITZ: Let me ask you first, you mentioned stability may be a problem, but in your summary, that doesn't seem to be clinically important.

DR. CARR: No. And I would defer CMC questions to Dr. Zhang, who I see in the rear there.

DR. VENITZ: Okay.

DR. ZHANG: My name is Ben Zhang from OPQ, CDER. For this question, although in ambient environments, this compound is not quite stable, but as we have stated in the slides, when it's carefully sealed and isolated from moisture,

oxygen, and sunlight, it is likely to be stable and can be stored.

DR. VENITZ: Okay. Thank you. Second question, what's the presumed mechanism of action? What's it supposed to be doing relative to salicylic acid, for example?

DR. CARR: Well, it thins the stratum corneum, but the precise mechanism of action in these indications is not understood.

DR. VENITZ: Thank you.

Any other questions? Dr. Carome?

DR. CAROME: Mike Carome. Given the FDA-approved either prescription or over-the-counter alternatives for each of the three conditions and the nature of the conditions, what's FDA's assessment of the clinical need for this type of compounded product?

DR. CARR: Well, it just offers patients an alternative therapy. In the case of acne, for example, there may be patients who don't want to take systemic medications or there may be some who don't want to commit to long-term topical therapy

and who would prefer to have their acne treated by entering into the physician's office once every couple of weeks. It offers no advantage, just an alternative.

DR. VENITZ: Mr. Mixon?

MR. MIXON: So is this product, if we were to compound it, going to be dispensed to the patient or given to the physician for office administration?

DR. CARR: It would be for in-office use.

MR. MIXON: Thank you.

DR. CARR: You're welcome.

MS. BORMEL: Pursuant to a patient-specific prescription.

DR. VENITZ: Dr. Vaida?

DR. VAIDA: Yes. I was going to ask that same question. So you're saying it would be for office use, but all those studies were saying it was applied daily?

DR. CARR: No, not in all the studies.

DR. VAIDA: Well, it seemed like a few of them that it was applied daily for a couple of

weeks. There was a couple that it was once every two weeks, but it is always done at the office?

DR. CARR: Thank you for pointing that out. You are correct. In some instances, it would be perhaps allowed for home use.

DR. DOHM: Just to be clear, we won't be able to limit where it's being used in terms of its addition to the list or exclusion of the list. If it's listed, it's just going to be a drug, but it won't be limited in terms of whether or not administering in a physician's office versus at home.

MS. DAVIDSON: Gigi Davidson. I had a question for Dr. Jarow that is somewhat related to this that I didn't ask. I'll use this as an example.

I think, by the four criteria here, this would qualify for addition to the list, and that's clearly FDA's recommendation. My question that I had for you, Dr. Jarow, and I didn't ask, and I should have -- the criteria for an IND are for a serious or immediately life-threatening conditions.

This is for acne, melasma, and warts, so this probably would not qualify for an IND if we did not put it on the list. This is more for my understanding of where that line is.

DR. JAROW: See, there are lawyers in the room, so you've got to be careful how you say that. It would qualify for an IND. It wouldn't qualify for an expanded access IND. So just to be that, but I'm not a dermatologist so if someone thought that this was a serious illness and could support that, then you potentially could with an unmet need.

MS. DAVIDSON: You clarified that. Thank you.

DR. VENITZ: Any other clarifying questions for Dr. Carr?

(No response.)

Open Public Hearing

DR. VENITZ: Thank you, Dr. Carr, again for your presentation.

We do not have a nominator, so no nominator presentation. We're moving right into our

discussion.

Yes, I'm sorry. We have an open public hearing. I apologize. Let me go through the preliminaries.

We will now proceed to hear the open public hearing speaker. 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 the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address the 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. With 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 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.

Our open public hearing speaker.

DR. DAY: Good afternoon. My name is A.J. Day. I'm with Professional Compounding Centers of America based out of Houston, Texas. We do not have a financial conflict of interest.

PCCA has nominated a number of substances for inclusion on the bulk substances list. However, none of those are on the agenda today.

The topic that I'm here to discuss with the committee is the IND process and the application process. First, I must say that I'm deeply appreciative of the opportunity to come here and speak to this committee.

These public meetings are very beneficial for all of us. I'm speaking for the compounding community overall. We are very thankful to the FDA for extending this opportunity.

We've heard a lot in all of the different PCAC meetings since the first one last February about the IND process. The first time that it came

up was in the first meeting, February of 2015, in the context of adding medications to the withdrawn or removed list.

If something was added to that list, how might patients that were utilizing some of those get access? That was the first time that that was brought up in this PCAC process, and it continued to be brought up in regards to some of the substances that were being voted on for the bulk substance list, the positive list, so to speak.

The FDA's recommendations on one of the substances that we discussed at that time was piracetam. Though their concerns were not about safety or any kind of a safety signal, it was about the lack of large scale clinical trials showing efficacy on the scale that was expected.

When we talked about the IND process as an alternative mechanism, we talked about the response time for people getting the information back, either a thumbs up or a thumbs down, from the FDA with regard to the IND.

I've summarized some of the responses, and

I've put in quotes, and as I go through these slides, there'll be a number of quotes. And my purpose in doing that was not to disparage anybody who made these statements or to make them appear in a negative light, but really to show the context in which the discussions occurred and to be as transparent and factual about where these statements came from as possible.

In that voting session for piracetam, some of the comments regarding why the committee members cast their votes the way they did talked about the IND process explicitly, if there's an alternative, so they won't be denied medication or the drug.

There's an alternative to putting it on the list; they can still go through an IND process. It also sounds like they may -- like it may be made available for the specific cases through the expanded-use IND, and that was in the context of some of the patient cases that I had presented for that meeting.

The individual cases of the patients -- there was another avenue which we heard

yesterday and that's because it was a two-day meeting; the IND process was initially discussed the day before -- is the rather rapid response.

The FDA had presented that the response time was typically less than 24 hours, so I do not see that the patient access should be denied because of that.

Fast forward to the October meeting of last year when we discussed the domperidone. A physician testified as to the difficulty accessing an institutional review board when trying to submit the IND for domperidone.

In that meeting, there were two different experts from the FDA. One of them said that our form says that, if IRB review cannot be accomplished, it directs them to contact the FDA Human Subject Protection Branch. Dr. Korvick added on, so again, we try to help facilitate that issue if they're working with us.

We also have individual patient INDs under this program or there are physicians who apply to enroll multiple patients if they have a clinic that

has more than one patient.

This IRB content in the IND process comes up in every single meeting, and we spend a lot of time discussing what is involved, what are the limitations, how do we actually navigate the process.

Continuing in that October meeting, Dr. DiGiovanna talked about -- and he made a statement, "To use in the equation that the expanded IND is an acceptable alternative really suggests to me that that's coming from someone who hasn't tried to get an expanded IND."

Dr. Davidson added on, "Would this drug," referring to domperidone, "be eligible for an emergency IND?"

The FDA's Dr. Griebel said, "An emergency IND is just another expanded access version. A single-patient IND in which a patient is in an emergent situation, you still have to have a form 1572. The only difference is that you can submit to the IRB after the fact of submitting the IND application. And the division has to scrutinize

the situation to see if this is truly an emergency situation for the patient."

Again, that same conversation amongst the committee, Mr. Humphrey, "I do recognize that there is a clinical need for this drug, but you can get it through the IND process. I may be somewhat a little biased because of where I work, but we deal with expanded access drugs nearly every week. And while the process is cumbersome and onerous when you first do it, after a few times, it gets a lot easier."

Dr. Pham added on, "I feel like I'm getting confused by our own advisory committee because I swear, in previous meetings, we've had votes where we voted no based on the fact that there was an IND process. I remember that being people's justification. The conversation in the past has always been, if there's a way to get it through an IND, go that route and hope for the FDA approve the process to -- especially if there's such a compelling need that they are going to be providers that will be looking to create a product that's

going for FDA approval."

So what are the criteria that the committee had agreed to that the FDA had put forth for consideration in this committee? There are four criteria: physical and chemical characterization of the substance, any safety issues raised by the use of the substance, historical use of the substance in compounding, and efficacy, any data of effective use of lack of effectiveness.

No single one of those criteria is dispositive. Those are the sole four criteria. Topics which end up taking a lot of committee discussion time and a lot of resources from both the committee and FDA but are absent from the evaluation criteria is the investigational new drug options, including expanded access. That is not one of the criteria to be evaluated. The vote should not be based on that.

FDA-approved medications for similar conditions as a nominated substance, we just heard about some of those in the case of pyruvic acid. What are other medications that are available?

That is not one of the criteria for any of the FDA processes here with the PCAC. Going back to the first meeting in February when that item was brought up, Dr. Venitz asked, "How important is the availability of alternative therapies to your ultimate decision?"

The FDA's Dr. Kashoki responded, "It is an important consideration, particularly when you think of the nature of the condition being treated."

We're adding in criteria to what is going in, but it's informal. It's off the record. The last thing that I see a lot of the conversations taking up time in the discussion on what should be evaluated is how a substance may be marketed.

There are rules over what can and cannot be said about compounded medications. If there are concerns about how something may be marketed once it's on the list, there are regulatory policies in place and appropriate action should be taken to carry out the existing regulations.

Let's discuss some of this IND process. The

FDA's presentations for the IND process in the past -- and I'm grateful to Dr. Jarow today for expanding on a lot of this and making it much more clear.

Every time I hear him talk, I swear it seems just so absolutely simple and I feel like I can take it on all by myself, which is not entirely true, so we'll talk about that a little bit.

Domperidone is the only medication for which we have an expanded-use packet available, a full protocol that's available. However, for the other discussions that we've had, there's a lot of unknowns.

What are the inclusion criteria for the patients that might be allowed to get into that protocol? Will the medication be compounded or is it going to be like in domperidone where it has to be a finished manufactured dosage form which is imported? And then, how does it get to the patient because, for domperidone, it goes through a single pharmacy. And nobody else is allowed to participate, regardless of their location in the

country.

If it's being compounded, what is the requirement for the letter of authorization that is a requirement in the IND process? And the biggest issue that we're finding in the community setting is access to the institutional review boards.

Something else that was presented today was also in the documents that were released by the FDA two weeks ago. It's that the FDA has 30 days to review the IND submissions.

In previous meetings, there have been discussions that the response time is typically 24 hours or about one business day. And there is no requirement for that kind of a timeframe to happen, so the discussion about patient access will become very relevant.

If we look at domperidone, and we took a step back, and I said, if the rules have been set that we need to go through an IND process, if we play exactly by the playbook that's been given to us by FDA, can we navigate it? Can we set up a system such that patients and physicians can easily

sign on to this and access the medications?

Now, one thing to note is that the expanded-access form for single-patient use is Form 3926, and the domperidone IND packet specifically says that it requires Form 1571 and 1572 which, as the FDA said, are not really tailored for single-patient use or for compounded medications.

So 3926 is valid only for individual patient INDs, and as we heard repeated many times in the presentation just a few minutes ago, for intermediate-sized and treatment INDs, you must use Form 1571. That is what we're really looking at for the patients affected by the decisions you're talking about.

The entire expanded access Form 3926 that's expedited and should take less than 45 minutes to fill out is not applicable to this patient population or to any of the substances that we're describing for the conditions we're discussing.

The form 3926 versus 1571 -- in the March meeting of this year, when we talked about quinacrine, Dr. Jarow talked about the

simplest, "If I was on the other side, if I was a rheumatologist who wanted the easiest, least burdensome approach, it would be if someone opened a treatment expanded-access IND that would be the least burdensome."

That is consistent with what we heard today. Adding on to that discussion, Dr. Jenkins from the Office of New Drugs added that, "There seems to be an assumption that no one is going to develop this drug," referring to quinacrine, "for a commercial use. And I don't think we should assume that to be the case. If it's not on the list, that may prove to be the incentive that someone needs to bring an application to bear."

Again, this is another criteria or another consideration that is not part of the criteria for evaluating should this substance be available for use in compounding.

Going back to IRB access, can we navigate this process? How feasible is it in a community setting? We contacted over 32 institutional review boards at hospitals and research institutions

around the country, including the institutions for every single voting member on this committee.

Before doing that, we even contacted and did a lot of research online. Indiana University's IRB does provide some details directly on their website that say before submitting the application to the IRB, you have to complete a 16-module training course per person.

Each investigator that signs on has to do this, and it takes a minimum of four hours to complete. There's paperwork submission that's over 25 completed pages, and if any single page is missing, it will not be reviewed. Approval is granted for one year and must be renewed annually.

We also contacted commercial IRBs, as well as physician groups, and patient groups for assistance with accessing IRBs and navigating the IND process, including the American Gastroenterologists Association and American College of Gastroenterology, along with a few other patient groups.

When all of those fail to give us anything

helpful with actually working with an IRB, we contacted individual physicians who we knew had previously prescribed domperidone to find out if they'd attempted to, had success with, or had roadblocks accessing and navigating the IND process for domperidone.

So the big question, can a physician, a community physician contract with your IRB at your institution or your research facility without being employed by or otherwise directly affiliated within a financial sense your institution?

The universal answer was no. We're located in Houston, Texas, where we have the Texas Medical Center. It's the largest medical center in the country. Contacted every single one of those hospitals and they all told us the same, no.

Can a physician contract with your IRB without being employed by or affiliated with your institution? Again, the institutions that you are all affiliated with universally said no or they refuse to call us back or respond to our emails, and we tried multiple times.

Now, if we look back at the guidance documents that FDA released two weeks ago regarding IND treatment uses, they talk about the requirement for a full IRB review. Partial review is not allowed.

They also talk about some of the complications, and they recognize that that proposes an additional barrier. However, the ends justify the means. There's a reasonable need for that full IRB review.

That's another requirement that we've got to pose to the IRBs when we're asking, can they be the IRB of record for domperidone. And the request was very simple. We've got an FDA-approved published packet. We simply needed somebody to be the IRB of record. The protocol is already approved.

When we contacted the commercial IRBs, only two of them responded to our outreach. The other two were completely unresponsive both via phone and email.

None of the IRBs had any experience with compounding medications. All of the INDs that

they've ever dealt with are through drug manufacturers, pharmaceutical companies.

There was one IRB that, after several days of back and forth where they're telling us, no, we will not do it and we're finding information on their website that indicates they might, they finally said, okay, we could be the IRB of record, but we'd never done this before. And here's our fee structure again. It's designed to work with the industry.

For a single-patient review IRB, the fee structure exceeded, well exceeded $3,000. And they asked me not to reveal the specifics because they consider that to be proprietary information.

That was an estimated fee because, again, they've never dealt with a compounded medication and a protocol that was already approved, so they don't know if that structure is going to get more expensive or not.

As far as timelines for the IRB, they said, depending on the workload for their full IRB, the turnaround for the full review could be as short as

10 to 12 business days, in addition to a couple of days to verify that the submission is complete. So you're looking at about three weeks calendar time in a best-case scenario.

Now, if we go back to the FDA guidance documents that were published, they actually talk about two different levels of individual patient expanded access. One is the IND. One is the protocol.

Now, based off of the conversations we have had in the PCAC meetings prior, we understood that the response could be very rapid, and you could initiate therapy for your patients immediately.

Well, the expanded access IND has a 30-day waiting period, but the protocol doesn't. So there's a little bit of confusion on our end about which one would be the best to approach and how do we have that discussion with the IRB.

We're having difficulty understanding the process, as well as a lot of difficulties securing IRB review. What do we do then?

The FDA instructs you, contact us, we're

here to help you. Now, in the domperidone packet, there is instruction specifically on contacting the Human Subject Protection Branch, along with a name and phone number.

We did call them. And just to note, they couldn't even respond to our request for help in less than 24 hours. When we did speak with somebody, we were told that we cannot make any specific recommendations of an IRB to use. However, there's an independent, for-profit IRB that kind of, as a business model -- and one of them would be the best to use -- those would be the ones that we contacted and we got a fee structure for.

They also referred us to an IRB database online where we could search by state. However, that was not very useful because a lot of those are for military sites, for private institutions that we don't have access to.

In addition to that, there's another packet, these documents that the FDA has released two weeks ago. The expanded-access physician fact sheet says

that, "If you need assistance with this, contact us here," and it's the Division of Drug Information.

So we did that and we contacted with a very nice, very professional pharmacist who was trying to help us, but didn't have a lot of knowledge about this process herself.

We asked, is that letter of authorization needed for domperidone? And we were told the packet does not say anything about it. That's why we asked. But moving beyond that, what type of IND do we need to file? There's the expanded access IND or expanded-access protocol.

The response was, I don't know what expanded access protocol is. I'm here to refer you to the FDA's website. You should carefully review the domperidone packet on the website.

When we directed her to the page that discussed the expanded-access IND versus the expanded-access protocol -- you saw the screenshots earlier -- her response was, we cannot interpret for you. We can only give you publicly available information. We can direct you to areas of our

website, but we cannot interpret anything for you.

So we asked, who would be able to help us determine what we need to apply for, interpret some of these things, so we're actually getting the right things done? And the response was, you need to hire a consultant.

If we go back to the FDA's guidance documents -- and we heard about, can you charge patients for some of these things -- it specifically says that you can charge for direct costs only, but you cannot charge or get reimbursed for administrative costs.

I'd like to some clarification on that at some point because it's directly contradictory to what Dr. Jarow just presented, along with the other requirements of what is required to apply and ask permission to recoup some of your direct costs.

What can you recover? You cannot recover your indirect costs and that includes the IRB fees and expenses, so you're looking at a minimum of $3,000 for the single-patient IRB review.

From our experience, that's going to be just

one piece of it, then if you're having to hire a consultant to navigate the IND process with the FDA, another fee to hire a certified public accountant. All of these fees add up.

Going back to the quinacrine discussion, Dr. Jarow said that if he or she, referring to the healthcare provider or the physician in a small community, does not have a local IRB, they can use a central IRB. And many of those provide their service for free for expanded access or compassionate use.

We've searched high and low for that unicorn and have been unable to find them, so we'd greatly appreciate some assistance, but when we asked for that assistance, we're told, "We cannot tell you any. We can't recommend an IRB to utilize."

One of the other criteria of expanded access is that the patient -- they are not a good candidate for an ongoing clinical trial. So in the case of quinacrine, if something is being studied for lupus, but this patient has been on quinacrine for lupus, yet they meet the inclusion criteria for

a clinical trial, they would have to go to that clinical trial before they could get lupus through an expanded-access IND. That is a requirement for expanded access.

The other point that he made was that there's no question if one was to take a single-patient approach in this. It would be more burdensome. The burden in patient access issues here are really the crux of our concerns on this entire discussion about INDs as it relates to compounding.

So there's a lot of confusion about -- to begin with, which form do we use? Do we use this expedited form, 3926, or are we required to go to the more convoluted less clear forms, 1571 and 1572? Confusion about expanded-access IND versus the expanded-access protocol and patient waiting periods -- when can we start treating our patient?

Extreme difficulty finding an IRB to work with, as well as the insurmountable fees for the IRB which would be typically shouldered by the physicians or, as presented today, whoever the

sponsor is -- however, even in that case, you have a number of fees for hiring a consultant to navigate the IND and the certified public accountant. And when you have all of these indirect fees -- and you're not allowed to make a profit on any of this.

You may be able to recover some of your direct cost with accessing the specific drug, but there's no profitability allowed through this entire process.

So who's going to be able to sustain this in the long run? Several hours of paperwork requirements for both the IRB, as well as then the FDA -- and through all of that, you still don't have specific information on how the patient will ultimately get the medication, assuming that the IND is submitted and approved.

Will it be compounded? Will it be an imported manufactured product? What sites will be allowed to participate in this process? And this notion of being under GMP -- the entire premise of 503A and community compounding pharmacy is, it's

exempt from GMP. So to note that as an added regulation and the regulatory status of the pharmacies is a tremendous burden as well.

Going back to that quote from Dr. DiGiovanna, "To use in the equation that the expanded-access IND is an acceptable alternative really suggests to me that it's coming from someone who hasn't tried to get an expanded IND."

In the case of quinacrine, it really seems like we're looking for ways where we have all of the evidence, but still have it go through an IND and have an IRB look at it rather than allowing it for use in compounding.

So my ask to the committee is that the IND process specifically should have no bearing on the PCAC evaluation process. It is not one of the criteria in evaluating substances for inclusion on the 503A bulk substance list. Thank you very much.

DR. VENITZ: Thank you, Dr. Day, for this very detailed presentation.

I'll allow one or two comments or questions by the committee. If there aren't any, if the FDA

desires in wanting to give a response given the fact that several potential shortcomings of the current process were detailed?

DR. JAROW: This is Jonathan Jarow again. I'm from the Office for the Center Director. I apologize that there is significant confusion, and part of that is FDA jargon.

One, as I mentioned in my talk, there are things called protocols and INDs. So when you open an IND, you have to submit a protocol. Let's just talk research INDs, get away from expanded access.

You open up an IND for a specific drug that's under investigation, and you submit a protocol. The FDA has 30 days to review that, and if you do not hear back from us, you can start that protocol. The protocol is the clinical trial, let's say.

If you hear back from us saying you can proceed, you could proceed earlier than 30 days. If there are, as a response from the FDA, that there are hold issues, clinical hold issues that you can't proceed, then you have to address those

before you can proceed. So none of this would be for an emergency situation. That's number one.

Number two, once you have an open IND that's proceeding and you're doing your protocol -- our industry person knows all about these things -- you can then add another protocol to that IND.

There is not a 30-day safety review period for an additional protocol submitted under an existing IND. And I did mention that in my talk, and it'll be in the transcript, I suppose.

If you're submitting a protocol to an existing IND, you don't have an existing IND for any of this, so you can't do this, but if you already have an existing IND and you submit a protocol, you don't have to wait the 30 days. That could be an expanded-access protocol or it could be a research protocol. It could be either one to an IND.

Let's talk about single-patient versus intermediate-size IND. Single-patient INDs have different regulations than an intermediate-sized IND.

All the things you just heard from him about charging under a single-patient IND are correct. You cannot charge administrative costs. However, under an intermediate-sized IND -- so if you go to the guidance that I put in the resources for you and look at that, there's a different section on intermediate-sized INDs. And you can charge in that situation.

So again, if you're doing a single-patient IND for domperidone, you cannot charge administrative costs. Okay? And I guess I'm not allowed to mention specific IRBs, but there is an IRB that opened a foundation, basically a charitable foundation for doing free IRB, or not free, but it's paid for by the foundation, for single-patient INDs. That wouldn't count for an intermediate-sized IND, but you have access to that.

In terms of timing and review, I would not recommend the intermediate-size IND, expanded-access IND for anything that you wanted as an emergency. This is not intended for emergency

treatment.

This would be something that you would set up, and then you can then use it and expand it to different healthcare providers.

An emergency IND is a single-patient IND. It's a completely separate situation. You'd need to submit it as that. There are different rules required for it. You don't have to have the IRB approval at the time of submission, although you're expected to get it, I think, within 12 days.

Rich? Richard left. But anyway, that's typically emailed, faxed, or telephone called-in to FDA. You speak to the review division, and you typically get a response within hours.

Regular expanded-access INDs, you do not get a response within one day. They typically take longer. The Office of Oncology recently looked at their data, and I think it was -- for a non-emergency, the average was, like, about two or three days.

For an intermediate-sized treatment -- I shouldn't use the word "treatment" --

intermediate-sized population expanded-access IND, it's going to take a lot longer and there's probably going to be back and forth during those 30 days, unless you got everything perfect in your protocol, et cetera. So there'll be a back-and-forth to get typically, I would anticipate, particularly if you are not experienced with doing this.

What else did I want to address? I think the general principle is that -- and I'm not the compounding committee here. The principle is that if you have a drug that you don't think that there could be safe use for all the potential indications that would be in a compounding environment that would normally be addressed by product labeling -- let's say if it was an approved drug, and you're concerned because, as was mentioned before, if you put it on the compounding list, you can't limit it to a specific indication -- correct me if I'm wrong -- unless you could sometimes by formulation, if it's IV or something like that, and you're only compounding the pill.

But if you're concerned about alternative uses -- and since you don't have product labeling to instruct healthcare providers and patient labeling to instruct patients for safe use of that product with contraindications for other things, but there is a specific indication that is for a serious or life-threatening disease where you have no alternatives, patients have exhausted all their alternatives.

You want it to be available to them in that setting, and it's not an emergency situation, the intermediate-sized expanded access IND is -- as I kept on saying, for someone who has never done it before, it's not easy, but it's doable. You could set it up once and then it's ongoing at that point.

It is for a specific indication, so to enter that intermediate-sized IND, you would have entry criteria that describe the exact situation where you think the benefits outweigh the risks for that specific drug and it's worthwhile for patients to have access to that in that setting.

They would meet those eligibility criteria,

they would be entered into that, and they could be treated chronically with that drug or for just a course of treatment, depending upon what the drug and the indication were.

I'd be happy to answer any clarifying questions.

DR. VENITZ: Okay.

DR. DOHM: If I may respond to two other points that were made by Mr. Day --

DR. VENITZ: Go ahead.

DR. DOHM: -- if you don't mind, there was a point at which there was a suggestion that the committee, at various times, has considered or taken in consideration factors that aren't explicit in the four-factor analysis that we use for evaluating whether or not to include a bulk drug substance on the list and I just want to make two points of clarification.

One is that the availability of therapeutic alternatives, including the availability of FDA-approved drugs, is a consideration that was brought to the committee as part of the safety and

effectiveness analysis that are factors in deciding whether or not to include a bulk in the list.

The second thing I wanted to mention is that Mr. Day is correct that the IND program is not one of the factors that we consider when we're determining whether it's on the list, but it certainly is a potential avenue to access a drug that is not placed on the list.

It, of course, provides safeguards for use of the product that aren't attached to a drug that's compounded outside of the IND process.

Thank you.

Committee Discussion and Vote

DR. VENITZ: Thank you. I'm pretty sure this topic will be continued in the future. Let's go on. Thank you, Dr. Jarow, and I'm pretty sure we'll see you again.

That takes us out of our open public hearing session, and we're moving back into our review discussion and vote as our next agenda item. We're back to the pyruvic acid. Any comments for discussion? Yes, Dr. Vaida?

DR. VAIDA: Just a quick one on this administering it. I know that FDA doesn't have any control on how it would be administered, but I guess just from the committee members, Dr. DiGiovanna, have you ever prescribed this pyruvic acid and did you administer?

DR. DiGIOVANNA: I haven't used it. It's my understanding it's used as a peeling agent. So my understanding of it is a physician would order it and would apply it in the office.

I could imagine how under some circumstances -- although I personally am not certain -- it could be taught to the patient how to do it, for example, on a specific lesion like a wart, and it might happen that way. But my understanding is it's generally used a peeling agent for large areas, pigmentation, acne, and that sort of thing, usually applied in the office.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Just again clarifying, so you talk about you order it. So you would diagnose the patient, you figure out what they need, and then

sort of send them away to get the product, and have them come back? Or how does that work, given that it would be available for office use?

DR. DiGIOVANNA: Again, I believe what would happen would be that a physician who tends to do this on a regular basis would have it in the office for the patients that have that, and then it would be applied at a certain time.

I don't know logistically how it would happen going forward. My understanding would be that, in the past, I believe they would have ordered an amount of it for them to be used for that week, or two weeks, or month, or however long it's useful for and apply it in the office.

MS. JUNGMAN: You'd typically be ordering it from a pharmacy as opposed to compounding it in the office. Correct?

DR. DiGIOVANNA: I would expect that, yes.

MS. JUNGMAN: Okay.

DR. VENITZ: Any other discussion items?

(No response.)

DR. VENITZ: Then let's proceed with the

vote. The question is posted on the screen. If you vote no, you are recommending that pyruvic acid not be placed. If you vote yes, you're obviously on favor of it being placed on the 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 component of an FDA-approved drug.

You know the voting process. Please press the button firmly on your microphone that corresponds to your vote.

(Vote taken.)

DR. HONG: For pyruvic acid, we have 9 yeses, 2 nos, and zero abstain.

DR. VENITZ: Let's go around the table, starting with Dr. DiGiovanna.

DR. DiGIOVANNA: So I voted yes. While I haven't used this specific product, I've used other similar to it, my understanding is they're applied in the office, and I think the FDA has done a good job of reviewing the materials on it. And I agree

with them that it should be available.

DR. GULUR: Padma Gulur. The safety data presented does not appear to pose any significant risks to the patients, and there's reports of efficacy. Based on that, I believe that it should be placed on the list.

DR. VENITZ: Jurgen Venitz. I voted yes. I would add to my predecessors that there is plenty of information of clinical efficacy, probably more than I've seen in any previous meetings.

MS. DAVIDSON: Gigi Davidson. I voted yes for the reasons stated. There's plenty of evidence to support efficacy and no concerns about safety.

MR. HUMPHREY: William Humphrey. I voted yes. I agree with the FDA's assessment.

DR. HOAG: Steve Hoag. I voted yes. The risk to benefit ratio seem favorable.

MS. JUNGMAN: Elizabeth Jungman. I also voted yes primarily because that kind of risk benefit calculation seemed to be favorable, given the evidence of effectiveness in human trials.

I did think that this one was harder because

of the -- the clinical need was not clear given the FDA-approved alternatives. But given the lack of concern about long-term safety effects -- and I also find it comforting given that, under 503A, you would not be able to use this product for -- you wouldn't be able to stock it for office use. That would likely create a preference for the FDA-approved product.

So you'd be using this really in situations where the clinician determined that there was a real need.

DR. PHAM: Katherine Pham. I voted yes for previous reasons stated and that I agree with the FDA assessment.

DR. VAIDA: Allen Vaida. I voted no. I really didn't think that was really that much of a hindrance for the other products that were available that the FDA said.

I still have concerns about if this was put in the hands of the patient to use because of the vapors and that.

DR. CAROME: Mike Carome. I voted no for

many of the same reasons Allen mentioned. I don't see a compelling clinical need for this product given the nature of the conditions and given the availability of FDA-approved alternatives. And there are very limited data on the efficacy of the product.

DR. WALL: Donna Wall. I voted yes for many of the reasons stated, but one last thing is that this product really needs to be prescription only. I would hate for someone else to be using it because of the risks associated with scarring and other things. It needs to be absolutely prescription only.

DR. VENITZ: Thank you. That concludes our vote, and we are moving to our next bulk substance to review, tea tree oil. We have Dr. Ko giving the FDA presentation. He is a medical officer in the Division of Dermatology and Dental Products.

Dr. Ko?

Presentation - Hon-Sum Ko

DR. KO: I'm Hon-Sum Ko, the medical officer in the Division of Dermatology and Dental Products,

and the topic now is on tea tree oil.

Tea tree oil has been nominated for inclusion on the list of bulk drug substances to be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for topical use in the treatment of nail fungus. The nomination has proposed use of tea tree oil at strengths of between 5 to 10 percent.

This slide just briefly goes over the condition that we are talking about, nail fungus infection. And I'll use the term onychomycosis synonymously with nail fungus infection.

This condition is most commonly caused by dermatophytes, and it can also be caused by other fungi like candida species and other yeasts. Tea tree oil has been reported to be used for this condition as applied to the nails undiluted, or with neat tea tree oil, or in combination with another antifungal in diluted formulation.

Now, I'm going to discuss the physical chemical characterization of tea tree oil. And for the purpose of this discussion, we are talking

about tea tree oil derived from the native Australian tree, Melaleuca alternifolia, just to make the terminology straight because there have been usage of the term "tea tree oil" to include oil derived from other plants.

For tea tree oil from Melaleuca alternifolia, there are two very similar standards to assure the quality of the oil. One is international and the other is from Australia, but they're very similar.

Tea tree oil is a mixture of organic compounds with over 90 percent of the contents fully characterized as monoterpenes, sesquiterpenes, and their associated oxygenated analogues. This slide shows some of the examples with strengths as recommended in those standards.

Impurities in tea tree oil, the likely ones are the one from the usual botanical sources, like heavy metal impurities from the source material for extraction, or the bioburden, like microbial content.

Now, with tea tree oil, the impurities are

expected to be low because the steam distillation process would not concentrate the heavy metals. Also, tea tree oil has antimicrobial properties.

In conclusion, for physical and chemical characterization, tea tree oil, when we're talking about that which meets the international or Australian standards, is a well-characterized natural product from a native Australian tree, Melaleuca alternifolia, produced by a relatively simple extraction process which is steam distillation.

Its major components have been fully characterized and quantified to account for over 90 percent in a typical sample, again, standards available to assure the quality control and natural variations.

As to the minor components accounting for the less than 10 percent of tea tree oil content, they are basically of the same type of terpenoids with similar physical chemical properties as those major components. And complete characterization or quantitative analysis of all the components is not

feasible.

Now, I'm going to go over the nonclinical assessment for tea tree oil. Pharmacology -- as we discussed earlier, tea tree oil has antimicrobial properties. In this nomination for nail fungus, we actually focus on the antifungal properties of tea tree oil. These have been documented in a number of in vitro and in vivo nonclinical studies.

As to acute toxicity, when administered orally, the LD50 for tea tree oil in rats is between 1.7 to 2.3 grams per kilo while rats dosed with a lower dose, such as 1.5 grams per kilo, would appear lethargic and ataxic. And it showed depressed activity levels.

For dermal application, with 5 grams per kilo of tea tree oil, experiments have shown in rabbits 2 deaths out of 10 treated animals. And with a lower dose, 2 grams per kilo, it caused slight diarrhea in the rabbits. We have not found repeat-dose toxicity data for tea tree oil.

For mutagenicity, tea tree oil and many of the components were negative in the Ames test. One

of the compounds, terpineol, exhibited mutagenicity in the Ames test.

Other in vitro systems such as the human lymphocyte micronucleus and chromosome aberration tests showed that tea tree oil was not genotoxic.

Again, in vitro studies of some of the components including cineole, d-limonene, linalool, phellandrene, beta-pinene, beta-myrcene, these were not genotoxic in in vitro tests with mammalian cells.

One of the components, beta-myrcene, was also studied with oral administration in rats. And it was shown that it was not genotoxic in bone marrow cells. So overall, available data on the mutagenicity of tea tree oil and individual components indicates low mutagenic potential.

Regarding developmental and reproductive toxicity, there are no published studies conducted with tea tree oil available.

Two of the components, alpha-terpinene induced delayed ossification and skeletal malformation in an oral embryofetal and

developmental study in rats while another, beta-myrcene, caused a higher resorption rate and higher incidence of retardation and fetal skeleton anomalies in the oral embryofetal and developmental studies in rats.

The limited data from the oral rat embryofetal developmental studies conducted with those two components just mentioned suggest that tea tree oil may pose embryofetal toxicity when ingested orally at relatively high doses. However, the limited data are not adequate to make a final determination.

For carcinogenicity, also, there are no published studies conducted with tea tree oil available.

One of the components, alpha-terpinene, was not carcinogenic when given intraperitoneally in a mouse study. But this is not a standard carcinogenicity study design.

Another component, beta-myrcene, was studied in mice and rats in a two-year oral carcinogenicity study and showed that carcinogen activity was

demonstrated in kidneys of rats and in mouse liver.

In conclusion for the nonclinical assessment, for acute toxicity, tea tree oil can be toxic when ingested or topically administered at high dose.

There's low mutagenic potential for carcinogenicity, developmental and reproductive toxicity. There are no data per se for tea tree oil, but the limited data available for some of the components suggest risks for embryofetal toxicity or carcinogenicity if given orally at relatively high doses.

Overall, the limited nonclinical safety data available are not adequate to determine whether neat tea tree oil is safe to use as a bulk drug substance in compounding.

This slide deals with human pharmacokinetics. There are no in vivo study reports for human pharmacokinetics to document systemic exposure after application of the components in tea tree oil.

There have been in vitro data. Overall,

this data from in vitro skin penetration studies suggest that components of tea tree oil can be absorbed after topical application.

Under dosing a condition of 10 grams per square centimeter, up to 8 percent of the applied dose could penetrate through the epidermis in vitro.

Now, I'm going to turn to human safety data. Adverse reactions from tea tree oil when applied dermally primarily would cause irritant and allergic contact dermatitis reactions.

For oral injections, there can be significant toxicity, including central nervous system depression, unsteady gait, abdominal pain, diarrhea, and generalized erythema.

There have been reports of some reactions of special concern, including prepubertal gynecomastia, linear IgA disease, as well as stomatitis and colitis.

Now, clinical trial data regarding human safety -- there have been dedicated human dermal safety studies on tea tree oil. Both pure and

diluted tea tree oil can cause skin irritation.

A study with 150 subjects for contact sensitization potential showed about 2 percent sensitization. For phototoxicity and photoallergenicity with tea tree oil, we don't have information.

Again, regarding clinical trials, we have not found safety data from clinical trials using tea tree oil in compounded products. Adverse reactions from clinical trials with tea tree oil are based on the use of neat tea tree oil or diluted formulations.

Again, these include the reactions described earlier such as irritation, erythema, edema, dryness, itching, and scaling, but systemic hypersensitivity has also been reported.

So in conclusion, for human safety, the safety data from use of tea tree oil suggests that systemic administration such as oral ingestion may be associated with significant toxicities.

Adverse effects from topical administration are primarily related to irritant and allergic

contact dermatitis reactions. Although systemic sensitivity has also been reported.

Next, I'm going to turn to a discussion about efficacy in the treatment of onychomycosis with tea tree oil.

We have found two randomized, double-blind, controlled clinical trials involving the use of tea tree oil for onychomycosis. One is with a comparison of two topical preparations for the treatment of onychomycosis with the tea tree oil and also with clotrimazole.

Another one was on the treatment of toe nail onychomycosis with a combination product having 2 percent butenafine and 5 percent tea tree oil in a cream formulation.

I apologize in this slide and the next because the order has been reversed. This is the study by Syed, et al. in 1999. It compared 2 percent butenafine hydrochloride plus 5 percent tea tree oil in a cream base with placebo cream. And this is for toe nail fungus due to dermatophytes.

The treatment was under occlusion 3 times a day for 8 weeks. And at the end of 36 weeks, 80 percent of subjects who used the combination cream but none of those that used the placebo cream had overall cure.

You may note that, in fact, the placebo cream was a matching cream also containing tea tree oil. This study actually demonstrates effectiveness of the combination product, but does not demonstrate contribution of the 5 percent tea tree oil because, first of all, the placebo was not giving -- patients who use the placebo did not show any overall cure.

Also, there's no treatment arm with butenafine hydrochloride alone. Without that, we don't really know whether the 5 percent tea tree oil has contributed to the effectiveness of this combination product or not.

This next slide is actually on the study by Buck in 1994. He compared 1 percent clotrimazole solution against neat tea tree oil. The products were administered topically 2 times a day for

6 months in patients having toe nail onychomycosis with dermatophytes.

At the end of 6 months of therapy, partial or full clinical resolution was reported in 61 percent of the subjects treated with clotrimazole and a comparable percent in those with tea tree oil.

However, this study did not have a placebo arm, and the clotrimazole solution is not an approved product, so we are comparing it with something that we do not know definitely about efficacy.

So unless the tea tree oil is shown to be superior to a product not approved, we really cannot say that it is showing efficacy in onychomycosis.

In conclusion, about the efficacy studies, we do have two randomized, double-blind, controlled trials to look at the treatment effect either with neat tea tree oil or in combination with an antifungal for onychomycosis.

Unfortunately, these have design problems,

and we cannot conclude that tea tree oil is effective either as a neat tea tree oil or has combination to efficacy in combination with another antifungal.

There are approved therapies for toe nail fungus, including oral, as well as topical drug products. Among the oral products are griseofulvin, itraconazole, and terbinafine. The topical products include ciclopirox, tavaborole, efinaconazole.

This slide is about historical use in compounding. Although tea tree oil-containing products have been available commercially for over three decades, they are available as topical formulations for a wide variety of skin, ocular, oral, vaginal conditions.

We couldn't find much in a way of information on pharmacy compounding with tea tree oil.

In conclusion regarding the four criteria we use for assessment, tea tree oil meeting the international or Australian standards is considered

well-characterized in physical and chemical properties.

For topical use, tea tree oil may cause local reaction such as irritation, erythema, edema, dryness, itching, and scaling while systemic hypersensitivity has also been reported.

There's a lack of evidence of efficacy in the treatment of onychomycosis with tea tree oil. There's also lack of information on past use of tea tree oil in pharmacy compounding.

For these reasons, we do not recommend tea tree oil be included on the list of bulk drug substances to be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Ko.

Any clarifying questions for Dr. Ko? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes, John DiGiovanna. I guess it's my understanding that because this was nominated for onychomycosis, that its topical use

for other conditions such as acne where there have been studies published is not something that's considered?

DR. KO: Well, we focused on nail fungus because the nomination provided one reference to support its use and the reference is about antifungal properties.

In fact, the nomination has not stated explicitly what exactly the proposed uses it has. It states that it has past use including nail fungus, something like that.

So back to your question about acne and these other things, we actually did look at them. It's just not in the presentation or in the document that you have.

According to a review by Natural Medicines assessed last year, most of the uses that people advocate for tea tree oil lack very good evidence. The three that the review stated that are possibly effective -- and these include the onychomycosis, tinea pedis, and acne.

We did review acne and also tinea pedis.

Again, those studies have all have design issues, so they actually would still not be able to support efficacy.

Now, I can't go through all of them at this point, but if you are interested, we can go offline on that.

DR. DiGIOVANNA: I guess what I'm trying to understand is that if we decide that this is not available for compounding, that we decide that on the basis of the information that we have.

If we only have the information where it's been evaluated for onychomycosis, we aren't even evaluating where it has been -- the studies that have been done for other indications and then it's not available for any indication topically.

Does that mean that, subsequently, if another nominator wanted to come back to the FDA and nominate it, for example for use in acne, that that would be acceptable to do that?

DR. KO: Well, that would be again reviewed. As I said, we did review those. It's just not in the document.

DR. DOHM: The answer is yes, that if it was -- you could renominate the same substance but for a different use, and then we would consider that nomination.

DR. DiGIOVANNA: Then is it clear somewhere that this has been nominated only for that indication and that someone on the outside would know that they could come back for and have, for example, the studies done on acne?

DR. KO: I think the nomination documents are in the package, so people can see what has been nominated for the compound at this point.

MR. FLAHIVE: This is Jim Flahive. The reviews state at the beginning what each bulk was reviewed for. If you look at the nominations, we try to review what was both nominated as a use and supported.

I highly recommend that people look at the nominations because it's not always cut-and-dried to tell what use is someone is trying to nominate. We do our best effort to do that.

DR. DiGIOVANNA: So that's kind of why I'm

asking this because it includes a mouthwash, and gels, and creams, and a whole variety of things. It does say nail fungus treatment in there, but it also says about use in surgery, and burn care, and dental care.

I find it difficult to extract from this exactly what the nomination is. And I guess my gut is assumption is what the FDA is presenting to us is a global presentation.

If that's not correct, then I need to understand the information that I'm getting. Do you understand what I mean? And if we decide that this is not going to be available for compounding based upon the onychomycosis failure of efficacy, then somehow it should be clear that the other potential indications weren't assessed.

DR. VENITZ: Mr. Mixon?

DR. DOHM: I would just mention that the review is clear as to the use it was evaluated for and what was presented with adequate support. That's the source that people could go to, to find out what, in fact, it was evaluated for and then

could, of course, renominate the same substance for a different use that it wasn't evaluated for. And we would consider that.

MR. MIXON: Yes, and it would be years before it came back up.

I just want to remind the voting members of this committee that pyruvic acid was nominated and FDA recommended approval of it.

In 16 years, I've never been asked to compound pyruvic acid whereas frequently, we're asked to put tea tree oil in a nail fungus preparation. And here, we are going to lose that for reasons that are totally unclear to me. I know there's no studies, but you know how expensive studies are.

Most studies are done by manufacturers who want to bring a $300-a-month prescription to the market. And the alternatives for nail fungus that are FDA-approved are very expensive, and they are -- for the oral ones, there's a lot of toxicity.

You can go on Amazon and buy pure tea tree

oil. Here's one right here that says, "Best for skin tag removal, nail fungus treatment, aromatherapy." To me, that's a medical claim.

Why tie the hands of the compounder who are just trying to help patients with their nail fungus and let stuff like that go?

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Yes. I just did a little Google search and tea tree oil is recommended as a topical treatment by Dr. Weil and is listed also in WebMD. That's just two sources, and there's a lot of sources on the web for this. And as we pointed out, as Bill Mixon pointed out, it's available from Amazon for this use.

DR. KO: Right. We agree with you that there are many products on the market with tea tree oil, both 100 percent as well as those in other formulations.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: I asked Dr. Axelrad this question before. I'll ask it again. In the case of dietary supplements, there would be nothing to

prohibit a pharmacist from going and purchasing a dietary supplement off the shelf, and using that to prepare a therapy for a patient and prescribed -- pardon me; that's my background -- by a physician.

I'm a little confused about why this is even on the list because if I were going to buy tea tree oil, I would probably get it from all the sources that have previously been mentioned.

Is this truly a bulk? And not placing this on the list, does that prevent us from buying pure tea tree oil from CVS, or Amazon, or some place that supplies it as a labeled product to make a preparation?

MR. FLAHIVE: This is Jim Flahive. I think that's a great observation, and a key difference is you can buy tea tree oil that's a cosmetic, but we're looking at tea tree oil as a drug.

Our review division evaluated tea tree oil and the data for it for its use as a drug and people simply want to make drug claims with tea tree oil that they use as a drug.

MS. DAVIDSON: But just to clarify, I still

could go buy pure tea tree oil as a cosmetic because it's not a bulk drug substance and use it to prepare a toe nail remedy if directed by a physician.

MS. BORMEL: Well, you're talking about buying tea tree oil as a cosmetic and making a compounded drug out of it. What we're assessing here is whether you can use the bulk ingredient for use under 503A.

I mean, if this does not go on the list until the time and then it becomes final in a rule, then that particular bulk could not be used in compounding a drug substance. The bulk could not be used to compound a drug under 503A.

Right now, you're saying that -- nothing would happen until the rule is final in terms, but yes, eventually, if it's something that is not on the final rule of bulk substances that can be used, you wouldn't be able to use it in compounding a drug product under Section 503A. I mean, availability as a cosmetic, availability as a dietary supplement, they're regulated in different

manners.

MS. DAVIDSON: I just wanted to confirm because that conflicts a little bit with what we had heard in a previous meeting about going and purchasing dietary supplements, and reformulating them.

DR. DOHM: One thing I'd like to add to that is there is a provision of the statute that allows for compounding from ingredients other than bulk drug substances. That's not at issue today and not being addressed today. But there is another provision with respect to that.

MS. DAVIDSON: Okay. I'm purely asking the question based on access. If someone wanted to go buy pure tea tree oil and paint their toe nails with it, there's nothing in our decision today that would prevent them from doing that.

DR. DOHM: Right.

MS. DAVIDSON: Okay.

DR. DOHM: We're only talking about compounding. I think the discussion that we were talking about in previous sessions -- maybe I'm

mistaking what you were thinking about.

We did discuss about compounding. If somebody were to buy a dietary or to get dietary supplement ingredients and compound another dietary supplement within the purview of CFSAN regulations, we're not addressing that at all.

We're only addressing it in the context of using a bulk ingredient for the drug, compounding a drug under 503A. So remember, dietary supplements have to be for oral ingestion. Cosmetics can affect the structure, the appearance of the skin or something like that.

DR. VENITZ: Two more questions. Mr. Mixon?

MS. DAVIDSON: Gigi, I think it's my understanding that even if we bought 100 percent pure tea tree oil from Amazon, or a mutual drug, or anybody else, we still couldn't incorporate that into a compound regardless of where it came from.

MS. DAVIDSON: I'm just trying to understand where the line is for when something is a bulk drug substance and when it's not. And I think they clarified for me that it's when it's used as a drug

regardless of its source. Am I correct?

DR. VENITZ: Dr. Pham?

DR. PHAM: I was just looking for more clarify on the statement about there being systemic hypersensitivity reported because, right now, I'm kind of leaning towards feeling like the topical may have a place, and there's local irritation side effects. I don't know that those were significant.

I'm more concerned about just that one-line bullet point about there being systemic hypersensitivity. What were those types of reactions? Were they respiratory stress, hives? And how often did that occur?

DR. KO: I found from, actually, the database from FAERs, the FDA reporting database, information about systemic hypersensitivity in case, which could have been confounded too. That's why we didn't have a lot of further discussion and just mentioned it since it also occurred.

DR. VENITZ: Last question, Dr. Jungman?

MS. JUNGMAN: So related clarifying questions here, so given that most of the most

serious AEs with the substance are related to the oral formulation and that this committee has, in the past, made recommendations that are specific to a particular formulation, I'm wondering would this substance -- and you might be the right person to direct this to.

Is there enough of a distinction between the oral and topical formulation that you could make a recommendation like this or is it just you're using the oil either way? And if so, if we were to consider just the topical formulation, would that alter FDA's recommendation in any way?

DR. KO: So let me clarify this. So-called oral formulation are basically oral rinses. They're not really for ingestion.

DR. VENITZ: Okay. Thank you, Dr. Ko. Let's then proceed with the nominator. We have Dr. Pytlarz from NCPA is going to be giving the nominating presentation.

Presentation - Alexander Pytlarz

DR. PYTLARZ: Good afternoon. Thank you for your time today. The first couple of slides are

the origin, and the previous presenter did a well job, so I'm going to kind of skip right through those and get to the heart of the presentation.

He mentioned the physical characteristics as well as the distillation process and the chemical component, so I won't focus on that too much.

This was an in vitro study that we found that talked about tea tree oil and the use of exposure to a couple of the fungi, and bacteria, and whatnot. And in this study, they looked at the minimum inhibitory concentrations and the minimum bacterial fungicidal concentrations of tea tree oil exposed to those.

In this study, they reviewed a few modes of measurement to determine the effectiveness of this tea tree oil. So again, I won't harp on the slides on these but just focusing on seeing that even small amounts of the tea tree oil, when done in vitro, had significant benefits over placebo . You can see the slides that go into the details of each of those.

As I mentioned, it talked about the

effectiveness on microbe respiration and again, the benefits of the tea tree oil, even at those small concentrations, had positive aspects and impact on that, as well as cell wall integrity.

I want to get more into the discussion of human use which is important for our discussion today. As the previous reviewer said, there's information out there that does show effectiveness and possible effectiveness not only in the fungal nail infection but in use in acne and in use in athlete's foot. And the rest of the presentation is here to focus on all aspects of that.

I did speak to the presenter of this, NCPA, and it was the intention of tea tree oil to be available to compounders in all aspects and not just for use in fungal nail infection. So to the question about that, at least that was the intention for NCPA for the submission of this bulk product.

As was mentioned in the previous presenter about the Buck study that was done in 1994. And it was concluded that because clotrimazole 1 percent

solution is not an approved treatment, it kind of makes the study a little flawed. But please note that back in 1994, there actually were no topical approved treatments of nail fungus for medication use out there.

So the effectiveness can be hopefully concluded from that, that the approved treatments of topical fungal nail fungus was in 1994, 2014, and again 2014 respectively, so kind of something to keep in mind that even that study was done, there was no approved topical treatment.

There was a little bit of concern with that in that study that the numbers were a little bit flawed, but the authors of that study did come out and say that there was a 35-percent loss within that study due to culture follow-up.

We kind of reviewed that study on our own and looked at it from a standpoint of how many were actually enrolled, how many were lost, how many patients were then left over, and comparing that clotrimazole 1 percent to the tea tree oil at 100 percent.

You can see that the effectiveness now at the bottom was pretty comparable at 11 percent for clotrimazole 1 percent, and tea tree oil at 7, as well as for culture negativity. And then full or partial resolution was about 61 or 60 percent respectively. The study did provide some useful information.

Again, the study did not compare anything with what was approved, but of course, at the time, there was no FDA-approved information on that. The study does provide information that tea tree oil may be helpful in relieving symptoms, improving nail appearance, and possibly assisting with mycological cure.

Of course, as was approved in 1999 and further, there are nail lacquers that represent an option for physicians to administer topical formulations that allow the vehicle to evaporate and form an occlusive layer that allows for direct administration of tea tree oil and other components directly to the area to help with that.

Compounding pharmacies really give

prescribers the option to include tea tree oil in preparations in combination therapies.

At the time of our submission of slides, we didn't have the opportunity to this, but on the 21st, NCPA received a written letter from a local physician, and I've got copies available for anyone that's interested, who wrote, "As a practicing physician since 1995, I've had the opportunity to treat fungal infections with a vast array of oral and topical agents.

"The use of tea tree oil has become an integral part of topical therapy in my practice due to its safe and effective nature and to remove it from the list of available compounds would be a detriment to my patients." Signed, Dr. William Knudson, dated June 21st of this year, a physician testimonial that I have regarding the use of tea tree oil.

Again, the second study that was presented looked at the double-blind, placebo-controlled comparing placebo with the combination tea tree oil.

I found it interesting that the previous presenter said that there was no studies out there that compared the safety of compounded preparations, but this really is a compounded preparation when you're combining two or more products together in any lab. That's basically the definition of compounding.

We do have some information about the safety of it out there. And we agree that there was -- it's hard to conclude because there was no comparison information, but we want to use this information, too. And this is just an outlay of the way the study was laid out in the treatment program.

But I want to really focus on the area that there was about an 80-percent cure rate with this with minimal side effects. And when you take this information and you -- especially in our world of compounding where there aren't a lot of -- we recognize that there aren't a lot drug-drug trials out there that have the information. You've got to take pieces of information and utilize it in

different areas.

When you'd look at that cure rate, and you compare it to FDA-approved products that is down in the bottom graph, and you show mycological cures of 55, and 60, and 32 percent or overall cure rates of anywhere from 1 to 52 percent, and you compare that against a combination therapy that does have tea tree oil that rates around 80 percent, you feel that there is some effectiveness that can be concluded from the use of that.

Again, we wanted to touch on a couple other areas because, again, this wasn't just completely focused on nail fungus. We did find a couple of study on the effectiveness with athlete's foot, and this was again a randomized placebo-controlled study that used tea tree oil at 25 and 50 percent with a third arm of being placebo.

It was a 4-week trial that looked at the clinical response of that, and again, just a layout of the way the patients were enrolled and the different outcomes that were related to this.

Again, this information was provided to you

ahead of time, so I'm sure you've had the opportunity to look at that.

Again, looking at the tables, you can see on table 2, over to the very right, again, the mycological cure rates for placebo versus 25, versus 50 percent.

The authors were able to conclude that the tea tree oil did have a higher rate of cure when compared to placebo, and that was considered statistically significant.

The clinical response at the end of 4-week treatment with four patients was significantly higher, and they felt that the effective cure rate was appropriate with tea tree oil.

Again, the last part with the efficacy in acne, this was a review study that was looked at on the efficacy, tolerability, and potential modes of action.

The authors looked at seven studies for the use of tea tree oil in acne. Five of those seven studies were looking at tea tree oil at greater than 5 percent versus -- the previous presenter

talked about large, large amounts of tea tree oil which, at least, in compounding is not really utilized.

We're talking about, again, that 5 percent range where they looked at that over a 4- to 8-week treatment area. And the summary slide, again, will provide some information, but the author suggested that tea tree oil applied twice daily for multiple weeks is likely to reduce the number of lesions seen in acne.

I want to focus on really just the first slide or the first line items that talk about comparing tea tree oil 5 percent with benzoyl peroxide and the efficacy, 45 versus 29 percent, but the big thing that jumps out to me is the tolerability and the frequency of adverse effects where benzoyl peroxide is around 79 percent versus tea tree oil at 44 percent.

Here, to present some information about the safety of that product even at a 5 percent range, of course, the outcomes of this both show that treatments were significantly reduced and

comparable.

The study concluded that -- they looked at five of the seven studies, and they reported adverse effects. One of the seven studies reported no serious adverse effects, but the rates of adverse reactions were actually higher and really the mainstay product for acne, which is benzoyl peroxide, compared to tea tree oil and that concluded tea tree oil was similar tolerability with other facial acne medications.

One final point about safety, a second review that was done -- and this is a quote from the study -- that looked at the rationale for continued use of oil rests largely on the apparent use for oil over almost 80 years.

The authors examined oral toxicity, included that incidence of oral poisoning in children and adults resulted in no deaths and everybody responded and recovered, as well as dermal toxicities really rarely ever happened.

I think for compounders, we are looking for the use of this in topical applications, not oral

for sure.

So just some final words, of course, they were already expressed again, but just to reiterate the importance that tea tree oil is readily available without a prescription as was mentioned.

Tea tree oil really provides physicians and allows patients access to alternative methods that will help improve medical conditions, allow physicians to provides patients with options when they failed standard treatments, and again as was mentioned, to allow options where it's not systemic medications that have the potential for other adverse effects that wouldn't be seen in tea tree oil, and lastly, because of what pharmacists can do to work with our patients to help them prevent any kind of adverse effects that may be seen with inappropriate use or storage and help prevent any incidental side effects.

I thank you for your time, and I'm happy to try to answer any questions you may have.

DR. VENITZ: Thank you, Dr. Pytlarz.

Any questions? Any clarifying questions by

the committee?

(No response.)

DR. VENITZ: I see none. Thank you, again.

DR. PYTLARZ: Thank you.

DR. VENITZ: We appreciate it.

Committee Discussion and Vote

DR. VENITZ: Now, we are supposed to have an open public hearing, but we have no open public hearing speaker, so we're going to move right into our discussion and vote.

I'm looking for any discussion items. Dr. DiGiovanna?

DR. DiGIOVANNA: Yes, John DiGiovanna. I appreciated the last presenter showing some of the data in a little bit more detail. It reminded me -- and I'm not certain that I'm exactly accurate about this, but it did remind me that it was 1999 that Penlac was approved. It reminded me that I was on the advisory committee at the time.

There was a discussion, my recollection, that it shouldn't be approved because its efficacy was so poor. However, my recollection is that I

argued at the time that there were no alternatives and that for a large percentage of the population, more so as the population aged, that has poor circulation in lower extremities from diabetes and congestive heart failure, that chronic dermatophyte infections in part that spurred and difficult to treat because of involvement of the nails, onychomycosis, leads to a scenario where frequent breaks in the skin lead to recurrent cellulitis, and lymphangitis, and progressive difficulty, and sometimes is really tremendously debilitating and leads to mortality and loss of limbs.

This is a chronic problem and having a topical therapy for individuals that couldn't tolerate systemic therapy because of other medications was a real need.

We didn't need to demonstrate so much that it was going to cure everyone or cure most of the individuals, but managing the disease was a distinct advantage.

I'm sure it wasn't because of my comments, but many people recognized that there was an

advantage for having a topical preparation for this. And there are others now. However, there are many patients who do not respond to those and having an additional therapy would be often a reasonable thing to have.

For tea tree oil, I understand, from the FDA's presentation, the toxicity is minimal. It's with the systemic utilization of the preparation, which probably is not related to this indication. It would seem to me that, if we could recommend that this be available, limited as a topical, considering it is so widely used in so many cosmetics and would have a real indication here for a population that could have some use for it over a long period of time, I think it would be a benefit.

Another reason why it's useful to have an additional treatment for a chronic infectious disease is because the organisms get resistant to the things that we use.

When someone has a condition like this for many decades, they've used most of the things that are available. I'm sure that most of you don't go

through the dermatologic literature as a regular basis, but some of the things that people have brought up and studied are, for example, treatments like Vaseline for treatment of the nails and a variety of topical agents that you wouldn't necessarily think would be of benefit and may not be of benefit.

There's a great need for people to try to manage these chronic infections. And my perspective seems to be that the toxicity of this seems to be limited. The safety seems to be good, and I think there may be a role for it.

DR. VENITZ: Thank you. Any other comments?

(No response.)

DR. VENITZ: So is everybody ready for the vote? You've got the go-ahead.

DR. KO: I would like to address some of the issues brought up by the nominator. This is in regard to the other indications that were brought up, and also, Dr. DiGiovanna asked about them.

Regarding tinea pedis, the discussion was brought out on the Satchell study. Now, the

nomination for tea tree oil that we have is for a strength of 5 to 10 percent whereas where the Satchell study used tea tree oil with 25 percent and 50 percent, so we're not exactly dealing with what is being nominated.

The other indication that was discussed was on acne. Studies regarding tea tree oil in comparison with benzoyl peroxide was brought up. And yes, there was a study showing that it was having percentage reduction in total lesions.

On the other hand, there was also another study comparing 5 percent tea tree oil to benzoyl peroxide that showed that it was inferior. In addition, there was another study that showed tea tree oil being inferior to an unapproved product as well.

I think we haven't fully known the efficacy of tea tree oil in these other indications, and so that's why we haven't actually put those into the review package.

DR. VENITZ: Okay. Thank you, Dr. Ko.

Any final comments? Yes, Dr. Pham?

DR. PHAM: I appreciate all the context. I do think, though, that when we were talking about the tea tree oil against the clotrimazole -- and the historical context definitely helps -- it's not like clotrimazole is placebo here.

It is also an active antifungal agent. Obviously, its absorption into that site is probably questionable, but the fact that it was not inferior to me still feels like a comparable conclusion.

I'm just curious, and I don't know if this information is available, whether there's actually that much of a fluctuation in strength that's being compounded. Can it can go from 5 to 25 percent? I'm not sure who would be best be able to speak to that.

DR. VENITZ: I'm calling back our nominator.

DR. PYTLARZ: Thank you. You're asking the question that if it's available from 5 to 25 percent?

DR. VENITZ: Introduce yourself again, please.

DR. PYTLARZ: Thank you. Alexander Pytlarz from the National Community of Pharmacists Association.

Just to understand the question, were you asking if it's available in strengths of 5 to 25 percent?

DR. PHAM: Yes, I was just wondering if there was kind of like an industry standard that limited the frequency. Like, in the frequency that you see, is it pretty much a tighter control than that or can it have that variable of a strength?

DR. PYTLARZ: In my experience from the physicians that we've worked with, it ranges anywhere from about 5 to 30 percent, 5 to 25 percent, yes.

I guess it's the experience of the physician when they've seen it used, in addition, when it's combined with other products like clotrimazole or terbinafine and stuff, they might reduce it.

DR. VENITZ: Thank you.

Are we ready for the vote then? This time my preliminaries are much shorter than usual. I

don't know why. If there's no further discussion, we will now begin the voting process. Please press the button firmly on your microphone that corresponds to your vote.

(Vote taken.)

DR. HONG: Tea tree oil, we have 8 yeses, 2 nos, and 1 abstain.

DR. VENITZ: Let's go around the table. I think we're going to start with Dr. DiGiovanna at this time.

DR. DiGIOVANNA: I voted yes. I think that with the large percentage of the population that battles dermatophytes in this area that have frequent resistance to the available therapies and the limited number of available therapies, I think there's a potential utility for this.

I think that the FDA showed quite well that, topically, there's very little adverse events that have been observed, and it's widely available. And I think, as a topical agent, there's a role for it so I voted yes.

DR. GULUR: Padma Gulur. I voted yes as

well, for it's a well-characterized substance, and it is widely available. The toxicity data presented was minimal.

While there may be some questions with regards to the efficacy, there is still data available that it is showing some efficacy in that area. And I feel like, given all of these considerations, it should be added to the list.

DR. VENITZ: This is Jurgen Venitz. I voted yes. I would add to my two previous speakers the longstanding use that has been around since '82, maybe even longer than that.

MS. DAVIDSON: Gigi Davidson. I voted yes for the reasons previously stated. I also think there's a pretty good body of evidence to support other multiple indications that weren't mentioned here like anal fissures and seborrheic dermatitis.

I also wanted to recognize what the presenter brought out at the conclusion of his presentation that the triad, the prescriber/pharmacist/patient relationship, could be a better arena to prevent misuse of OTC

products, that this would be a very carefully controlled environment to prevent misuse.

I would qualify all these statements by suggesting that if it is added to the list, it be limited strictly to topical use.

MR. HUMPHREY: William Humphrey. I voted yes for many of the same reasons already stated.

DR. HOAG: Steve Hoag. I voted abstain because I support its use topically, but in other routes, I'm not so sure. It may not be appropriate, but for topical use, I would support its use, so I kind of split the difference.

MS. JUNGMAN: Elizabeth Jungman. I voted no because I didn't find the evidence of effectiveness compelling in light of other alternatives. I will qualify that, though, by saying that I considered only the nomination that was included in the briefing documents.

If there are other indications for which there is more compelling evidence of effectiveness, that wasn't part of my vote.

DR. PHAM: Katherine Pham. I voted yes. I

found that the comparison to other active antifungal agents was enough for an indication that is difficult to treatment to begin with and that even the FDA-approved therapies can sometimes fail, that this could be another alternative.

I would hope that it was being used for refractory use, but I know that we can't control for that here. I was a little concerned still by the multiplier of strength that can be prescribed.

I don't know that the evidence presented is compelling enough to say that it should not just be limited topical but also to its strengths, probably like 10 percent or less, and I'm not in any place to say that. But if it did get brought back for a topical use for other indications, it would also be helpful to see potentially some recommendations steering towards optimal concentration.

DR. VAIDA: Allen Vaida. I voted yes, although with other drugs on the market, I usually don't vote yes for things like this, but I really didn't think there was a strong case against safety, that this was an unsafe product. And I

know this is oftentimes a tough condition to treat.

DR. CAROME: Mike Carome. I voted no primarily because I think there's insufficient evidence that it's effective for the proposed use that we were asked to consider.

DR. WALL: Donna Wall. I voted yes for the reasons previously stated. Again, this is yes for topical use only.

DR. VENITZ: Thank you. We are almost done, but before we can really wrap it up, we're going to take a break. So I want to remind everybody on the committee not to talk about any of the topics that have been discussed as a committee. And let's all reconvene at 3:45 p.m. for our last session.

(Whereupon, at 3:35 p.m., a recess was taken.)

DR. VENITZ: Let's reconvene the meeting, please.

Before we begin the last session, I want to introduce our newest addition, a special government employee who will be part of our discussion. He is Dr. Jeffrey Brent, distinguished clinical professor

of medicine at the University of Colorado, and he will help us on the DMPS topic. Thank you.

We will now continue with the FDA presentation first. And I'm asking Dr. Suh, who is a clinical team leader in the Division of Hematology Products, to give us the lead.

Presentation - Kathy Robie Suh

DR. SUH: Good afternoon. My name is Kathy Robie Suh. I'm a clinical team leader in the Division of Hematology Products in the Office of Hematology and Oncology Products in CDER.

Today, I will present the assessment for dimercapto-1-propanesulfonic acid, which I will refer to as DMPS in this presentation. This slide shows the review team for this nomination. The DMPS nomination is for the use, treatment of heavy metal poisoning. The applicable routes of administration for the nomination are oral, and IV, and intramuscular injection.

The materials received for this nomination consisted of literature publications which were mostly anecdotal case reports and uncontrolled

series of cases of exposures to various heavy metals in patients who were treated with DMPS. The available information for the assessment was limited, but what was available was reviewed.

No product containing DMPS is marketed in the US. The available chemistry information for DMPS was obtained from the Heyl Scientific Product Monograph, which is a document that has information regarding a DMPS product that is marketed in Germany.

FDA does not have access to the information used to support the market approval of the European DMPS product.

DMPS is a chemically-synthesized small molecule. It is usually supplied as its sodium salt. It is non-hygroscopic and exists as the monohydrate.

DMPS sodium salt monohydrate has a molecular weight of 228.3 Daltons. The monohydrate is stable in the crystalline form. It's relatively stable in aqueous solution, but it's labile to oxidation.

The Heyl Monograph states DMPS is purified

by release from the lead salt. There are potential in-process impurities including lead, allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid.

Potential heavy metal contamination can be monitored using USP compendial methods. However, as you know, in the U.S., compounding regulations do not require evidence of adherence to good manufacturing process requirements, so there's no assurance that the in-process levels of impurities do not exceed safe levels.

These next two slides summarize available animal and nonclinical information for DMPS, again, based on the German product monograph and also a 2009 World Health Organization document.

DMPS chelates heavy metals, but the mechanism of action is not fully characterized. It increases urinary elimination of arsenic and interferes with arsenic methylation.

For mercury, it promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal

and distal tubular cells.

Administered intravenously, it mainly distributes in plasma and kidneys and has an elimination half-life of about 20 to 60 minutes.

In nonclinical studies, DMPS has relatively low acute toxicity and relatively low chronic toxicity in dogs and rats. There's no evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems. There are no data available on central nervous system or respiratory system effects.

DMPS is not mutagenic in the Ames test and it shows no reproductive toxicity or teratogenicity. These toxicity assessments do not address the potential toxicities of any potential impurities such as, for example, lead or allyl bromide, which is a known mutagen. There is no information available on carcinogenicity of DMPS.

This slide summarizes the safety information that we know. Exposure to DMPS is not without risk. There have been cases of serious skin reactions, including the case of Stevens-Johnson

syndrome in an 11-year-old boy and one death due to severe diffuse desquamation in a patient who received DMPS.

The most common reported adverse reactions are dermatologic reactions, nausea and vomiting, hypotension, increases in serum transaminases, transient bronchospasm, fever, and leukopenia. Most reported reactions have been typically mild or moderate in severity.

This slide summarizes the clinical evaluation of effectiveness. There are a number of publications of clinical experience with DMPS in the literature for various uses, including the uses listed here.

Most of the reports are uncontrolled investigations or anecdotal cases and are cases of treatment of various heavy metal exposures.

The literature reports do not include sufficient information to reliably evaluate the effectiveness of DMPS for treating heavy metal poisoning, though as mentioned earlier, the nonclinical studies clearly establish that DMPS can

chelate heavy metals. The reports of use in humans do not allow a conclusion of a clinical benefit of administration of DMPS to people.

Most of the studies described a single or group of persons with exposure to heavy metals who are given DMPS and show an increase in excretion with those metals.

Though symptoms are sometimes described, the symptoms are non-specific such as fatigue, memory loss, headache, and change in those symptoms, if it's documented, is not shown to correlate with degree of metal excretion.

Most series lack controls, and where controls are used, the studies do not adequately establish baseline characteristics, do not control for factors such as effects of supportive care such as the hydration, removal from the source of exposure to heavy metals, for instance. Most of these studies do not include a clearly stated measure of treatment success.

There are no adequate scientific studies that demonstrate the effectiveness of DMPS as used

in drug products for the treatment of heavy metal poisoning or other uses.

There are FDA-approved drug products for treatment of heavy metal poisoning as listed in this slide. These drug products were approved on the basis of safety and efficacy data submitted to the Agency to support adequate labeling for the use of these agents for the treatment of toxicity due to the various heavy metals as indicated.

The drug products include calcium disodium versenate for lead, Chemet or succimer for lead, BAL for arsenic, gold, and mercury poisoning, Cuprimine, a penicillamine for Wilson's disease. It's also approved for cystinuria and active rheumatoid arthritis and trientine approved, a second line in Wilson's disease.

This slides summarizes the historical use of DMPS in compounding. At the 1998 meeting of the Pharmacy Compounding Advisory Committee, it was stated that compound dates to the mid-1980s.

In the literature, we find clinical use of DMPS mentioned as early as 1958. Just internet

searches, just looking at intended uses implied or asserted on those sites, seems to focus on two things: this very large representation of treatment of persons with presumed mercury toxicity due to mercury amalgam dental fillings. And also, there are some mention of treatment of persons with autistic disorders.

In conclusion, our review has found that DMPS is well-defined and can be identified consistently, but manufacture may leave residual impurities including lead, and we do not know the levels of these in compounded products.

Clinical investigation of use of DMPS has not been adequate to establish safety, and there's no clear evidence for clinical benefit of DMPS as currently used.

There are FDA-approved medications available for treating heavy metal poisonings. Historical use dates to the 1950s.

In conclusion, based on the information that we have, we recommend that DMPS not be included on the list of bulk drug substances that can be used

in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Suh.

Let me ask the first questions. The uncontrolled and anecdotal reports that you reviewed -- what was the preferred route of DMPS administration?

DR. SUH: In most of the administrations, the route was oral. We see a lot of oral administration in the mercury amalgam studies, but there also were parenteral administrations.

DR. VENITZ: Were they single-doses or were they repeat doses?

DR. SUH: Some were single-dose, and some were multiple dose. Many of the studies looked at administration of a dose and then urinary excretion of the heavy metal.

Maybe one thing to note is that even in cases where the agent was being given, the DMPS was being given to treat, let's say, mercury poisoning due to dental amalgams, even in studies where some

patients did not even have such amalgams, an increase in excretion was seen. So the efficacy of the treatment really has not been established in any of those controlled studies.

DR. VENITZ: Thank you. Then my second question; in the approved agents right now for lead, arsenic, and mercury poisoning, how were they approved? What clinical evidence did support their role?

DR. SUH: Well, the approvals date, I think -- our earliest approval is BAL, I think, which was approved back in 1945. And then there, I think, in 1953, we had versenate, calcium disodium.

DR. VENITZ: What they did actually look at clinically?

DR. SUH: There are studies that provide sufficient data to support the labeling of the product. And this both has to do with a demonstration of efficacy, as well as a demonstration of safety for the product as marketed.

DR. VENITZ: Was efficacy defined as

increased excretion of the heavy metals or did they look at clinical symptomatic?

DR. SUH: Excretion; excretion is measured.

DR. VENITZ: Okay. Thank you.

Any other questions? Dr. DiGiovanna, did you want to --

DR. DiGIOVANNA: Yes, John DiGiovanna. I'm not familiar with the management of this group of diseases, but are the approved medications useful for all of the heavy metals or is there an unmet need? Are there some toxicities that are not managed by the approved drugs?

DR. SUH: If you look at the literature, you'll certainly find -- now, I'm thinking about U.S. use and U.S. labeling. You find that some products are used for agents for treatment of toxicity of agents that they're not really approved for, if you will.

For instance, BAL is really the only product that is labeled, if you will, for arsenic poisoning. However, penicillamine, if you look at textbooks and reviews, recommendations and things

that are also used, we do find that penicillamine and succimer, for instance, are used for arsenic poisoning, though neither one of those had sufficient data to support labeling for those uses. However, those approved products have some quality assurance in the manufacture.

DR. VENITZ: Dr. Gulur?

DR. GULUR: Of the approved products that are FDA-approved, how many of them can be given intravenously?

DR. SUH: Intravenously, as labeled, if you want to speak to what we have labeled, the BAL is administered. It's an oil-based product, and it's administered by deep intramuscular administration. The others are oral products as labeled.

DR. GULUR: Do you see an indication, especially with, say, arsenic and mercury in a large dose toxicology or poisoning, where intravenous might offer an additional benefit to intramuscular?

DR. SUH: The intravenous administration -- well, let me just say, for BAL,

there is known -- it's an uncomfortable one, uncomfortable treatment that has to be given on a repeated base, so we certainly would welcome alternatives. And of course, alternatives would have their own set of adverse reactions or problems. But would an alternative be welcome? Certainly.

DR. VENITZ: Dr. Brent?

DR. BRENT: I wonder if I could speak to several of these points, and thank you for that nice overview.

You had mentioned that you didn't feel that there was sufficient efficacy data for DMPS and that we had other agents for which efficacy has been demonstrated.

The answer, the truth is that none of the agents, whether you're talking about the approved ones or DMPS, have ever shown efficacy in terms of outcome for metal poisoning.

What they have shown is efficacy in terms of enhancing metal excretion, and DMPS has shown that just as well as the other agents that are currently

approved.

To get to the question that was raised about intravenous, it's true we do not have now a water soluble intravenous chelator available for serious heavy metal poisoning.

This is a really serious deficit. Now, most of the times for metal poisoning, we can get by with oral chelators. We can sometimes give BAL, but BAL, as you mentioned, is very difficult drug to give. It has a high side effect profile.

It cannot be given intravenously. It's a deep, painful injection. It's in peanut oil. People can be allergic to it. And it's a very inadequate agent. We also have very little experience with it. It's been used, but there's very little experience with it.

DMPS is a good intravenous chelator in terms of enhancing metal excretion. So in that sense, it does fulfill a niche that is currently not filled.

Patients who have serious arsenic or mercury poisoning in the acute phase, which is a time when you want to treat them, can have significant amount

of gastroenteritis, and it can be very hard to actually get them to take an oral medication.

There is this niche in terms of an intravenous chelator that DMPS will definitely fill. All that being said, I'm very sympathetic to your observation that so much of the use of DMPS in this country today, as compounded, is for things like treating people with dental amalgams and treating autism, for which there's no evidence of any efficacy. But in terms of serious heavy metal poisoning, it does potentially, as an intravenous preparation, fulfill a very important niche.

DR. SUH: I should say that this nomination came in for all routes of administration and was evaluated as such. And the other point I would make is that in saying that DMPS has not been shown safe and effective, I am not saying that it is not safe and effective.

We do though, I guess, also have to be cognizant that, at least, as in the German monograph cited that being as it's purified from a lead-containing source itself. In the compounding

arena, we have no knowledge of what the levels of those residual impurities from manufacture might be.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: In veterinary medicine, they use an injectable arsenical to treat heartworm disease in dogs. And we are frequently presented with unintentional self-administration by a student or a veterinarian, and they have become intoxicated with arsenic.

In years past, we have researched heavy metal chelators for treatment of those incidents, and we commonly came across a German product, which was available from a company in Houston, Heyltex. And that was listed as the internationally recommended drug of choice for arsenical and mercury poisoning.

Is that product still available? Does that represent an alternative to patients in acute need of heavy metal chelation for mercury or arsenic? And what would be the options there?

DR. VENITZ: Do you want to answer?

DR. SUH: Others may know, but to my knowledge, that European product is still available. And I think when we look at global, worldwide, what might be the preferred drug being marketed in Europe, that very well could be. But I know that if you look in some others, you, again, get -- well, from the U.S. perspective, you get a different first-line, if you will, recommendation.

In terms of availability, we've talked some about getting things under IND, so I don't particularly want to rehash those routes. Being able to obtain that product under an appropriate IND setting for emergent use is possible.

DR. VENITZ: Dr. Brent?

DR. BRENT: Yes, you do bring up a good point, and the product is the European by Heyl as a manufacturer.

With regard to this issue about potential lead contamination, Heyl actually has a certificate of analysis that they provide. And there's not much lead in it. It's about 4 micrograms associated with a 2-gram dose.

So lead poisoning would not really be a significant issue, particularly since you really only need to use this drug for a very short period of time where you'll get people over the acute phase, and then they can be transitioned to an oral agent. So I don't think the lead contamination issue is a significant issue.

DR. VENITZ: Thank you. Any final question for Dr. Suh?

(No response.)

DR. VENITZ: Thank you, Dr. Suh.

Then we have our nominator. Third time is a charm. Dr. Anderson is going to nominate.

Presentation - Paul Anderson

DR. ANDERSON: Thank you. So many, many of the points I'm going to make have been discussed, so I'll go through this reasonably quickly.

Under efficacy, I did want to bring up a severe case of mass acute poisoning where DMPS was used and was life-saving. That was in 2003 in Maine, and it was a felonious poisoning of some people at a church. Sixteen people were poisoned

and transported to ER.

Cary Medical Center was the first place that they went where they were exhibiting all of the signs of acute arsenic poisoning. We were able to contact, first, Dr. Karen Simone, who was involved in the triaging and assessment of the drugs to be used. She's currently the president of the American Academy of Clinical Toxicology.

They took the sickest people over to Eastern Maine Medical Center, and they were put on the standard BAL therapy because as was mentioned earlier, BAL is the only one with the on-label arsenic indication.

Knowing, as was mentioned, the painfulness of that approach -- the treatment protocol is Q4 hours for two days, and then you decrease after that in the acute phase.

The worst patients got the BAL right away, and the BAL was failing according to the toxicologist. So the medical resident got a hold of Dr. Simone. She called a group of toxicologists, including Dr. Michael Kosnett, and

they recommended to start DMPS.

Dr. Kosnett also sent us a note -- neither of these doctors could be here to bring this, but they sent notes for me to present, so this is his.

"Thank you for bringing this to my attention." He read the FDA review brief and believes it's incorrect in several instances. And he believes that, in toxicology, there is a clear need for DMPS and would like it to be available.

At the time, in 2003, Dr. Kosnett was aware of a compounding pharmacy in California which was actively producing injectable parenteral DMPS and so they were called after hours and were able to get the product because it was already in production.

It should be of note, when considering emergency use in an acute arsenic poisoning, for instance, that if a compounding pharmacy had to make product from base raw material, it takes a minimum of 16 days to get the material produced into a parenteral form. So that would be outside the window of use for an acute poisoning.

Fifteen out of the 16 were treated with IV DMPS. For reasons that I could not unearth in the investigation, the one patient who was not was the only patient who died out of the acute group.

There were no adverse events reported and the Attorney General is on record as confirming it was arsenic poisoning that was done. Essentially, the person laced the coffee with a large, large amount of arsenic.

We also sought counsel from UCSF and the Vancouver Poison Control Centers, and obviously the caveat that every poisoning is unique in individual. They also recommend the intravenous route over the BAL, Q4 hours, and then decreasing the dose for a couple of reasons.

One is their feeling is that the IV use of DMPS would be a faster and more efficacious way of getting the arsenic out of the body and also, it's also much more tolerated by the patient, pain-wise, et cetera.

As was mentioned earlier, there is a large amount of peanut oil in the injection, and not

everybody can handle that.

The other thing that the poison control were clear on is that the side effect profile are lower with DMPS than BAL.

The other thing, as was mentioned just a few minutes ago, is in many cases, especially in arsenic poisoning where there's a great deal of nausea and vomiting going on, the oral products that are available may not be appropriate for use in the acute stage.

With regard to safety, as was mentioned in the first setting, a lot of the data -- and in fact, all of the data that we could unearth really comes from European sources because that's where the drug began, as the Heyl monograph was mentioned but others as well.

Looking at human safety using the FAERS data system we looked at, there were two cases that came up. Of interest, the first case was a moderate adverse event of a hypotensive crisis when the physician gave the DMPS intravenously too rapidly which later I'll bring up.

This is a drug that I've used in clinical practice a fair amount; that is, one of the administration cautions is there's a definite administration rate that is supposed to be used. The patient recovered.

In the second case, the association of DMPS administration and the patient's death in my, and my most people who have read the case, opinion are not correlative because the patient injected themselves with elemental mercury.

Complicating that as a method of suicide, he received the inappropriate treatment of diphenhydramine and was sent home, which is an unusual treatment for elemental mercury injection.

Then 10 days later, he went to the ED after he had had a DMPS treatment, and he died of mercury deposition throughout the body which would've come from the mercury injection most likely.

These are the citations. Again, all are European, but they look at human use of unithiol and its use as an antidote in a number of instances of poisoning.

This is an American pharmacy that is ISO 9001 compliant, and so their adverse event reporting system is ISO 9001 compliant and follows GMP.

Since 1999, there's been 10,000 plus orders. Patients receiving it are estimated because of the dose size versus the dose administration so quite a large number of DMPS at just this one pharmacy and there are a number of compounding pharmacies that do produce DMPS.

They're approximating doses at around 67,000. The complaints received through their ISO 9001 compliance system to-date have been zero and that was the one pharmacy I could get clear data from.

Now, alternatives were brought up, and the discussion I'm about to give has already been really given so I'll just give it very briefly, but I'd want to put a point on it.

Versenate, the only metal that is not a label indication as far as poisoning with versenate is really arsenic and then mercury. Chemet is an

oral, as you know, substance, and it does not have a label indication for arsenic either. It is also going to be oral and probably not appropriate in acute toxicity.

We talked a lot about BAL. And the major issue with BAL is the volume of inert oil that's being given; that's peanut oil. The pain, the frequency, and in the case, at least in 2003, where they started with that, is both the product they could get and the standard of care, they had to abandon it for non-efficacious use.

Penicillamine and syprine don't have an arsenic indication either. With mercury, there's maybe possibly a little bit of crossover, but arsenic and mercury are really excluded from most of these.

As was brought up, there were the U.S. label indications. But if the experience, at least in that one very bad acute poisoning, was of note, it probably is true that DMPS is preferable in acute arsenic poisoning.

I've done many thousands of parenteral

administrations with DMPS over the last 20 years. We have not had any serious life-threatening or high-grade adverse events during that time.

I discontinued the use of BAL and penicillamine mostly due to oral intolerance with penicillamine and pain, and patient compliance with BAL. Also, occasionally, there's difficulties in sourcing drug.

So again, it's extremely safe when ordered, monitored, and managed by a qualified physician. And as was brought up a little bit earlier, another one of the substances, having it available through 503A would assure that it was only filled through qualified physicians.

The other thing that I think becomes of note is if it is going to be used in an emergency, and the product has to be synthesized from base product, it would not be able to be synthesized in enough time to deal with the emergency. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Anderson.

Any comments or questions? Mr. Mixon?

MR. MIXON: Thank you. First of all, I'd like to just say how fortunate we are to have Dr. Brent here. I just finished looking through your 50-page CV. I'm very impressed; clinical emeritus professor of toxicology.

My question is for Dr. Anderson. I'd like to get a little more clarification on why you think it would take 16 days for a compounding pharmacist to produce this preparation. That's just not true. We can have it done in a matter of hours if we had the pure active ingredient.

DR. ANDERSON: I will defer the answer to that to the pharmacist who will be commenting in the public session.

MR. MIXON: Okay. I just didn't want the --

DR. ANDERSON: Yes.

MR. MIXON: -- the committee to have the wrong impression about that.

DR. ANDERSON: Thank you.

DR. VENITZ: Dr. Carome?

DR. CAROME: In the numbers you gave on your

personal use, Dr. Anderson, you said 5,000 doses or 5,000 patients you used --

DR. ANDERSON: Doses.

DR. CAROME: Doses.

DR. ANDERSON: Doses, yes.

DR. CAROME: What number of patients would that translate into approximately?

DR. ANDERSON: At this point in the day, I don't have the reverse math written down. It is over a 20-year period, though. So it's a series as was mentioned earlier, and so there's some division involved there.

DR. CAROME: With those, are the majority of those -- was that for acute arsenic or mercury poisoning or did you also use it for some of the other indications that we see being used like autism and concerns about amalgam-related mercury?

DR. ANDERSON: I see. Yes. So that's a very excellent question which I should've prefaced with. I've never used DMPS or any other chelator for things like any of those instances.

In the beginning, I was in practice in an

area where there were still arsenical pesticides available and being used, and we had a lot of exposures to deal with. So really, it was that exposure, yes.

DR. CAROME: If you could go to your slide 13, if someone could put it up? So these are numbers from one pharmacy alone?

DR. ANDERSON: Correct.

DR. CAROME: I guess you probably don't know this. Do you think this will be an extraordinary high incidence of arsenic and mercury poisoning to be making this much?

What is the incidence? Do we know the incidence roughly in the U.S. of arsenic and mercury poisoning?

DR. ANDERSON: Yes. Because I'm not connected to and don't have the background data from this pharmacy, I really can't speak to that at the moment. I can only speak to what my practice has been. Yes, sorry.

MS. DAVIDSON: I did research that before this meeting, and the most recent data I could find

was 2010. There were 927 arsenic exposures in the U.S., no statistics on mortality.

DR. VENITZ: Dr. Brent?

DR. BRENT: You were referring to poison center data. Poison center data generally reflects far more exposures, or even possible exposures, or non-exposures than really serious exposures.

I had an opportunity to mine a database that we use, which is called the Toxicology Investigators Consortium -- it's a big consortium with almost all practicing toxicologists across the country -- to see their use of DMPS

The consortium started in 2010. Since 2010, not a single medical toxicologist has found a reason to use DMPS in this country, the reason being that we would reserve it for really high quality acute arsenic or mercury poisoning, which is rare, which is very rare.

As we can see here, there's probably a lot of illegitimate use of it, and I recognize that as a concern. And that is a big concern. I was listening a little while ago when you were

talking in the presentation that was given, I believe, by Dr. Jarow.

I gleaned from that, that while we can advise for routes of administration, we cannot advise approval for indications. But I think even the routes of administration issue is a big one because a lot of it is being given orally and there's no real legitimate oral need for it.

I think one suggestion to get around this problem would be to only allow intravenous use of the medication and probably would be even better, if possible -- and I notice this was the American College of Medical Toxicology's recommendation as well -- to allow it to be used for intravenous in-hospital use. And I think that would cut down a huge amount of the illegitimate use that we see.

DR. VENITZ: Thank you, Dr. Brent.

Any other? Dr. Davidson?

MS. DAVIDSON: I just had one comment on the availability of the alternatives. Being, again, in a veterinary institution, I'm constantly looking for chelators because our patients ingest all kinds

of heavy metals all the time.

Calcium versenate is gone. It is not available. It can be compounded, I believe, because it does have a monograph. BAL is currently available but is frequently on the short supply list. And penicillamine right now is available for $25,000 for a bottle of a hundred tablets.

So it does leave many practitioners with no alternative, except some sort of compounded preparation. In this case, it would be calcium versenate or maybe the DMPS.

DR. VENITZ: Dr. Dohm?

DR. DOHM: I just want to comment that the committee can certainly recommend limitations outside of route of administrations such as hospitalization use. But it's unclear that we would be ever be able to enforce such a limitation or put that limitation on the substance because it's so downstream from the compounder.

So the compounder doesn't need to know necessarily whether or not the drug will be used in a hospital setting or otherwise for purposes of

compounding the drug.

Although that can be a recommendation as to the limitation, it's clear that we would be able to do much about it, just so you know.

Then the other point I'd like to make is that with respect to intravenous formulation alone, it's my understanding -- and please correct me if I'm wrong -- some of these other uses such as for autism is also IV.

DR. VENITZ: Dr. Gulur?

DR. GULUR: This is just a clarification on what you had asked. So if we were to say in-hospital use, that cannot be enforced, but intravenous can be enforced?

DR. DOHM: We can limit the route of administration so we can limit the compounder to IV. But as I said, I believe that the autism use -- and I'm not sure about the dental amalgam -- is also IV.

DR. VENITZ: Any final comments to Dr. Anderson's presentation?

DR. DiGIOVANNA: I have one.

DR. VENITZ: I'm sorry. Go ahead.

DR. DiGIOVANNA: It's my understanding that the discussion we had earlier about different types of INDs is that the single-patient emergency IND that is one that could be enacted within a short period of time, 24 or 48 hours, would be one that would be applicable for a rare event that would occur a few times a year in the U.S. and might be managed in a tertiary care center would be an appropriate way of fulfilling the need for that rare situation.

DR. VENITZ: Mr. Mixon?

MR. MIXON: If we'd limit the drug to that extent, it just simply won't be available, period. I mean IND or not, compassionate use or not, it won't be available. I just want to echo what Gigi said. Remember, we have drug shortages all the time. And when this drug is going to be needed, it's going to be needed now, not three weeks from now, and that's where the compounder can really come to the table and help the patient, if it's available.

DR. VENITZ: Last comment. Dr. Jungman?

MS. JUNGMAN: I actually just want to understand Mr. Mixon's comment. So what would it be that would make it unavailable? In my understanding, you said that, if it's not available sort of for the broad spectrum of uses, then there wouldn't be a case for continuing to keep it available for this kind of acute toxicity use. Or what would be the reason that it would become unavailable if we had to kind of go through that emergency IND step?

MR. MIXON: If the committee votes to add it to the do not compound list, then that's the end of it. If the committee votes for it to be available, whether it's only intravenous or intravenous for use in hospitals, then presumably, our chemical manufacturers will continue to produce it, and stock it, and make it available. So the availability would be there.

Does that answer your, Elizabeth? I'm not sure.

MS. JUNGMAN: I guess. Thank you.

Open Public Hearing

DR. VENITZ: Dr. Anderson, I think that concludes your presentation. Thank you very much.

Let's then move on to our final open public hearing. Let me read into the record the OPH statement.

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 relationships 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 conjunction with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, that 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. With 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.

So I'm now asking our last open public hearing speaker to come to the podium or the microphone and present.

MR. McGUFF: All right. Thank you very much. My name is Ronald M. McGuff; call me Ron. I am the owner of McGuff Compounding Pharmacy Services, Incorporated in Santa Ana, California. We've been in business for 17 years. We compound with bulk drug substances. We create sterile and non-sterile drug products.

I have some background information based on some of the questions that have been asked. The Heyl product is available in the United States. It just returned. It is being compounded now by compounders.

I need to go back to the first part, which says I do have a financial relationship with this product, and I paid for my own way to get here.

The FDA has indicated in its brief to you and at this meeting, the FDA has indicated a vote

by this committee against inclusion to the approved bulk drug substance list will not restrict access to DMPS.

FDA indicates a physician or a hospital that needs DMPS will be able to obtain this drug through the expanded-access or intermediate-sized access IND process.

This may not be true. Let me explain. One of the most difficult activities of a compounding pharmacy performs is to locate raw material manufacturers that are willing to sell very small quantities of active pharmaceutical ingredients and comply with the regulatory overhead that is part of compounding pharmacy today.

The economic reward for these manufacturers is very small, and there is the added potential for regulatory review and product liability lawsuits. Please understand, there will be no access to any drug if a raw material or API is not available.

Simply put, if the API is not available to the manufacturer, no drug will be available to use in an IND.

The 15 persons in the Maine poisoning, who were just talked about here, were poisoned and survived. They were very fortunate because we had the DMPS on hand and available when this emergency occurred.

The current system requires the physician to write a prescription for an identified patient to obtain the drug. This works. This system works very well.

Today, under the current system, DMPS API is available. If the FDA does not include DMPS on the approved list, the API is deemed not to be safe and not to be effective for compounding. This obviously is not good news to the DMPS manufacturer. This alone may cause the manufacturer to leave the U.S. market.

A bit about Heyl. Heyl is the only company that we have been able to locate that manufactures DMPS that meets all the requirements for the FDA. We've looked high and low at alternative sources, and we cannot find one, so we are dependent upon one manufacturer for DMPS.

But the FDA tells us to replace the current prescription system with the expanded access or the intermediate-sized IND process. I believe the additional bureaucratic overhead will keep many physicians away, as they are already overloaded with work. This will lead to an even smaller market for DMPS.

The DMPS API manufacturer has to balance the FDA statement of not safe and not effective, smaller purchases in an IND market, higher cost, and greater liability to the economic particulars of staying in the market.

I believe based, on my experience with Heyl and 17 years of working with suppliers, that the sole API manufacturer will want to reduce their liability and simply exit the market.

The reward is not equal to the risk. Again, there will be no access to any drug if the raw material or the API is not available. It makes sense to keep the status quo. It works.

Additionally, there's no guarantee that a manufacturer, physician group, or physician will

apply for an IND of any type, no guarantees to that. If there is no active IND, DMPS will not be available. There will not be a market to sell to, simple as that, so the DMPS in the United States will not be available.

So how long will it take to get DMPS to a physician to treat a patient if another arsenic poisoning exists? Unfortunately, I disagree with Bill here. When you compound a sterile drug, just the act of proving that it's sterile takes 14 days. By the time you understand there's a need for production, and if you can get it in production on day 1, you bring it out, you put in quarantine, you wait for 14 days until you get the sterility test back.

Then on the 16th day, you go ahead and deliver. This does not take into effect or account the time of getting an emergency IND together, the time of getting DMPS from Europe through customs, which is an interesting thing all by itself, to us to compound. This is merely the time it takes to compound a sterile drug, 16 days.

For acute poisoning, 16 days may be too late. Patients will probably die and for no good reason. FDA has not reported a single death directly attributable to DMPS in 47 years of record keeping. The system, as it stands now, works. The status quo works. No harm will be done if you vote to include DMPS to the approved list.

(Pause.)

MR. McGUFF: A vote against inclusion is a vote to potentially remove DMPS API from U.S. soil, significantly increase the time to obtain sterile DMPS in case of another poisoning, take away a readily available tool for physicians to improve patient healthcare, and it adds bureaucratic burden to physicians when none is needed.

In addition, just one other quick comment, the CDC recognizes that arsenic poisoning could be used as a terrorist agent. We've kind of shown that in Maine, that 16 people ingested arsenic poisoning. I believe that would relate today to a terrorist attack.

So thank you for your time.

DR. VENITZ: Thank you. Are there any questions or comments by the committee? Mr. Mixon?

MR. MIXON: I just want to clarify. Thanks, Ron, for letting us know about the sources of this. I just assumed that PCCA and others had it. My comment about we could have it available in hours of course assumes we have the active ingredient on hand, so Ron just added valuable information about that.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. I'm just a little confused what the status quo is. When you get someone acutely intoxicated with arsenic or mercury, are you making IV preparations of DMPS and waiting 14 days for sterility test? Or are you making it and then using it? Are you not using sterile -- so I'm completely confused by the status quo.

MR. McGUFF: No problem. No problem. I understand the question is about is it available currently and how is it available, if it is currently available.

We get enough prescriptions, and this is how it works. We receive a prescription from a physician, and we compound for that prescription. Under 503A, they allow us to anticipate those prescriptions.

It's anticipatory compounding. We do keep a supply of DMPS on hand all the time in anticipation of those prescriptions that we're going to receive. It is on hand, and it is from the Heyl raw material.

DR. CAROME: Just to follow up, how many prescriptions are you filling a week, say, or a month?

MR. McGUFF: The information that you saw was from my pharmacy.

DR. CAROME: So you have an epidemic of arsenic poisoning, or you're using it for other things?

MR. McGUFF: We respond to prescriptions from the physicians.

DR. DiGIOVANNA: That was sort of my question, but can you give me a little bit more

about the demographics? I believe was that 5,000 prescriptions or what geographic area?

MR. McGUFF: The McGuff Compounding Pharmacy -- I'm sorry. The geographic area we ship to -- we have licensing in every state that requires licensing; 49 out of 50 states require licensing. The territories and protectorates, we also are allowed to ship to.

Basically, we're allowed under California law, which is where we're located. We can ship to any US licensed physician within the United States.

Yes. Sorry.

DR. GULUR: He's my boss. So what age group are you dispensing the majority of your prescriptions to?

MR. McGUFF: I beg your pardon?

DR. GULUR: How old are the patients?

MR. McGUFF: I don't recall. Excuse me. I am not involved in the prescription receipt process. We have pharmacists that when we receive prescriptions, if we don't have enough information relating to other drugs that the patient is taking,

allergies and things of that nature, we will call the physician back and ask about that.

Typically, physicians don't indicate what the treatment is actually for. It's just they're looking for this particular drug.

DR. GULUR: Is the age group difficult to determine from the prescription, the age of the patient, perhaps by dose, the dose that you are dispensing?

MR. McGUFF: As a gut feeling, I would say we don't -- we do get birth dates so we have the data. Have we extrapolated that from the data? We have not, but we can certainly do so if you'd like to, if you'd like us to do that.

DR. GULUR: Thank you.

DR. VENITZ: Last question. Dr. Davidson?

MS. DAVIDSON: I'd like to follow up on that just a little bit. The medical toxicologist recommended -- they recognize an appropriate use of DMPS, and they recommended in their letter monitoring of physicians by appropriate state regulatory agencies.

I would like the committee to consider that if we try to change prescribing practices by limiting supply, have we really changed prescribing practices? I would suggest that, not with just this drug but if we're really concerned about inappropriate prescribing, I would mention pain gels as another possible example of that, that we focus on getting the appropriate regulatory agencies to consider appropriate actions for those prescribers and not cut off supplies of drugs to needy patients.

I realize that is entirely out of the purview of this committee and the FDA, but I would suggest that as a place to start instead of cutting off supply for people that really need it.

MR. McGUFF: Thank you.

Committee Discussion and Vote

DR. VENITZ: Thank you for your presentation.

That concludes the open public hearing portion of this meeting, and we won't take any further comments from the audience.

Now, we're moving on the committee's discussion and vote. We already had a lively discussion, but I'm opening the floor for any comments, discussion items. Dr. Pham?

DR. PHAM: I just wanted to give a little context also in use in pediatrics and actually ask this of Dr. Brent because I believe BAL does not have any pediatric indication, or information, or sort of dosing data. So I think that only oral options are available.

However, there is oral. There's data on oral dosing of DMPS in children. It's not IV, but with a lot of things with pediatrics, we have to extrapolate. So just any sense of place in therapy for pediatric poisoning?

DR. VENITZ: Dr. Brent?

DR. BRENT: Certainly, we see significant heavy metal poisoning in pediatrics in lead encephalopathy, for example, which is an absolute medical emergency that mandates IV therapy where we don't have IV agents really available. So there is a very important role there, yes, totally agree.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome, again. As you know, I don't get to vote on this one because 1999 Public Citizen opposed including this product on the bulk drug list with concerns that it was being -- the compounding of it was being abused.

I am pretty much convinced that there is a narrow need for this drug for patients with acute severe arsenic or mercury poisoning and that the drug is -- there's data to support its use in that narrow thing.

I remain concerned that there's a tremendous amount of abuse and misuse of this drug when it's compounded. But I think there is a narrow appropriate use, and doctors should have access to it in that case.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Yes. I think, basically, I was going to say something very similar here that we have to acknowledge that the majority of the use here is not in these acute toxicity situations.

So I'm just kind of thinking through this

supply problem because what I hear us struggling with is, should we encourage a use for which there is very little evidence of effectiveness in order to maintain a level of supply for the very limited use that we -- and I think that's -- I don't really actually know how to resolve that.

How do you convince a manufacturer to continue to maintain supply without allowing kind of broad uses that are not supportable? But I think that is -- certainly, I wanted to kind of at least make it explicit what I think we're kind of talking about.

DR. VENITZ: Dr. Brent?

DR. BRENT: Your point is exactly right. And that's I think what we're all struggling with here.

To me, the best way of dealing with this -- and I realize we can't police this necessarily -- but at least to express the spirit of the way it should be done would be to have it available for in-hospital intravenous use.

Nobody is going to be admitting people to

hospitals to treat their autism with chelating agents or to treat their dental amalgams with chelating agents.

Will people expand outside of that? Well, yes, I suppose they do to some degree at their own risk. But I think that's the best we can do here to try to encourage legitimate use and discourage illegitimate use.

DR. VENITZ: Mr. Mixon?

MR. MIXON: Dr. Brent, when your patient population needs this drug, where is it obtained from, do you know? Is your hospital able to compound it?

DR. BRENT: Medical toxicologists are all aware that when we need it, if we need it, that we go to McGuff because they're the ones that have the pharmaceutical-grade preparation available. They can get it very quickly from them.

DR. VENITZ: Last question. Dr. Jungman?

MS. JUNGMAN: I think I hear your point. I think realistically, if we put this on the 503A bulks list, there's a big market here, and it will

continue.

I think that the idea that we sort of count on folks to say, "Well, this committee thought that, really, it should only be used in hospital use so we're not going to compound it outside of that setting," I think is unrealistic. If it's on the list, it's on the list. It's legal for people to do it.

DR. VENITZ: Very last --

DR. DiGIOVANNA: Sorry. If we were to be able to put it on for only in-hospital use, would that include infusion centers, which are pretty widely available?

DR. VENITZ: Very, very last --

MR. MIXON: I'll make it brief. If we say it's available only for in-hospital use, I will submit that Mr. McGuff will not be able to provide it on a timely basis because he won't have the demand for it to keep it available ahead of time.

I'm not speaking for him. I'm just speculating, but I bet you that'll be the outcome.

DR. VENITZ: Let me proceed with the vote

because we're already behind schedule.

DR. BRENT: I'm sorry. Can we make this vote contingent upon the requirement for in-hospital intravenous use?

DR. VENITZ: I was going to read -- this is your first vote, so the vote is yes, no, or abstain, but then I'm going to go around the table, and you can add any comments like any additional restrictions that you'd like on the record. But the vote is you have three buttons to push basically.

Let me just read the whole preliminaries again since we do have Dr. Brent joining us.

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.

In order to perform the voting process, please press the button, yes, no, or, abstain,

three times on your microphone. You will have approximately 15 seconds to vote.

After you've made your selection, the light will continue to flash. Let me know if there's any problems. So go ahead and vote.

(Vote taken.)

DR. HONG: For DMPS, we have 7 yeses, 4 nos, and zero abstain.

DR. VENITZ: Now, let's go around the table. And Dr. Brent, let's go ahead and start with you.

DR. BRENT: I believe I've already expressed my beliefs here of what would be the appropriate way of using this drug. There's a lot of illegitimate use in this country. We want to discourage that.

We do want this to be available where it is necessary, and sometimes it is necessary. To me, the best way to attain that would be to have it available as an intravenous preparation for in-hospital use. I realize that could still be misused, but I think that's the best we can do.

DR. VENITZ: So no, you voted to not put it

on the list?

DR. BRENT: I voted not to support the --

DR. VENITZ: So we have the correct the official records. You meant to vote in favor of putting it on the list, which is not what it currently rates. That's all right.

The actual vote is going to be --

DR. BRENT: My actual vote was to be yes.

DR. VENITZ: Right. So it would be 8, 3. It would be 8 yes, 3 no.

Dr. DiGiovanna?

DR. DiGIOVANNA: This is one of the more difficult challenges. And from a philosophical perspective, the fact that a drug can be abused but is also necessary in certain circumstances -- I don't believe it should not be available in life-saving circumstances because other people may choose to abuse it.

However, the difficulty here is that it may not be available if it's needed. And unfortunately, in a world that we are living in, it very well may be needed on a very short-term basis

and a very emotionally-impacting basis. So I think for those individuals who need it, it should be available, and I certainly would limit it to in-hospital intravenous use if that is in any way possible.

DR. GULUR: Padma Gulur. I voted no. I feel very strongly that it's needed as an intravenous preparation having personally had to use it once. It has an extremely important role to play in severe arsenic poisoning, and it's the only intravenous formulation that we have available.

However, I voted no because what I heard here was that the incidence of mercury and arsenic poisoning of that severity is really low. There's very few people who are exposed to that.

It's true we are all under the terror -- we feel the fact that people can take advantage of the situation and poison the country. But in the meantime, we also heard that to go through this route, which is to rely on the compounding pharmacies to provide this, we would have to make sure that they could use it for other purposes so

it was economically viable for them.

It seems to me that the right way to do this is this needs to have another avenue, that if there is a drug that is that needed by this country, the only way to get it is to also make it available for potential abuse.

It does not seem to be the right way to do things and I would hope that there are other avenues that can be followed for these drugs to be legitimately used for the purpose that they are needed for.

As rightly pointed out, intravenous use, hospital would be a great restriction, but if it cannot be assured, then we are putting another larger population at risk by putting it on the list.

DR. VENITZ: Jurgen Venitz. I voted yes. Just two comments to support that. Number one, we had not only testimony today but also background submissions that, I think, very strongly argued in favor of keeping it on the 503A list.

Number two, in response to something, I

think, Dr. Day mentioned, I think implicitly or not or explicitly or not, we do consider alternative treatments, both the availability and the comparative efficacy, if you like.

This is one of those cases where that definitely went into my decision-making. I would also strongly encourage the IV-use only. Everything else, I don't think we can enforce. But I do think we can make sure that it still can be sterilely compounded.

MS. DAVIDSON: I voted yes and quickly just would limit it to IV use in-hospital as has been stated. And I also wanted to make a comment that it wouldn't need to be made in anticipation at risk of losing money.

USP 797 does have a provision for emergency release of product prior to testing results within certain parameters, so it is certainly possible to make this within the hour that Mr. Mixon mentioned.

MR. HUMPHREY: William Humphrey. I voted yes. I believe the toxicologists that there is a clear indication for this drug in acute

life-threatening heavy metal toxicity. And I also would recommend that it be used intravenously in hospitals.

DR. HOAG: Steve Hoag. I voted yes. This was a very difficult decision, but I figured the risk-to-benefit ratio was in favor of keeping it on the list.

MS. JUNGMAN: Elizabeth Jungman. I voted no for many of the same reasons as Dr. Gulur. I am very concerned about the acute toxicity situation that has been discussed quite a bit here, but the vast majority of the use is a use for which I didn't see a lot of support and was just uncomfortable exposing that significant majority of patients, given where the data is on that.

DR. PHAM: Katherine Pham. I voted yes even though every fiber of my being wanted to abstain, but I don't believe in abstaining.

I didn't have time to make this comment in previous discussion, but I did research a little bit further. There had been a nomination for this to go on the essential medicines list in the World

Health Organization back in 2010 and went through a pretty decent independent clinician review that brought it up for nomination there.

They ultimately decided that DMPS would not be included due to insufficient evidence, and I think that was back in 2011. Although that made me feel like I should say no, at the end of the day, it goes back to the criteria that we're all charged with looking at, which is whether or not there are alternative therapies available and there is not in this route. So I kept it very practical, and I said that it should be available only as IV.

DR. VAIDA: Allen Vaida. I voted no for all the reasons that Dr. Gulur has already made.

DR. WALL: Donna Wall. I said yes because of the severity of the poisoning. We really need to have that kind of product. We know it's being misused, but then we keep opioids on the formularies and use them, and they're being misused too.

The key is to having the medical communities step up and make sure that they are working with

folks and that drugs are being used appropriately, and if they're not, to sing out loud.

Adjournment

DR. VENITZ: Okay. Thank you. That doesn't just conclude our vote, it also concludes the meeting.

I want to thank everybody for what turned out to be a very lively and productive meeting. I hope you all have a safe trip home, and we'll see each other again in November, I believe.

Thank you.

(Whereupon, at 5:08 p.m., the afternoon session was adjourned.)