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.)