FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Monday, May 8, 2017

8:31 a.m. to 12:03 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Hong, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Michael A. Carome, MD, FASHP

(Participation in May 8th session and artemisinin discussion)

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director, Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

John J. DiGiovanna, MD

Senior Research Physician

Laboratory of Cancer Biology and Genetics

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Center for Cancer Research

National Cancer Institute

National Institutes of Health

Bethesda, Maryland

Padma Gulur, MD

(Participation in May 8th session)

Vice Chair, Operations and Performance

Duke University School of Medicine

Department of Anesthesiology

Duke University Medical Center

Durham, North Carolina

Stephen W. Hoag, PhD

(Participation in nicotinamide adenine dinucleotide disodium reduced, nettle, ubiquinol, and vanadyl sulfate session)

Professor

Department of Pharmaceutical Science

University of Maryland, Baltimore

Baltimore, Maryland

Katherine Pham, PharmD, BCPS

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Jurgen Venitz, MD, PhD

(Chairperson)

Professor and Vice Chairman

Virginia Commonwealth University

School of Pharmacy, Department of Pharmaceutics

Richmond, Virginia

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

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PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

TEMPORARY MEMBERS (Voting)

Elizabeth Unger, MD, PhD

(Participation in May 8th nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide disodium reduced session)

Chief, Chronic Viral Diseases Branch
Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases
Office of Infectious Diseases
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Atlanta, Georgia

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:31 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning. Please let's convene our meeting. I would first like to remind everyone present to please silence your cellphones, Blackberry's, and other devices if you have not already done so. I would also like to identify the FDA press contact for this open session meeting, Ms. Lyndsay Meyer.

If you're present, please stand.

Thank you. Let me start by introducing our panel for today. Dr. Braunstein, starting with you, please briefly introduce yourself.

DR. BRAUNSTEIN: Hello. I'm Ned Braunstein. I'm senior vice-president for regulatory affairs in pharmacovigilance of Regeneron Pharmaceuticals, and I'm the industry representative.

DR. CAROME: Mike Carome, director of Public Citizen's Health Research Group, and I'm the consumer representative member.

DR. HOAG: Hello. I'm Steve Hoag from the University of Maryland School of Pharmacy, where I'm a professor in pharmaceutical sciences.

DR. WALL: Good morning. My name is Donna Wall. I am a representative of NABP.

DR. PHAM: I am Katherine Pham, the senior officer of the Drug Safety Project at The Pew Charitable Trust, and I am representing public health advocacy.

DR. DiGIOVANNA: I am John DiGiovanna. I'm a dermatologist, and I'm a senior research physician at the National Cancer Institute.

MS. DAVIDSON: I'm Gigi Davidson. I'm the chair of the USP compounding expert committee, and I'm representing USP.

DR. VENITZ: I'm Jurgen Venitz, clinical pharmacologist and professor at Virginia Commonwealth University.

DR. HONG: I'm Cindy Hong, designated federal officer for the Pharmacy Compounding Advisory Committee.

DR. GULUR: Hi. I'm Padma Gulur. I'm an

anesthesiologist and professor and vice chair for operations performance at the Duke University.

DR. UNGER: Hi. I'm Elizabeth Unger from the Centers for Disease Control and Prevention in the chronic viral diseases branch.

CAPT KULICK: Hi. I'm Corrinne Kulick. I was the clinical analyst on the NADH review.

DR. CHAN: Hi. Good morning. I'm Yen-Ming Chan. I'm an ORISE fellow with the Office of New Drugs.

DR. LAWSON: Good morning. I'm Rosilend Lawson. I'm acting lead of the Pharmacy Compounding Advisory Committee team.

MS. BORMEL: Good morning. I'm Gail Bormel, from CDER Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

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

DR. GANLEY: Charlie Ganley, director of Office of Drug Evaluation IV.

DR. VENITZ: Thank you, and good morning again. My name is Jurgen Venitz. I'm the

chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC, and I will now call the committee to order.

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 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 will be reminded to please refrain from discussing the meeting topic during breaks or lunch.

Today, we will receive updates on certain issues to follow up on discussions from previous meetings, including quality standards and conditions at certain compounding facilities.

We will also cover five bulk substances nominated for inclusion on the list of bulk substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act: nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide disodium reduced, nettle whole plant, ubiquinol, and vanadyl sulfate.

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

As described in the April 17, 2017 Federal Register Notice, the committee will be discussing

six bulk drug substances nominated for inclusion on the Section 503A Bulks List. The Federal Register Notice identified the uses FDA reviewed for each of the six bulk drug substances being discussed at this meeting. These uses reflect those for which adequate support was provided in the nomination.

In addition, the nominations and the FDA's reviews for the bulk drug substances, which are included in the briefing document posted on FDA's website, identified the proposed and reviewed uses, dosage forms, and routes of administration.

The nominators of these substances have been invited to make a short presentation supporting their nomination.

To the extent that the nominator's presentations include information about additional uses, dosage forms, or routes of administration, I'll remind the committee that these additional uses, dosage forms, and routes of administration are not part of the agency's review because the nominators either did not nominate those uses, dosage forms and routes of administration, or they

were not adequately supported.

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 Board of Pharmacy, the United States Pharmacopeia, and of 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 the 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, or 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; teaching/speaking/writing; patents and royalties; and primary employment.

During this meeting, the committee will discuss five bulk drug substances nominated for inclusion on the Section 503A Bulks List. FDA will discuss the following nominated bulk drug substances and the uses FDA reviewed: nicotinamide adenine dinucleotide for reducing fatigue in multiple sclerosis; nicotinamide adenine dinucleotide disodium reduced for reducing symptoms of fatigue in chronic fatigue syndrome; nettle whole plant for glycemic control; ubiquinol for glycemic control; and vanadyl sulfate for diabetes, hypoglycemia, hyperlipidemia, heart disease, and preventing cancer.

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

Based on the agenda for today's meeting and

all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note that Dr. Steven Hoag has been recused from participating in the discussion of voting for the nicotinamide adenine dinucleotide session of the 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 the United States Pharmacopeia.

Section 102 of the Drug Quality and Security Act amended the Federal Food, Drug, and Cosmetic Act with respect to the advisory committee on compounding to include representatives from NABP and the 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 under particular matters at issue. Instead, they serve as the voice of the NABP and USP, entities with a financial or other stakes in the particular matters before the advisory committee.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ned Braunstein is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals.

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 topic at issue that could be affected by committee's discussions. Thank you.

DR. VENITZ: Thank you. We will now proceed with the FDA introductory remarks from Dr. Julie Dohm.

I would like to remind 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.

FDA Introductory Remarks - Julie Dohm

DR. DOHM: Good morning. As I mentioned earlier, I am Julie Dohm, the agency lead on compounding. I would like to welcome you to the seventh meeting of the Pharmacy Compounding Advisory Committee.

Today and tomorrow, we will discuss six bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used for compounding under Section 503A of the Act. As mentioned by Cindy, they are NAD, NADH, nettle, ubiquinol, vanadyl sulfate, and tomorrow, we'll be discussing artemisinin.

Today, we will also provide you with an inspection update of compounders under Section 503A of the Act. Tomorrow, we will also present a category of drug products nominated for placement on the list of drug products that cannot be compounded under Sections 503A or 503B because they present demonstrable difficulties for compounding. That topic is oral solid modified release drug products that employ coated systems.

As in the November meeting, we have scheduled time for the nominators to speak and time for an open public hearing after each topic. I would also like to provide you with an update on policy documents that the agency has issued since the committee last met in November.

In December, FDA published a proposed rule to amend its regulations to add a list of bulk drug substances that may be used in compounding under Section 503A of the Act. This is also known as the 503A Bulks List.

This proposed rule identifies the criteria by which bulk drug substances will be evaluated for inclusion on the Section 503A Bulks List and proposes to add six bulk drug substances that have been discussed at previous PCAC meetings to the list. It also proposes that four substances that have been discussed at previous PCAC meetings not be included on the list.

The comment period for this proposed rule closed on March 16th. We have reviewed the comments and will respond to them in the final rule.

Also in December, FDA issued two final guidances, one concerning the agency's policies regarding the prescription requirement under Section 503A of the Act, the other concerning electronic drug product reporting for outsourcing

facilities under Section 503B of the Act.

The final guidance entitled, Prescription Requirement Under Section 503A of the FD&CA, sets forth FDA's policy concerning certain prescription requirements for compounding human drug products for identified individual patients under Section 503A of the Act.

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

The final guidance entitled, Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act, updates reporting instructions for drug compounders that choose to register as outsourcing facilities.

Finally, in December, FDA issued two draft guidances concerning the agency's proposed policies regarding compounding and repackaging of

radiopharmaceuticals by state-licensed nuclear pharmacies and compounding and repackaging for radiopharmaceuticals by outsourcing facilities. Each draft guidance document was available for public comment for 60 days. The comment period for the draft guidances closed on February 27th.

In January, FDA issued a revised draft guidance entitled, Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. That guidance describes the conditions under which FDA does not intend to take action for violations of the Public Health Service Act and the FD&C Act when a state-licensed pharmacy, a federal facility, or an outsourcing facility dilutes, mixes, or repackages certain biological products outside the scope of an approved BLA.

The agency also issued a final guidance in January entitled, Repackaging of Certain Human Drug Products by State-Licensed Pharmacies and Outsourcing Facilities. That guidance describes the conditions under which FDA does not intend to

take action for violations of certain provisions of the FD&C Act when a state-licensed pharmacy, a federal facility, or an outsourcing facility repackages certain human drug products.

FDA's policy documents, including the draft and final guidances, and the proposed rule that I just discussed, appear on the FDA's compounding website under the section titled, Regulatory Policy Information.

Again, thank you for your participation on the Pharmacy Compounding Advisory Committee. We look forward to a productive meeting and to continuing to work together. Thank you.

DR. VENITZ: Thank you, Dr. Dohm.

We will now begin with our first formal FDA presentation. Dr. Rothman will discuss compounders under Section 503A of the FD&C Act, quality standards, and FDA findings.

FDA Presentation - Sarah Rothman

DR. ROTHMAN: Good morning. My name is Sarah Rothman, and I am senior policy advisor in the Office of Unapproved Drugs and Labeling

Compliance in CDER's Office of Compliance. Today, I'm going to provide an update on some of the things that we're seeing when we do inspections of compounders. As you all may recall, there were some questions that were raised during our last meeting about the status of compounders and what we're seeing during FDA inspections.

As you may recall, during our last PCAC meeting in November 2016, we saw a photo of a compounding pharmacy that used technology such as barcode scanners, computer-connected weighing scales, powder containment enclosed work area, and we briefly discussed some of the compounding practices and technology, and concluded that additional information would be helpful at this meeting.

Today, we'll discuss some examples to help illustrate the range of compounding technology and practices that we see during our inspections, and we will also provide an update, and we'll review the quality standards applicable to compounding at 503A pharmacies.

The manufacturing standards maintain that compounders impact the quality and safety of compounded drug products. Compared to drugs compounded in outsourcing facilities or conventional manufacturing facilities, drugs compounded in 503A compliant pharmacies are subject to less rigorous manufacturing standards and are potentially at greater risk of product quality problems such as variability in potency and purity.

As you know, compounders that are regulated under Section 503A of the FD&C Act include state-licensed pharmacies, federal facilities, and licensed physicians that have not elected to register with FDA as outsourcing facilities.

503A pharmacies number in the thousands, and they're primarily regulated by the states. FDA does not inspect the vast majority of the thousands of compounders who seek to operate under Section 503A because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA.

Therefore, the agency is generally not aware

of potential problems with their compounded drugs or the quality of their compounding practices unless it receives a complaint, such as a report of an adverse event or visible contamination.

FDA works with states to identify and take appropriate action against compounders whose practices present the greatest public health risks, and we continue to work to strengthen our collaboration with the states.

Finally -- and this will become more important later in the presentation -- it's important to note that all compounders are considered manufacturers under the Act. Even though their drugs can quality from certain requirements of the Act, they remain subject to all other requirements, and we'll go over that in more detail in a bit.

As you can see from the slide, we've conducted numerous inspections of compounders. This data is a bit dated. We've now inspected over 400 compounders, and we've taken appropriate regulatory action, which can include warning

letters, working with the Department of Justice on enforcement actions, and when a pharmacy appears to be compliant, we refer the inspection to a state.

We've also seen numerous recalls associated with compounded drugs. In the majority of these cases, it's been due to a lack of sterility assurance of drugs that were required to be sterile.

This slide shows warning letters issued to facilities seeking to operate under Section 503A of the Act and includes warning letters issued between December 6, 2013 and December 8, 2016.

As you can see, more than 90 percent of the warning letters contain violations of Section 501(a)(2)(A) of the Act, which is the insanitary conditions provision.

Compounding with domperidone was cited in 23 percent of warning letters. As you may recall, we discussed domperidone at a prior PCAC meeting. Compounded drugs containing domperidone are not eligible for the exemptions in Section 503A because they are not the subject of an applicable United

States Pharmacopeia or National Formulary monograph.

Domperidone is also not a component of an FDA-approved drug, and it does not appear on a bulks list. It was also identified in the FDA guidance as a substance that presents significant safety risks.

Violations of Section 501(b) of the Act were cited in 5 percent of warning letters. Under Section 501(b), a drug is adulterated if it purports to be or is represented as a drug, the name of which is recognized an official compendium, such as United States Pharmacopeia, and its strength differs from or its quality or purity falls below the standards set forth in such a compendium.

Finally, Section 501(c) violations were cited in 3 percent of warning letters. Under Section 501(c), similar to Section 501(b), a drug is adulterated if its purity or quality falls below that which it purports or is represented to possess. Because most of the warning letters cited

violations of insanitary conditions, we will discuss this topic in greater detail in the next few slides.

Before we go into that, however, there was a question that came up at the last meeting about Form FDA 483 and whether FDA cites GMP violations during inspections of compounders. So we wanted to explain a little bit about what a Form FDA 483 is and how that fits into the regulatory paradigm.

The purpose of a Form FDA 483 is to notify an entity's management of objectionable conditions. It is issued to the entity's management at the conclusion of an inspection when the investigator has observed conditions that may constitute violations of the Act or related regulations.

Observations are made when, in the investigator's judgment during the inspection, conditions or practices observed would indicate that a drug has been adulterated or is being prepared, packed, or held under insanitary conditions, or there's another violation of the Act.

Form FDA 483 is not intended to be an all-inclusive list of every possible deviation from FDA laws or regulation. It's important to note that the Form FDA 483 contains observations, not violations. It does not constitute a final agency determination of whether any condition is a violation of the Act or regulations.

FDA considers the observations on the Form FDA 483, along with the investigator's more thorough accounting of his or her findings in the establishment inspection report, and any documentation or other evidence collected during the inspection, as well as any responses from the compounder when it decides what action, if any, to pursue.

I won't read this to you, but just to highlight the preliminary nature of the information on the Form FDA 483, this language is included on every Form FDA 483, and it explains that the Form FDA 483 contains observations and is not a final determination of the agency's determination regarding compliance.

Now, we had some warning letters. Warning letters are issued when FDA finds that an entity has significantly violated the law. I stress very significantly. We issue warning letters when we find violations of regulatory significance.

The warning letter identifies -- it could be poor manufacturing conditions; it could be labeling issues; it could be monograph deviations as we saw with the 501(b) violation. The warning letter also makes clear that the entity must correct the violations, and it provides directions in a timeframe, usually 15 days, for the entity to inform FDA of its plans for implementing corrective actions.

The agency generally performs a follow-up inspection after issuing a warning letter after giving the firm an opportunity to implement appropriate corrective actions to ensure that the corrections have been made.

Now, we will discuss how the 483s and warning letters fit into FDA's regulatory and enforcement process for compounders under

Section 503A.

Just to provide a brief overview, as many of you know, Section 503A describes the conditions that must be met for drugs compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, to qualify for exemptions from three requirements of the Act: pre-market approval requirements in Section 505; labeling with adequate directions for use in Section 502(f)(1); and CGMP or current good manufacturing practice requirements in Section 501(a)(2)(B).

If a drug is compounded in accordance with all the conditions of Section 503A, the drugs are eligible for exemptions from these requirements but only if they are meeting all the conditions of Section 503A.

This slide lists some of the conditions that must be met for compounders for their drugs to qualify for the exemptions in Section 503A. It lists most of the conditions. Of note, conditions that concern the advisory committee in particular

are conditions concerning bulk drug substances, difficult to compound list, and withdrawn or removed list. And we're of course going to be discussing bulk drug substances and difficult to compound nominations at this meeting.

Going back to the question of whether FDA cites GMP violations during inspections, in response to stakeholder input, we announced the change in our inspectional procedure in August 2016 for compounders seeking to qualify for the exemptions under Section 503A.

This change affected the inclusion of GMP deviations on 483s for compounders producing compounded drugs under Section 503A. Again, the 483 contains observations and not violations, but this affected the types of observations that we include on the 483.

Because a 483 does not represent a final agency determination regarding a facility's compliance, formerly, FDA investigators identified deviations from drug production practices on a 483 that could lead to quality problems without regard

to whether the deviations constituted CGMP deficiencies or other deficiencies, such as insanitary conditions.

Investigators, as of August 1st, now make a preliminary assessment regarding the entity's compliance with Section 503A before closing an inspection. If an a 483 is issued to the entity, it does not include observations that represent deviations only from CGMP requirements, unless the investigator's preliminary assessment is at the entity compounds drugs that do not qualify for the exemptions under Section 503A.

After the inspection, FDA conducts a thorough review of the evidence to evaluate whether the entity compounds all of its drugs in accordance with the conditions of Section 503A and other applicable provisions of federal law.

When FDA's more thorough post-inspection review differs from the FDA investigator's preliminary assessment and reveals that an entity fails to produce drugs in accordance with conditions of Section 503A, FDA considers citing

GMP violations and any regulatory action that it plans to issue.

It's important to note that even before this change in procedure, the Form 483 represented observations, and it was a list of what an investigator observed during his or her inspection and when the investigator identified deviations from quality standards that were important to producing a quality product. The investigator included those observations. We never included GMP violations in a warning letter, unless the facility was making drugs that were not eligible for the exemptions in Section 503A.

In our experience, in the majority of cases, compounders that we've inspected have been producing drugs that were not eligible for the exemptions.

Importantly, although drugs compounded in accordance with Section 503A are exempt from certain requirements of the FD&C Act, including GMP requirements, they remain subject to all other provisions of the Act that apply to conventional

manufacturers, including but not limited to the prohibition on preparing, packing, or holding drugs under insanitary conditions.

Because Section 503A does not provide an exemption from the prohibition on insanitary conditions, FDA investigators continue to include observations on Form FDA 483 that appear to constitute insanitary conditions without regard to the firm status of compliance with Section 503A.

Investigators may similarly include on 483s observations that appear to violate other legal requirements from which Section 503A does not provide an exemption. For example, if a drug is super-potent, there's no exemption in Section 503A for that, or sub-potent.

As I mentioned earlier, FDA has identified insanitary conditions in the majority of sterile drug compounders that we've inspected since enactment of the DQSA, and also since the 2012 fungal meningitis outbreak.

As you may know, Section 503A of the Act states that a drug is deemed adulterated if it has

been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth or whereby it may have been rendered injurious to health. To assist compounding facilities and state regulatory agencies in understanding insanitary conditions, FDA issued a guidance entitled, Insanitary Conditions at Compounding Facilities in August 2016.

The guidance provides examples of insanitary conditions, and it provides guidance on what to do if a compounder or a regulatory agency identifies insanitary conditions at its facility.

Compounding under insanitary conditions creates a significant risk of contamination, and I just want to emphasize that, and it could lead to widespread patient harm as we've seen too often, as we saw in the 2012 fungal meningitis outbreak and other outbreaks since then, particularly when a compounder engages in large scale non-patient-specific compounding and distribution of drugs.

FDA, again, may not be aware of compounders

making such drugs, and some states have insufficient resources to adequately oversee compounders. In such cases, patients in states in which the pharmacy -- if the pharmacy is preparing drugs under insanitary conditions and is not adequately overseen by the state, the pharmacy is putting the patients and other states at significant risk. We've seen instances, including the 2012 fungal meningitis outbreak, in which patients and other states, but not the pharmacy's home state, were injured.

As explained in the draft guidance, there are insanitary conditions that are applicable to both sterile and non-sterile production, and there are those that are just applicable to sterile drug production.

Although maintaining sterility is not a requirement, of course, for non-sterile drugs, non-sterile drugs can become contaminated with microorganisms of a type or at a level that could cause serious patient harm. Non-sterile aqueous solutions are particularly susceptible to microbial

growth if contaminated.

Contamination can include non-viable filth in the presence of unintended drug components as well. An example of an insanitary condition applicable to both sterile and non-sterile drugs is handling beta lactam or hazardous drugs without providing adequate containment segregation and cleaning of work surfaces, utensils, and personnel to prevent cross contamination.

An example of an insanitary condition applicable to production of sterile drugs is use of a sterilizing filter that is not pharmaceutical grade.

In this slide and the next few slides, I'll provide some examples and photos of insanitary conditions FDA has observed during inspections of compounding facilities. They highlight the public health risks posed by insanitary conditions and illustrate the importance of FDA's continuing enforcement of the prohibition on insanitary conditions regardless of whether a facility is a compounder or a conventional manufacturer. There

are the things that should never be there.

For example, FDA observes many compounders using non-sterile disinfectants in areas where sterile drugs are produced. We also observed poor personnel practices that increase the risk of contamination.

This photo shows visible mold on a ceiling tile in the clean room of a compounding facility.

This is a photo of filth under the hood, including multiple pieces of medical supply waste and dust build-up in the pre-filter for the ISO 5 hood, posing a risk of contamination to compounded drugs.

This photo shows a compounding area that is supposed to meet ISO 5 conditions for aseptic processing. You can see that a glove box is located in an unclassified carpeted room where the room air was not HEPA filtered. Note also the wooden stool in the photo on the left.

This photo shows a gowned employee working in the clean room with legs exposed.

The HEPA filter in the top photo is located

immediately above the ISO 5 workbench and was observed to have been stained on the filter surface.

The bottom photo is a picture of the non-sterile, stainless steel caulking gun that was used to force non-sterile product through a sterilizing filter. Due to excessive pressure, the drug product exploded, causing a stain on the HEPA filter.

This photo shows a damaged sleeve used in an aseptic glove box, risking contamination.

This is a picture of a toaster that was used to dry heat sterilize and depyrogenate glassware. A toaster oven is not capable of reaching a high enough temperature to be effective.

This photo shows exposed insulation in the ceiling above the doorway to a clean room.

A regular kitchen dishwasher with tap water as a water source is in this photo on the left. The dishwasher and the home detergent in the photo on the right were used to clean the compounding equipment that was intended to be sterile. There

was no subsequent cleaning step. And this is pretty self-explanatory, a dead insect.

Related to insanitary conditions, FDA continues to receive reports of serious adverse events and product quality defects, including contamination related to sterile and non-sterile compounded drugs. And if you look at the second example here, that was a situation where we had insanitary conditions. Two people died and 15 people were injured after receiving contaminated calcium gluconate.

We also included here an example of adverse events associated with a non-sterile drug that was super-potent. We continue to receive both types of adverse events.

In contrast to the previous photos of insanitary conditions, this photo and those that follow are examples of adequately designed compounding areas. In this photo, you see a pellet punching machine used in the production of implantable pellets.

The next photo, you see an appropriately

garbed employee, as well as some laminar airflow hoods.

In here, you can see an automated pumping system that compounds multiple sterile ingredients into a finished solution in a single patient bag. This type of system is often used to compound total parenteral nutrition or TPN products.

Finally, on the left side of the photo, you can see the incubators used to incubate cultures, as well as part of the quality control process. On the right of the photo, you see an autoclave used to sterilize equipment.

In summary, FDA's oversight efforts we believe have had a significant public health impact. We've seen many compounders implement corrective actions after FDA inspections and after receiving FDA warning letters. Some have voluntarily recalled compounded drugs or ceased sterile operations, some until implementing appropriate corrective actions and others permanently.

However, we continue to receive reports of

serious adverse events associated with compounded drugs. It's important to remember that while compounders who meet the conditions under Section 503A produce drugs that are exempt from CGMP requirements, their drugs remain subject to CGMP requirements if the conditions of Section 503A are not met. And of course, they always remain subject to the prohibition on insanitary conditions.

We intend to build on our initial efforts over the past few years by continuing to implement provisions of the DQSA. Julie spoke about some of the recent guidances that we have issued, as well as to continue our inspection and enforcement efforts to take appropriate action to protect the public health while working with stakeholders in the compounding community, in the medical community, and patient advocacy groups, as well as with our state partners. That's all I have. I'm happy to take any clarifying questions.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Rothman. We

have time for clarifying questions. Yes?

MS. DAVIDSON: Sarah, can you talk a little bit about the follow-up process and the follow-up inspection after a 483 is issued or potentially even a warning letter.

DR. ROTHMAN: Sure.

MS. DAVIDSON: How does the pharmacy know when they've corrected the deviations, and more importantly, when do consumers know that a pharmacy has met all the requirements to continue operation?

DR. ROTHMAN: Sure. FDA has a process. If we conduct a surveillance inspection of a compounder -- or this goes for any conventional manufacturer as well -- and we don't find any violations of regulatory significance, we have a process on our website called FMD 145, Field Management Directive 145, where we send a letter to the firm, and we release a copy of the establishment inspection report.

For compounding, we actually are posting those letters on our website so that everyone can see that we didn't pursue any regulatory action.

If we've issued a warning letter and the violations have been corrected to our satisfaction, we would typically issue a warning letter, closeout letter and post that. Also, if it's a 503A pharmacy, we typically refer the pharmacy to the state for future oversight if the conditions of 503A are met and if there's no insanitary conditions that rise to a significant level, and we post that on our website.

For outsourcing facilities, on our dashboard, you can see where it says -- we have the status of the inspection, and it says "open" if we're still considering what to do with respect to the compounder. It'll say "closed" if we decided no further regulatory action on our part.

Unfortunately, we haven't had many compounders that have reached that stage, which is why you don't see too many letters, but we do have some up.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. This sort of follows up on Gigi's question. Could you describe

what the process and timeline is for converting an observational finding in a Form 483 into a determination of noncompliance with the law?

DR. ROTHMAN: Sure. We are actively working to decrease our timeframes, I'll say that, so I can't give you an exact timeframe right now. What happens is the firm usually responds to the Form 483 in 15 days. Sometimes we receive multiple responses from a firm, which can delay things because we'll be sort of down the road of taking some action, and we get more responses that might be in a different place. Sometimes we do additional inspections if we need to refresh the evidence.

We meet and we look at all of the evidence that we obtain from the inspection, any responses from the firm, and we, as a group, decide what type of action is appropriate.

Actually, if you look at the most recent GAO report, they lay out our process in a lot of detail. We have weekly meetings where we go over the recent inspections and decide where they fall

in terms of risk and what action to pursue.

Then if we decide to do a warning letter, we work on writing the warning letter. All the appropriate offices contribute to the warning letter, and we issue it. But we are actively to working to decrease our timeframes on doing that.

DR. VENITZ: Any other questions? Yes?

DR. GULUR: Thank you for your presentation. Would you be able to clarify how it is decided which compounding pharmacies are going to receive inspections?

DR. ROTHMAN: Sure. We do three types of inspections: surveillance, follow-up, and for-cause inspections. As I mentioned, one of our challenges is that we don't know all of the thousands of compounders that are out there. So we do risk-based inspections of compounders that we know of with the focus on compounders that if we have information about the scale of their distribution, how much they're doing, if they're shipping interstate.

We have a number of factors that we consider

past history of adverse events, past recalls; a compounder may have gotten a warning letter 10 years ago, so we know about them, and we are doing a surveillance inspection.

Many of our inspections are for cause. I don't have the exact number with me, but I would say a large portion of them are for cause. We receive a complaint such as an adverse event or a complaint of contamination or something along those lines, and we go out to do an inspection. We always invite the state to come with us.

Then the third type is follow-up inspections, and that's when we've already issued a warning letter; we've done an inspection; and we need to follow-up to see if the firm has implemented appropriate corrective action. We'll go out and do a follow-up inspection.

Those are three situations in which we inspect.

DR. PHAM: Since that August change, do you feel like when you've come in, the majority of those areas still hold to the 503B exemptions, or

do you feel like it ends up being more of a 503A once you've determined?

DR. ROTHMAN: I don't know how many are in compliance with Section 503A. I don't have that information with me, but a large majority we find are not complying with Section 503A, and we have to cite GMPs on a 483 because we're finding noncompliance with 503A. It's definitely -- I don't have the exact numbers with me, but it's many.

DR. VENITZ: Dr. Wall?

DR. WALL: You've had a lot of really good pictures and things talking about the pharmacies, but there are two other sections, looking at the federal facilities and the physician compounders.

What have you found when you've gone in to look at the physician compounders? And what percentage of the time would you say that you've been looking at those as compared to everybody else?

DR. ROTHMAN: We've been focusing on pharmacies -- since the 2012 fungal meningitis

outbreak, we've been focusing on pharmacies.

We have recently done a couple inspections of physicians for cause. There was one -- there was an outbreak of infections recently at a physician's office in New York, and we conducted an inspection. The state was already in there, and the physician had stopped compounding by the time we went in.

We haven't been focusing on physicians, but we have been looking at ways -- we understand that there are concerns about compounding in physicians' offices and compounding in federal facilities, and we are looking at ways to improve compliance, whether it be through more oversight or strengthening stakeholder collaboration, working with the State Federation of Medical Boards, and NABP; we've been talking with Carmen.

We've also been talking with CDC about situations that they have been seeing in clinics. So we're aware of the issue, and we're looking at the best way to focus our resources to address it.

DR. VENITZ: Any other questions for

Dr. Rothman?

(No response.)

DR. VENITZ: Thank you again for your presentation.

DR. ROTHMAN: Thank you.

DR. VENITZ: We are now moving into our first order of voting business, the discussion of nicotinamide adenine dinucleotide, and we have FDA present the results of their review. Dr. Chan will present.

FDA Presentation - Yen-Ming Chan

DR. CHAN: Good morning. My name is Yen-Ming Chan. I'm an ORISE fellow with the Office of New Drugs, and I will be presenting FDA's review of nicotinamide adenine dinucleotide. I will refer to this substance as NAD in the rest of the presentation.

This slide shows the individuals who worked on the review. NAD has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for use in

reducing fatigue in multiple sclerosis.

The nominated route of administration and dosage form is oral capsules. The chemical structure of NAD is shown in the picture on the right. NAD is an endogenous substance that consists of two nucleotide moieties. The substance is water soluble and is unstable. It has been shown that NAD is an unstable chemical that degrades when exposed to temperature above minus 20 degree Celsius, alkaline pH, light, and moisture.

NAD may degrade to byproducts such as nicotinamide adenine mononucleotide and adenosine monophosphate. These two byproducts may further degrade to several degradants, including nicotinamide riboside and nicotinamide.

NAD is typically manufactured through yeast fermentation. Likely impurities may include manufacturing components such as bioburden, residual solvents, and reagents used in purification. Other impurities may include degradation products of NAD, such as nicotinamide

mononucleotide and adenosine monophosphate.

In conclusion, NAD is a well-characterized substance in terms of its chemical and physical properties. However, NAD will be unstable when compounded in the nominated oral capsule dosage form under ordinary storage conditions.

Due to the instability of NAD, it is unclear what dose level of NAD has been delivered to either animals or human subjects reported in the literature that we're going to cover in this presentation.

In terms of general pharmacology, in the human body, NAD is formed through two pathways. NAD is synthesized from tryptophan. In addition, NAD is also recycled through salvaged pathways from other related substances, such as nicotinamide.

NAD is involved in a wide range of biological reactions. NAD is a coenzyme for energy production and metabolism. In addition to its coenzyme role, NAD is a source for enzyme that are involved in post-translational modifications leading to changes in protein functions.

In various proof-of-concept animal studies, the potential benefit of exogenous NAD administration has been explored. It appears that exogenous administration of NAD might help protect against teratogenicity, liver damage, DNA damage, and infarct formation.

I have mentioned earlier in the presentation that since NAD is unstable, the stability issue of NAD calls into question what dose level of NAD was delivered to animals reported in the pharmacokinetic literature that I'm going to present.

In a perfused rat intestine model, when NAD was given orally, it was shown to be absorbed in the small intestine. Similar results was also seen in in vivo rat model.

NAD is hydrolyzed to various related compounds during digestion. When NAD is administered orally and intraperitoneally, the breakdown products of NAD can be detected in the urine. When administered intravenously, NAD can reach the brain in rodents.

In the 21-day repeat-dose study, IV injection of nicotinamide, which is a precursor of NAD, did not result in NAD accumulation. No toxicokinetic data were found in the literature from animal studies. Furthermore, we did not locate any clinical pharmacokinetic data for NAD.

There was very few studies conducted with NAD. The lethal dose for 50 percent of animals, also known as the LD50 in mice, was determined using the IV injection route of exposure. The LD50 of NAD is 4.3 grams per kilogram body weight.

The approach of determining the LD50 has been abandoned by modern toxicology testing paradigm as it does not provide sufficient safety information that are useful for assessing human safety. No published literature was found for repeat-dose toxicity, genotoxicity, developmental and reproductive toxicity, or carcinogenicity for NAD.

In terms of adverse events reports, four clinical trials investigating the effects of oral dosing of NAD in humans were found. None of these

studies was conducted in patients with MS. No safety data were reported in these four studies. Cases retrieved from the FDA adverse reporting system, FAERS, and CFSAN adverse event reporting system, CAERS, are confounded with the use of multiple substances.

It has been mentioned earlier in the presentation that NAD is unstable and may degrade to several degradants when compounded. Some degradants, such as nicotinamide, are precursors of NAD. They can be absorbed and produce NAD in the human body.

There are human dosing guidelines for niacin, which includes nicotinamide and nicotinic acid. Both are precursors of NAD. The U.S. RDA for niacin is 50 milligrams a day, which is the dietary intake level required to prevent symptoms of pellagra. Doses above 1000 milligrams of nicotinamide have been associated with gastrointestinal events, such as vomiting, in case report literature. However, most GI events occurred when the dose of nicotinamide was above

3000 milligrams.

Furthermore, doses above 3000 milligrams of nicotinamide have been associated with signs of liver toxicity. However, liver abnormalities were reversible once nicotinamide was discontinued.

It should be noted that the nominated dose of 5 milligrams of NAD is comparable to the daily dietary requirement of niacin. Niacin is also approved as a drug product. The active ingredient in the drug is nicotinic acid. Niacin, which is nicotinic acid in this case, in therapeutic doses for hyperlipidemia is associated with adverse events.

I would like to point out and remind the committee that once a substance is included on the list of bulk drug substances that can be used to compound under Section 503A, the substance can be used to compound drug products for any use and without limits on dosing.

The additional information related to the relationship between nicotinamide, nicotinic acid, and NAD can be provided at the end of this

presentation if the committee is interested in knowing about this more.

In conclusion, since there is insufficient nonclinical safety data, potential toxicity profile associated with administration of NAD, particularly on a chronic basis, cannot be determined. In addition, there is minimal clinical safety data available. However, data from related compounds may provide some assurance of safety of NAD for low doses.

Moving on to the efficacy, no published clinical literature was located that investigated the effects of administration of NAD in the treatment of MS-related fatigue or MS in general. One observational study reported that NAD levels in the blood are about 50 percent lower in the MS patients than in controls.

It should be noted that since only the level of endogenous NAD was measured in that study and there was no exogenous NAD administration involved, the causality between exogenous administration of NAD and MS cannot be established using

observational data reported in this study.

Multiple FDA-approved MS drugs are available. The FDA-approved drugs for the treatment of MS are available in injectable, oral, and infused dosage forms. None of these approved drugs, however, have a specific indication for treatment of MS-related fatigue, which is a commonly reported symptom of MS.

In conclusion, there is no clinical data to support the use of NAD in the treatment of MS-related fatigue or MS in general.

There is insufficient information available to determine how long NAD has been used in pharmacy compounding. Based on internet searches, NAD is being prepared as a topical ointment for use in rosacea. In addition, clinics across the U.S. advertise intravenous NAD for addiction recovery. Its extent of use in compounded drug products cannot be determined.

NAD is not listed in the British, European, or Japanese pharmacopeias. NAD is currently marketed as a dietary ingredient in dietary

supplement products.

The National Institutes of Health's Dietary Supplement Label Database does not list NAD as a single-ingredient formulation. However, NAD is on the labels of dietary supplements with multiple dietary ingredients.

In summary, while NAD is a well-characterized substance, it is likely to be unstable when compounded in the nominated oral capsule dosage form under ordinary storage conditions. There are insufficient nonclinical and clinical data to characterize the potential toxicity for the treatment of fatigue in MS, which is a chronic disease.

There is no clinical data investigating the effects of exogenous administration of NAD on MS-related fatigue or MS. Also, there is insufficient information available to determine how long NAD has been used in pharmacy compounding.

Based on internet searches, NAD appears to be available as a compounded drug in both topical and IV forms.

In conclusion, a balancing of the four evaluation criteria weighs against NAD being added to the list of bulk drug substances that can be used in compounding under 503A of the Federal Food, Drug, and Cosmetic Act.

This concludes the review of NAD.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Chan.

At this time, we will accept clarifying questions from the committee. We ask that you limit your questions to verifications only since members will have further opportunity for discussion and questions after we heard all of the presentations.

Dr. Wall?

DR. WALL: There's a discussion in here about it being unstable. Can you provide more clarity, like you break down 10 percent in 2 minutes or are we talking about 1 percent in 3 months? Give me some more focus as to what that breakdown is.

DR. CHAN: Yes. It is unstable, and I will

defer this question to Dr. Ben Zhang.

DR. ZHANG: This is Ben Zhang from OPQ. NAD is supposed to degrade in -- we're talking about the period of 4 weeks or months. And it will first break down into nicotinamide mononucleotide and adenosine monophosphates. Further degradation may happen, but we don't have the detailed study for the degradation.

DR. WALL: You're saying that over a three-month period of time, the entire compound will break down into those two entities or a percentage? Or what are we looking at?

DR. ZHANG: We don't have the specific number for the percentage. But it is very likely that within one month or so, this compound will -- the degradation will go to like half or something like that. We don't have the -- again, the stability -- we don't have very specific or detailed systematical study on the stability of this substance, so it's based on our estimation.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. I have

two questions. The first is on your slide number 9. You mentioned that the nominated dose of 5 milligrams of NAD is comparable to the daily requirement of niacin. And above that, you talk about exposures leading to signs of liver toxicity of doses of 3000 milligrams, which is 600-fold higher.

Do you have any information on how many individuals would have been exposed, wherever this data came from, to such enormously high doses? Because that sounds like quite a comfortable difference between the recommended dose and the dose that's been associated with reversible toxicity.

DR. CHAN: Yes, that's correct. These data comes from -- majority comes from the Institute of Medicine when they put together the niacin chapter. The original literature that they cited are case report literature that reports on the use of nicotinamide in a therapeutic setting that normally goes from 1 gram above. And then most of the situations, the dose levels are above 3 grams,

which is 3000 milligrams. And those are in the therapeutic settings.

DR. DiGIOVANNA: You mentioned also that when a substance is placed on the list, that it can be used for any use without limits on doses. Isn't that true of all of the preparations that have been placed on the list, except for those perhaps that have been suggested to only be used by a certain route, like topically?

DR. CHAN: That is correct. Once a substance is put on the list, there is no restriction on dosing. So a prescriber can prescribe any dose for any indication.

By the way, I'll also defer this question to Dr. Dohm, if you can further clarify.

DR. DOHM: I don't have any further clarification. That's correct. It is true for substances on the list.

I think here, it's pertinent to point out largely because we're talking about a range of doses and potential adverse effects associated with higher doses.

DR. DiGIOVANNA: Going forward then, I would think there would be many substances that are toxic at a certain level or at certain levels. Should that be a consideration in placing a substance on the list if it's true for all of them?

DR. DOHM: I think when there is known safety effects associated with certain doses and there's no limitations on the dosing of the prescription, it is something to take into account.

DR. DiGIOVANNA: I still don't understand because it seems to apply to every substance that goes on the bulk substances list, could be compounded at any dose. And any dose means doses, some of which would not have any toxicity information. So I don't see how we can include that as a criteria if it applies to all of the substances.

DR. DOHM: I think it's a matter of relevance. To the extent that you think it's relevant for your determination with respect to this particular substance that there are adverse effects associated with high doses and that there

is no way for the Agency, at least, to limit the dosing of the drug as it's prescribed, it's up to you to take into account.

DR. DiGIOVANNA: My second question is on your slide number 13 where the historical use of compounding -- and you say that the extent of use cannot be determined. That has appeared in several of the discussions about the other compounds also.

So I wonder how that is assessed? How do you determine that you can't determine the extent of use? Does that go by scouring -- doing a Google search? Or do you survey pharmacies that are doing compounding to see how much has been used? Or do you survey companies that manufacture those compounds to see how much of the pharmaceutical grade might have been sold or produced?

DR. CHAN: Our team did internet searches for most cases, but I will also defer this question to Dr. Dohm.

DR. LAWSON: I'll answer that. I'm Rosilend Lawson. We do an internet search, a Google search, and we look at -- extent of use means how

widespread is it in other countries, and we look for historical use in compounding in pharmacies in other countries, as well as the United States. That, for the most part -- and you're right. A lot of these substances, we can't determine if it's being used in other countries as a drug.

DR. VENITZ: Gigi?

MS. DAVIDSON: To follow up on that, is there a threshold for which you consider a long time of compounding use? I think compounding emergence kind of happened in the early '80s, and so the practice is still relatively young in the scheme of things. And if you're surveying compounding journals, things like that, for your data -- I'm just curious, where do you consider something established?

DR. LAWSON: As far as the time, the length of compound, that's usually in the reviews data, that we found evidence of compounding from 1980s or for centuries. We'll put that information in the review for length of time in compounding.

DR. DOHM: I'll just add to that briefly,

just to emphasize that there's no information submitted to the agency on the use of a substance in compounding. So the best that we can do is try to be systematic about the search engines we use and the types of searches we do to try to assess the historical use.

DR. VENITZ: Go ahead.

MS. DAVIDSON: I also wanted some clarification on maybe why this is different from the nicotinic acid-approved product. I wasn't able to glean from the nomination or the briefing materials because there was constant comparison to nicotinic acid in the briefing materials. I don't think I understand.

Did you say that nicotinic acid has more adverse events than NAD, and that's potentially why it's being nominated?

DR. CHAN: The reason we do this -- we also present information on nicotinic acid and also other precursors because they are precursors of NAD, and they are available in a diet. And there are relevant information available. That is the

reason why.

In terms of adverse events, there's well-established in the literature versus that we didn't find anything for NAD. So we thought the related compound could help inform the safety of NAD to some extent.

MS. DAVIDSON: Okay. Thank you.

DR. VENITZ: My question is actually related to this very slide that you have up, and that is the dietary ingredient. What doses are used in those dietary supplements? What doses of NAD?

DR. CHAN: What doses of these. I wonder if Dr. Kara Welch is here. I'll defer this question to Dr. Cara Welch from CFSAN.

DR. WELCH: Hi. I'm Cara Welch, from the Office of Dietary Supplements at CFSAN. Dietary supplements don't have established doses. It's just the level at which the manufacturer believes the product is safe. We don't have pre-market review or approval of the products, so we don't have a registration of the levels at which they're marketed.

DR. VENITZ: The answer is you don't know what doses --

DR. WELCH: The answer is we don't know.

DR. VENITZ: Okay. Thank you.

Any other clarifying questions for Dr. Chan?

(No response.)

DR. VENITZ: Okay. Thank you again.

DR. CHAN: Thank you.

DR. VENITZ: We will now proceed with the nominators' presentations. We have one presentation, Dr. John Humiston from Fagron. I hope he's here. Please come to the podium.

Nominator Presentation - John Humiston

DR. HUMISTON: Thank you. Good morning. My name is Dr. John Humiston. I am a family practice physician from San Diego, California, and I have an inherent focus on addictions also.

For my disclosure, I am independent. Fagron asked me to come here because of my experience with using NAD, and they do pay me a consulting fee for training physicians sometimes, but generally, I am working independently.

Hopefully, my presentation will answer some of the questions that just came up from Dr. Chan's presentation and from Dr. Rothman's. I just want to throw in, for Dr. Rothman's presentation, boots-on-the-ground view, it's very important that there is regulation of compounding pharmacies. The variability in quality, as we have seen, is too large. Some pharmacies are great on their quality, like Fagron's, but there are others that -- let's just say the FDA's actions have been needed.

So I just wanted to give you a little boots-on-the-ground view there.

Dr. Chan talked about the importance -- or some of the functions of NAD, nicotinamide adenine dinucleotide. There are a number of functions that's primarily in redox, but probably the therapeutic effect is related to some of its other actions as a cell-to-cell communicator and perhaps in the DNA repair.

Let's just say the mechanism of action is unknown. We're sure all familiar with that, that phrase. But it does do something. It's observed

to do that. My thought maybe it's in the sirtuins where it has to do with the aging process. It's hard to say, but I'll explain what it's observed to do, and maybe we can get a better idea.

The NAD has been used in intravenous form since either the late '60s or '70s. There was a nice study put out by I think a Dr. Halleran that talked about hundreds of patients getting IV NAD for the mitigation of withdrawal from a number of substances. It did not tend to have a lasting effect when used by itself, but it did make withdrawal from substances remarkably easier and more successful.

What has been added lately is an amino acid complex of glycine d-phenylalanine, D,L-phenylalanine, and L-threonine that has seemed to potentiate the effect, give it a more profound and lasting effect than the NAD alone.

My comments are going to be related to this combined therapy, so it'll be very hard to say that this is related to NAD alone. However, NAD is by far the largest component of this therapy.

The amino acids will end up being probably up to 24 milligrams total in a day. When I say a day's therapy, I'm referring to about an 8-hour intravenous infusion. Only about 24 milligrams of these amino acids combined with anywhere from 800 to 1800 milligrams of NAD.

So there was a question on what is being used currently, and Dr. Chan's presentation talked about 3 grams a day being associated with toxicity. As I just said, today, practically speaking, 800 to 1800 milligrams, 1800 milligrams to be the most that anyone would get in a day.

This is a study of 40 patients that showed this combined amino acid plus NAD. We have D1. D1 is day 1, D10 is day 10. By some standardized measures, psychological measures, we were able to show a nice impact over these 40 patients with a variety of drugs, including narcotic, alcohol dependency.

This is 10 days of IV treatment, going anywhere from 5 to 8 hours per day to do a slow infusion. The idea is to bathe the nervous system

in this mix of NAD and small amount of amino acids and that this was observed. Here, we're looking at the difference in distress, depression, anxiety, again, for these 40 patients.

Then to show that this doesn't have an abuse potential -- in other words, you don't want people to be hooked on NAD, which of course, they would not be. But that's why this was done, to show that they had an improvement in some of these measures of joy and motivation, et cetera. But it was nothing excessive. And I think this all relates to the general neurological improvement that they had.

Right now, I'd like to show you some brain scans of 4 patients that were done in the summer of 2014. The idea here was to see can we show something physiologically different. These were performed at the Daniel Amen Clinic in Southern California. The Amen Clinic has done more brain scans than any entity, I believe, in the world.

This one patient, a 34-year-old woman with a strong history of Adderall and Ritalin many, many years, very, very difficult with her social skills

mentation, very impaired after so many years of these prescription drugs.

This is a perfusion scan. Generally, the more scalloped and mottled it is, the worse it is. You can see up in the upper left, there's sort of a perfusion defect; about a month later, mild changes. This is really a circulation scan, so you see some improvement, but this is not so much about circulation as it is potentially about neurotransmission.

We look at these, the active phase, qEEG, there's a certain amount of activity that's normal. Mostly the white areas are normal activity. So this would represent a decreased, diminished amount of brain activity. Then you can see between the first and the second that there is a visible change; back to the first, and then the second again.

That's very nice, but what's the clinical output? She had a calming down of her anxiety, restless legs, et cetera. By day 7 -- I think she did about 10 or 12 days of treatment, there's

something called brain zaps that you may be familiar with. It's acute antidepressant withdrawal. That resolved very quickly. Then a month afterward, she said that she was having no relapses and felt better.

Second one here is this a 54-year-old man who had very extensive cocaine use, and came in essentially because he was having heart arrhythmia and it wouldn't go away. I had to clarify to him that'll happen if you stay on cocaine. So that was his motivation for coming in.

Interestingly, pornography and cocaine, both are very strong in the dopamine receptor. He had a strong addiction to both, so it's kind of a combined addiction.

What we did with him was we did the two scans just two weeks apart. It was rather a short window, but I really wanted to see how quickly some changes could be seen.

Again, the circulation scan, not much to be seen there. All right. This is his pre-scan for electrical activity. Then you can see some

improvement, especially in the lower left, pre- to the post. Again, it was only 2 weeks, and he's a little bit older, but we did see a measurable improvement.

His cravings were gone by the fourth day, and he became much more social. Instead of sitting there in the chair and not talking to anybody, he started interacting with people, which is actually a sign of recovery, a very important sign.

This man, a 25-year-old ex-Navy gentleman, happens to be my son-in-law, was injured in combat in the foot, was put on Lyrica, pregabalin, a GABA agent to decrease nerve pain. Informed it wouldn't be addictive, but after a few years of that, he was addicted to it. In fact, had a lot of irritability, anger, lost his night vision. He had excellent night vision; that disappeared.

Here's the perfusion scan, a little smoother on the post, again smoothness, there is less scalloping. As you can see again, there's the pre- and then here's the post-scan.

This is very interesting. Look at his

electrical activity scan, a lot more than on the other patients. Then as we go to his post-treatment -- if you go to the post-treatment, there's actually less. Again, let's go back to the pre-treatment, and then again, lots of white areas, and then again visibly less, more towards where these other people were.

The answer here is that this is a GABA agent Lyrica, pregabalin. The inhibitory functions of the brain were suppressed, so there wasn't enough inhibition of thoughts, lights, et cetera.

What we see is a restoration of inhibitory function. In other words, the other scan showed a reduction of normal neurotransmission, whereas his pre-scan here was showing excess of neurotransmission, which of course will happen once you impair the GABA receptor, and then something more normal.

Of course, the most important thing, he had a nice restoration of behavior, the night vision came back after his fifth day, memory resolved. The last thing he had was a left orbital sort of

twitch, which went away after a few months.

The last patient here, this was an interesting man, 70 years old, no drug history, just 30 years of pornography addiction. Could we possibly show a difference both clinically and electrically in somebody who has been through an activity, overstimulating the dopamine system?

Sort of Eeyore-type personality, we wanted to see what would happen here. Perfusion scan, so there's a little difference there, and then electrical. Okay. So it didn't look too bad. Again, these activities do not cause as much receptor damage as substances can. But you can see in the post-study here that there is some improvement; there's some increase. There's the pre- and here's the post-.

His statement was very interesting. When the IV NAD and amino acids are running, "I don't ruminate on thoughts." That was his statement. Now, of course, we don't want it to work just when it's running. That's hopefully a predictor of how he'll feel later. But he's noted to become more

social and start to laugh and joke a little bit.

So I thought that was a pretty good effect for somebody who really did not have any drug history to think of.

The doses, again, as I mentioned were at 800 to 1800 milligrams a day. I think that in the past, we've seen very few cases where people became tired, red eyes, headache, insomnia. I think those are the cases where on a higher end, it became a problem. We found that if you pretreat the patient with intravenous vitamins and some IV glutathione, that seems to completely, 100 percent, take away that possibility.

I want to comment also on the fact that Dr. Chan was having trouble coming up with the words, the research, the studies, the background for this. I think in fairness to her team, part of the problem here is that this is used for addictions.

Addictions, I think in society and in the field of medicine, are really just kind of sidelined. Nobody really talks about it much.

It's something that doesn't make the mainstream, partly because they're -- well, I think it's mostly because of the nature of addiction. But I think secondly, there hasn't been much really biologically that's been helpful.

So I think that it's a hard thing to look up and find. I hope that makes some sense, but there is some difficulty in finding that type of information. I think it's also been a very small select group of people that have been involved in this type of work, so that would make it hard also.

I think that -- well, let me just describe the treatment protocols that we've been using -- and I've been doing this since 2004, and there are a few other physicians who are involved in this also -- is anywhere from 7 days for alcohol, which is the easiest to thing to treat. Alcohol, marijuana, and narcotics respond the most quickly.

When it comes to benzodiazepines and perhaps Remeron, these are some of the more difficult things to treat. You'll see the same therapeutic

improvement, just over a longer period of time, needing treatment up to 15 or 16 days.

The material is lyophilized from compounding pharmacies that have that capability. Both the NAD and the amino acids are compounded together into a lyophilized formula with a fixed formula of amino acids and a variable amount of NAD.

The variability amount of NAD will change the effectiveness on which receptors in the brain. It's well beyond me to understand how that works, but we have seen that it does work in practical application.

It is inherently safe, but as was mentioned here by this gentleman and others that any substance, regardless of how natural it is, will find its toxic level. We have found that this is for impaired people. People dealing with addiction are generally impaired in their health, they're able to tolerate this very well without any -- I mean, they have the withdrawal they go through, but it does not appear that the treatment is introducing any stress to their body. The other

sense, it's really causing a healing situation.

I think the answer to this is to get some clinical studies on the program. We have Dr. Gabe Rosenberg at Emerald Neuro-Recovery [sic] in Indianapolis, is applying for NIH funding. He has an interest both in heroin treatment, alcohol, and also post-concussive syndromes because there's been some nice effect with that.

That, I believe, is the future. It does have a great future, but it bears more study. Glad to take any questions for anything I haven't covered yet.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Humiston.

Dr. Carome?

DR. CAROME: Mike Carome. For your figures 1, 2, and 3, could you go back to those?

DR. HUMISTON: Are you talking about slides 1, 2, and 3.

DR. CAROME: I didn't see slide numbers. You showed earlier on three bar graphs, labeled figures 1, 2, and 3.

DR. HUMISTON: Oh, yes.

DR. CAROME: It's not clear to me what this represents, but I assume this is summarized mean data from your group of 40 patients.

DR. HUMISTON: I didn't actually do this study, I'm sorry. This is done by Sarah Broom and a group down in Louisiana.

DR. CAROME: Okay. Is there a control group for this data? This is everyone who got the NAD and the amino acid treatment, I'm assuming.

DR. HUMISTON: Yes. I'm not aware of any other pilot study or controlled study. Some are collecting data, but this is the only finished study. I don't believe there is a control group with this for comparison purposes.

DR. CAROME: How do we know the effect, whatever the effect is, has to do with the NAD and the other components of what you're being given versus the vehicle, versus changes over time in the national history of detoxification?

DR. HUMISTON: That's a good question. Obviously, it'd be more complete if there were

absolutely a control group, somebody receiving IV placebo for 5 to 8 hours a day.

I guess we'll have to infer that because this is a 10-day period having to do with people who came in acutely addicted, that they would not naturally see this type of response. But that's an inference, right? So that's the best we can say.

I think also, the magnitude of the response. But you're correct, there is not a control group there.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: Where is this published?

DR. HUMISTON: This was -- let's see. I think my slides are in there, on the references. This was not -- I don't know if it's published in literature. It was presented at the Society for Neuroscience in, I believe, 2014. And the reference should be there in the last slide. You can find that there -- are my slides in the booklet?

DR. DiGIOVANNA: No.

DR. HUMISTON: They're not. Okay. It is on

the docket under this meeting. It may be under a Dr. Mestayer's name. I think I incorrectly -- but it is there as the PowerPoint presentation for this meeting.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Hello. This is Ned Braunstein speaking for industry. I think that one of the statements you made, I think sums up the current state of what this work is, in that additional research, you said, is needed.

There's a mechanism for doing research with unapproved drugs, and that's to obtain an IND and do human experimentation consistent with the Code of Federal Regulations, and the Declaration of Helsinki, and all of the other requirements for informed consent that that would entail.

In this country, we don't have, at least up to now, two pathways to allow the use of drugs, one, whereby drugs are tested and rigorously evaluated and then approved by FDA; and another way whereby experimental drugs are put on a list to allow them to be used without that rigorous

testing.

I think this is very early work that you're showing, perhaps interesting, I don't know. I'm not an expert in the field. But for additional experimentation, this should be done under an IND.

DR. VENITZ: Dr. Gulur?

DR. GULUR: Thank you for your presentation. I'd have to support the remark just made, which are that the results displayed here do seem preliminary. There is a lot of questions they raise, and further clinical research will definitely be indicated.

Some small remarks would be with regard to the duration of treatment and the duration of follow-up of these patients. It appears addictions and craving, as we've all recognized, are long-term conditions and long-term issues. A lot of the results presented here were perhaps a text from a patient a month later, some other reports, individual case reports of relapses within two months. The duration of follow-up would be critical in these studies as well.

Again, having a well-structured, well-designed research study would definitely help support the findings in this study for the better.

DR. HUMISTON: It certainly would. I'm all in favor of that. My purpose is to stand here and let you know that this works, from a person who's doing it. Addiction is an epidemic in our society, unfortunately. I'd much rather not treat this, but we have a heroin epidemic; we have an ADHD epidemic; the entity called post-acute withdrawal syndrome, including prescription drugs, psychotropics that aren't taken as prescribed is a reality.

So the American public needs this. There's a compelling reason -- everything you've said is also compelling, and it's true. In the short period of time that I have in here, I didn't have time to present everything. I didn't want to rush through tons of information in a short period of time. But the practitioners who are doing this find that their response rate could be anywhere from 60 to 80 percent, and that includes -- we're

calling response people who have long-term sobriety.

There's a lot more information on the docket that was not appropriate to present now mostly because of time constraints. But there are some patient statements, there are statements from other doctors, and there is recently one that was just completely on a head trauma and addiction patient who had quite an extensive neurophysiologic workup done that was finished on May 1st. And that showed the difference between day 1 to day 10.

So when you don't have a lot of data to present -- the data is there, but it's not as formalized as it needs to be. When you can show a very non-disputable, short-term, physiologically measurable result, not just by clinical result, but by differences in measurable neurophysiologic metrics, that's very impressive.

The question is, does that last? Well, we have found clinically that it does. So we're at that stage with it. But I think that the important point here is that this is such a compelling need

in the public and a growing need, unfortunately, that that's I think what has to steer the mission and the decision here.

DR. GULUR: I had one more clarification request actually. I see FDA pointed out this substance was proposed as an oral for multiple sclerosis as the indication. However, the presentation we've just heard is about IV, and it's for addictions. And we're just wondering how to reconcile that information.

DR. DOHM: You correctly point out that this was not a route of administration that the agency reviewed. It also wasn't a use that the agency reviewed. So the information in our evaluation does not discuss this particular use or route of administration.

It hasn't been nominated for that use, which is a question I actually had for the presenter. Is there a reason that Fagron did not nominate it for this use and for this route of administration?

DR. HUMISTON: I ask that of Fagron too as I was sitting out there. I didn't want to certainly

waste anybody's time. Fagron had asked me to present. I am not familiar with the other uses. My impression is those other uses would be very minor. I've not heard of them in a clinical practice.

I guess I saw this an opportunity to bring up, at least to the FDA's knowledge, that this is the most relevant clinical use today, I'm fairly certain. I really haven't even heard of -- I've seen NAD as an oral supplement, but I've not heard of another practitioner or a patient using it.

It may have some indication that I'm not aware of, but this is, I think, the relevant indication in the current state of affairs. I hope that still fits in with the purpose of the meeting.

DR. GANLEY: Yes, I just had a question. There's been issues about what the stability of NAD is. How is it provided to you --

DR. HUMISTON: Thank you for you mentioning that. Again, this is the lyophilized substance. I know that when Fagron was working on this formulation back in 2012, it took them eight months

to work out the process to get it stable so that the sterility was there. And the potency, the potency is very -- it cannot be too much nor too little for each of the five amino acids and for the NAD.

Those lyophilized together, and then they go through a third -- Fagron uses a third party laboratory to test sterility and potency. When we get the product, it will be labeled for up to four months from the time that we get it.

I think both sterility and potency go beyond that, but they have chosen that four-month window. And we have certainly seen that it seems to perform the same through that time.

DR. GANLEY: I guess my other question has to do with why NAD as opposed to nicotinamide or niacinamide, which are the same, that are available in the intravenous forms?

DR. HUMISTON: That's beyond my expertise. I don't know. I can speak for it clinically, that it works very well. I assume those other substances have been tried.

DR. GANLEY: I guess my question deals with that nicotinamide is going to be converted to NAD in the body from salvage pathways.

DR. HUMISTON: Right.

DR. GANLEY: I guess why is it important to get NAD in versus these other --

DR. HUMISTON: I think that's the same question as what essentially is the mechanism of action, and why is that potentiated by adding a few select amino acids. It's my understanding from the amino acid physiology, amino acids are inherently very competitive, unlike many other nutritionals. So the proportions of one to the other had to be worked out through empirical trial over many years. So that has worked out.

How do those work together, what is the actual mechanism that allows people to come off of drugs, cold turkey in almost all situations, and you can very, very successfully treat them with a minimum withdrawal, really, it's the mechanism of action.

That's the bigger question. What is really

happening? That's beyond my level of my expertise to know what's happening in the nervous system.

DR. VENITZ: Last question, Dr. Carome.

DR. CAROME: You put a lot of weight on the pre- and post-brain scans. Do you have brain scans in similar patients who don't receive NAD formulations? Do the brain scans change just during the normal detoxification treatment process?

DR. HUMISTON: That is a great question. I don't have that. The thought here is that because the people haven't changed much, there's a minimal change generally with detox. Of course, it depends on the person and the substance.

Obviously, cravings and the neurological impairment, et cetera, will tend to last much longer, if not indefinitely in some cases, and to be much more minimal when you don't do any real treatment.

The assumption here is because we're having such a much larger visible clinical change, that you would also be able to track that. I think that has been done by other people just out of interest

to see what's happening, but I haven't looked up that data. But that would further elucidate what's going on. You're right.

DR. VENITZ: Okay. Thank you, Dr. Humiston. That concludes our nominator presentation.

DR. HUMISTON: Thank you.

Open Public Hearing

DR. VENITZ: We're now going to move into the open public hearing. Let me read into the record.

We will now proceed to hear the open public hearing speakers. I will read the following OPH statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationships that you may have with the product and, if known, its direct competitors.

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

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

The FDA and this committee place great importance in the open public hearing process. The insights and 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, and I'm calling the first speaker.

COL JOHNSON: Sir, that would be me. Mr. Chairman, committee, FDA, fellow colleagues, I am Colonel Retired United States Air Force Jeffrey A. Johnson, and I'm a pharmacist. I'm a PharmD and also a naturopath. I am here representing Medisca, which is a pharmacy compounding supply company, and that would be my comment as far as any potential concerns.

Just a real quick because I know I have very limited time, but just to give you a real quick thing on me. I graduated from Purdue University in 1978 with my BS in pharmacy. I completed my naturopathic studies in 1999, and I finished my

PharmD in 2003 from the University of Kansas.

I've been a compounding pharmacist throughout my 40 years, and I believe as a pharmacy clinician, compounding is part of the armamentarium that we have to have as clinical pharmacists to try to meet the needs of our patients and that triad of where the provider is the one that writes the prescriptions for us to direct us on how to do our compounding.

We're kind of like a bank. I don't cash a check unless it's written appropriately. And as a pharmacist, I will only fill a prescription if it has been written appropriately by a provider.

I don't have any slides, and my apologies for that. I just wanted to address some of the discussions that have come up.

First off, just so we understand some of the history of nicotinamide, it was actually started to use in 1950, and NAD had been studied and used in hyper-cholesterol patients and other conditions. It's been well-studied, although I will admit that it's not been looked at within MS. I agree with

the FDA there.

I also want to thank Dr. Humiston for his presentation, because even though we looked at it from a presentation of IV, which the FDA did discuss that they saw that in their study, I think the extrapolation over to how it could be possibly used in MS in an oral condition is not hard to make because he showed how depression and some of the fatigue factors that we see in addiction could be addressed by using nicotinamide.

As far as the degradation concern, as it was brought up, I think you would find that with a compounding pharmacy, we would do a 30-day supply, and it would be resupplied with a new batch each time the prescription came in so that that degradation should not really be a concern.

Some of the things I wanted -- I had made some other notes as things were going along here, so let me look at it. There also is and according to the criteria that is supposed to be looked at -- there's basically the four criteria, and excuse me while I read these off: any safety

issues raised by the use of the API in the compounding pharmacy; physical/chemical characteristics; available evidence of effectiveness or lack thereof; and history use of the API in the compounding pharmacy arena. It has been used for several years, and there actually is a USP monograph for nicotinamide.

Let's see, one of my other -- again, give me a second here. I think really, bottom line, up front that we have to look at is that, as it's been brought up, this is being used effectively. And if we pull it off the market, what do we have left to use? I think that's one of things we have to keep in mind. And I agree that there is a proper way to go after research, but I think we have to encourage that research to occur and encourage the industry to pick that up and carry it on.

I think again, in conclusion, I would recommend to the PCAC that we do approve it for continued use in compounding, and then also encourage, at the same time, that we look for further research opportunities because there's a

ton out there.

Sir, that's what I have. I'm open to questions.

DR. VENITZ: Thank you. Thank you very much. Any questions on behalf of the committee? Then I thank -- okay, go ahead, Dr. Wall.

DR. WALL: You said that you use it in compounding. How do you use it? What do you use it -- what's the patient using it on?

COL JOHNSON: Ma'am, what I've seen nicotinamide used for -- and as Dr. Humiston mentioned, I've seen it used in total parenteral nutrition, but I've also seen it mainly used for some of the instances in alcohol abuse and using that to help as he pointed out in his presentation which was very good.

DR. WALL: So you're only seeing it being used as a compounding pharmacist for IV purposes; you're not seeing it being used for the oral or the topical?

COL JOHNSON: Ma'am, all I can tell you on the oral is I have seen the over-the-counter

products dispensed in that respect, once again, by prescription, because that's been my career. I've only worked in a federal facility, and we only do things by prescription.

MS. DAVIDSON: Dr. Johnson, can you help me understand -- I still do not understand why this substance would be used over nicotinic acid, niacin, and niacinamide?

COL. JOHNSON: Ma'am, I guess for me, I kind of -- and this is probably inappropriate, but I'm going to say I kind of lump them all together because I do see nicotinamide -- I'm not saying they're equal, but I see them as very, very comparable to one another. I think using nicotinamide or niacin, if you tell me you'd prefer me to use niacin over nicotinamide, okay, I'm going to be all right with that. But I still think, in a sense, they're all of the same family.

So since they're all the same family, then it seems to me to make sense if you're going to use one, you should have the opportunity to use the other. Now granted, there's some breakdown

differences once it gets into the body. But still, really in reality, you're looking at nicotinamide in that family, that class.

Does that make sense?

(Ms. Davidson nods in affirmative.)

DR. VENITZ: Thank you, Dr. Johnson.

COL JOHNSON: Sir.

DR. VENITZ: Let me ask then our second OPH speaker to step to the podium.

MS. D'AGOSTINO: My name is Doreen D'Agostino, and I'm a patient. I have no financial interest or attachment with or to any doctor or pharmacy. I wanted to make a statement about my experience with the amino acid IV therapy treatment for addiction.

Three years ago, I had been put on a very strong pain medicine called Suboxone by my orthopedic doctor because of a back injury and back pain. And he told me that I could get off it at any time. I was concerned about how it would affect me, side effects, and so on.

So that was three years ago, and each time I

tried to stop it on my own or taper off, I went into a very, very severe withdrawal process. I was completely depressed. I slept too much, slept too little, had no appetite, lost weight, no energy.

I was literally in a constant state of withdrawal. Then, I would have to go back on it. And I went from doctor to doctor, trying to find someone -- because the orthopedic doctor didn't know, he said I could just stop it comfortably. That was a lie. And I went from doctor to doctor. I even went as far as to put myself in a rehab program for a week on a daily basis and stop the drug. It was awful. It was just awful.

Not any other doctor could help me. I then started researching on my own online and came across people talking about amino acid IV therapy and that it helped them withdraw from whatever the addictive drug was that they were on. And they started talking about the neuroreceptors, the damage that was done, and how this seemed to help, but I didn't know where to go.

So I went to a nurse practitioner in New

York, armed with everything I could find, printed out. With my research, I walked into her office and talked to her about it. And she said, "Yeah, I treat with amino acids," and I could do IVs. It turned out that she never told me that she had seen Dr. Humiston at a conference two months before I walked in her office, and he presented the treatment that he talked about earlier.

She kept me for about four months, twice a week, going in, IVs, and nothing worked. I felt worse. I tried to stop the drug; I couldn't. And finally, she brought up Dr. Humiston's name. And then I quickly went online and found some information, and some videos about the William Hitt Center, and amino acid IV therapy, and his treatments, and he was in San Diego.

I quickly called, got him on the phone, and talked to him, and booked a flight, and I was out there three days later.

The treatment lasted for 10 days. The first few days, I was completely out of my mind with cold, not hungry, not sleeping. It was very, very

difficult. I would go in every morning and get the [indiscernible] and the glutamiathine [ph]. And then I would be on a slow drip of amino acid IV therapy for what seemed like 7, maybe 8 hours a day for the first few days, and by the 5th day, I started to turn a corner.

I just felt my life coming back, my motivation coming back, the depression lifted, the sleep, I was sleeping. I could eat again. I felt hopeful again. And I was completely amazed that this treatment helped me and was working, and with no side effects whatsoever. I just felt great. By the 5th, 6th, 7th, 8th day, I literally was walking around and walking around the neighborhood with my IV. I just had all this energy, and I felt amazing.

I got back to New York -- and this is two years ago. I got back to New York, and I got my life back. My life, I was a new person again. I was off the evil Suboxone, horrible drug that nobody should be on as far as I'm concerned. But anyway, especially someone like me being on such a

strong drug. And I never had a craving again. I never -- my whole life changed. My entire life changed. I got my life back. It saved my life.

There are so many people I know out there in the world I live in, in New York, and elsewhere, that people I know who wish that they could tell someone about this treatment. And I do know people -- I was with people at the clinic in San Diego, and I saw people -- patients who were addicted to heroin and another one who was also on Suboxone, and turned around and got their lives back, and walked out like new people. And it works.

It's so important for people like me. There is so many people out there, and I just wanted to let you know that this saved my life, and it can save a lot of other people's lives. Thank you.

DR. VENITZ: Thank you very much. Any questions by the committee.

(No response.)

DR. VENITZ: Thank you again.

MS. D'AGOSTINO: Thank you.

Committee Discussion and Vote

DR. VENITZ: The open public hearing portion of this meeting has now concluded, and we will no longer takes comments from the audience. We will move the panel into the panel discussion of NAD.

Any discussion? We had FDA present, we had the nominator present, or one of the nominators present, and we had open public hearing speakers. Any discussion? Dr. Pham?

DR. PHAM: I think the very obvious question that most of us are trying to consider now is how are we trying to rationalize and vote when what's on the nomination is one route and dosage form and use, and what we're hearing is different. So I don't know. Maybe guidance from the FDA?

DR. VENITZ: Dr. Dohm?

DR. DOHM: Again, this is largely a question of relevance. We did not evaluate it for drug withdrawal recovery use. We also didn't evaluate it for IV. I think some of the information that the FDA did present and evaluate, would be relevant for those uses, although certainly, since we didn't

review it and evaluate for those uses, it's not exhaustive.

The nominators may renominate the substance for an additional use, such as this one, and we can bring it back to this committee if that's what they would choose to do. But I just would caution that some of the information we did present would be relevant to those uses. And to the extent that they are, the agency has opined on them.

DR. PHAM: My follow-up comment for discussion then is if we are focusing on the data that was presented, I do feel that there are oral alternatives in the same family that are available.

So I do have some concerns with NAD being put on the bulks list as an oral capsule. I do think that what we've heard is that there is definitely promise of its potential use in injection and in combination injections, but I think that the safest way to make that information available for both providers and the public is to collect it in a way that allows for good monitoring and proof of efficacy and safety.

Trying to get it researched through an IND and making sure that when it is compounded, it's compounded with all the considerations placed, for example, the stability concerns, and if there are best practices on how to stabilize the product, that would be great to share and put into that IND. But it is such a huge public health crisis right now, and there's a lot of work that's to be done.

I think that there is actually national attention right now on addiction programs and good treatments for that, so hopefully that is an area for continuing research. But I do think that the safest route for that ongoing research is through an IND.

DR. VENITZ: Any further discussion?

(No response.)

DR. VENITZ: Last chance. Okay. Then it looks like everybody is ready for the vote. Let me read into the record the question that we're voting on. You have to vote yes, no, or abstain.

FDA is proposing that NAD not be included on the list. Should NAD be placed on the list: yes,

no, or abstain? And hold on. I have to give you voting instructions.

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. After everyone has voted, the vote will be complete.

Voting will be on the drug product just presented, and the vote question relates to whether this product should be included on the 503A bulk list.

Any questions about the procedure?

(No response.)

DR. VENITZ: Then please proceed and vote.

(Pause.)

DR. VENITZ: Not everybody has pushed a button, so push it again if you've already done so just in case.

(Pause.)

DR. HONG: Can everyone vote again, please? Thank you.

(Vote taken.)

DR. HONG: Okay. For question 1, we have 1 yes, 7 nos, and zero abstain.

DR. VENITZ: After completion of the vote, we will read the vote from the screen into the record, and then hear individual comments from each member. Let's start from my right.

DR. CAROME: I voted no because of the concerns raised by FDA about the stability of the product and because of a paucity of evidence that the drug is safe and effective for the proposed use.

DR. WALL: I voted no, again looking at the stability, but I would encourage the presenters to come back with readmitted -- or send it back in if you're looking at IV data, although I have questions about really taking drugs like that and putting them into the veins.

Also, when you're looking at some of the data they did present, how do I know it's this drug doing it? How do you know it's not the vitamins, or the minerals, or the amino acids that they're

also combining in these multiple entities? I would need to see more data that this is really having that direct effect.

DR. PHAM: Katherine Pham. I voted no, although it does share some similarities in the general pool of nominations that we've heard about regarding lack of clinical evidence on safety and effectiveness. I did think that some of the safety data that was extrapolated to oral could infer at that low of an exposure, it may be safe. However, what compelled me to really vote no was the commercially available alternatives that are on the market, but, again, agree with my colleague, Dr. Wall, regarding a renomination of the appropriate dosage form that was spoken to at length today.

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

MS. DAVIDSON: Gigi Davidson. I also voted no because of the conflict between the nomination for oral use and the lack of evidence to support

why use of NAD over approved forms for oral use would not be acceptable.

I regret that there was not more included in the nominator's presentation about IV use and would agree with the statements made that this might be worth exploring under an IND.

DR. VENITZ: I voted yes even though I didn't see any compelling or even convincing evidence of clinical efficacy. I do think it appears to be quite a safe compound. Obviously, I'm outvoted, so I would go along with my fellow committee members and encourage to resubmit.

DR. GULUR: I voted no for reasons already stated. Thank you.

DR. VENITZ: Okay. Thank you. That takes care of our -- oh, I'm sorry. I apologize.

DR. UNGER: Hi. I voted no for the same reasons. Thank you.

DR. VENITZ: Again, my apologies. I'm right-eyed, not left-eyed.

Okay. That takes care of our first voting business. We will now have our morning break.

Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves, with any members of the audience. Please return to your seats at 10:50 a.m; 10:50 a.m. please. It's a short break, I know.

(Whereupon, at 10:46 a.m., a recess was taken.)

DR. VENITZ: Let's continue this morning's session, the NAD story part deux continues. We now have Dr. Corrinne Kulick present on nicotinamide adenine dinucleotide disodium reduced, NADH, and she will give the FDA presentations. Dr. Kulick?

FDA Presentation - Corrinne Kulick

CAPT KULICK: Good morning. My name is Captain Corrinne Kulick, and I will be presenting the FDA's review of nicotinamide adenine dinucleotide disodium reduced. I'll refer to this substance as NADH throughout this presentation. This slide shows the individuals who worked on this review.

NADH has been nominated for inclusion on the

list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act for use in the treatment of chronic fatigue syndrome. I'll refer to the term "chronic fatigue syndrome" throughout this presentation for consistency with the nomination.

The nominated route of administration and dosage form is oral capsules. The chemical structure of NADH is shown in the picture on the right. NADH is an endogenous substance that consists of two nucleotide moieties and is the reduced form of NAD.

NADH is water soluble and is unstable and substantially degrades when exposed to temperatures above negative 20 degrees Celsius, acidic pH such as in the stomach acid, oxygen, light, or moisture.

NADH is first produced by the manufacturing of NAD, which is typically done through yeast fermentation. NAD is then reduced to form NADH. Likely impurities may include manufacturing components in degradation products of NADH, specifically NAD.

In conclusion, NADH is a well-characterized substance in terms of its chemical and physical properties. NADH will be unstable when compounded in the nominated oral capsule dosage form under ordinary storage conditions and after ingestion in the stomach acid.

NADH's instability calls into question whether the formulations used in the various studies discussed in this presentation provided a dose of NADH that the studies reported.

NADH is an endogenous coenzyme involved in many oxidation reduction reactions in a freely reversible reaction with NAD. The ratio of NAD/NADH plays an important role in regulating the activity of various enzymes, including those involved in glycolysis, the tricarboxylic acid cycle, and fatty acid oxidation. However, the mechanism by which NADH might exert an effect, if any, in chronic fatigue syndrome is unknown.

We identified a very limited number of nonclinical studies that describe the pharmacokinetics of NADH. In one in vitro study,

the absorption of NADH was assessed in intact dissected small intestine using fluorescence microscopy.

Under the conditions of this study, NADH was absorbed in the small intestine in rats, suggesting that if protected from stomach acid, NADH may be absorbed in the small intestine.

In the first of two in vivo studies, the pharmacokinetic profile of NADH was assessed in mice. Under the conditions of this study, a single intraperitoneal dose of NADH increased urinary excretion of nicotinamide, whereas a single oral dose of NADH did not increase urinary excretion of nicotinamide.

Although there is no direct evidence that nicotinamide in the urine is an appropriate biomarker for NADH metabolism, this study suggests that NADH may be systemically absorbed by the intraperitoneal route but not by the oral route of administration.

In the second in vivo study, the bioavailability of NADH to the central nervous

system was assessed using fluorescence spectroscopy. Under the conditions of this study, maximal change in cortical NADH fluorescence was greater for intravenous NADH administration than intraperitoneal NADH administration. Some increase in cortical NADH fluorescence was observed with the oral NADH administration.

We did not identify any published literature providing toxicokinetic data for NADH, and we did not identify any published literature providing clinical pharmacokinetic data for NADH.

The acute toxicity of NADH was investigated in one 14-day study conducted in dogs administered oral NADH at doses of 20 milligrams, 100 milligrams, or 150 milligrams per kilogram per day using the ENADA tablets. ENADA is a brand name for what the manufacturer purports to be the stabilized orally absorbable form of NADH. In the oral dosing regimen, there were no observed dose-response toxicity and no signs of overt toxicological effects.

In the intravenous dosing regimen in the

same study where ENADA tablets were dissolved in saline, a dose-related decrease in body weight and food consumption was seen among dogs treated with greater than 500 milligrams per kilogram per day during the maximum tolerated dose phase.

Clinical signs at the 500 milligrams per kilogram per day fixed-dose regimen included tremors, and blood pressure, and heart rate changes. Heart rate remained higher compared to baseline at all time points evaluated.

Treatment-related histopathological signs showed mononuclear inflammatory perivascular infiltrate cuffing of blood vessels in the brain, suggesting an inflammatory reaction to the treatment.

The chronic toxicity of NADH was investigated in one 26-week study conducted in rats treated with either oral NADH 5 milligrams ENADA tablets or placebo. The only potential toxicity observed in this study was at the level of the eye and involved two treated females. One showed slight bilateral ocular lens opacity at week 25,

and the other showed unspecified eye lesions at week 24 and was euthanized.

We did not identify any published literature addressing the potential for genotoxicity, developmental and reproductive toxicity, or carcinogenicity for NADH.

Turning now to human safety, from the FDA voluntary adverse events reporting databases, we identified one FDA adverse event report where NADH was listed as a single-ingredient product. The patient inquired about whether one of the 15 drug, herbal, or dietary supplements, including NADH that he was taking, could be decreasing the effectiveness of his prescribed medication for weight loss. No adverse events were reported.

We did not identify any CFSAN adverse event reports where NADH was listed as a single-ingredient product.

With regard to clinical trials and safety of NADH, we identified two U.S. clinical trials using oral NADH for the treatment of chronic fatigue syndrome. One trial reported several non-serious

adverse events related to NADH, including single cases of being overly stimulated, mild loss of appetite, heartburn, increased incidence of gas, and an odd taste and dryness reported on the first day of taking NADH tablets. The other trial reported that there were no adverse events related to NADH.

We identified 12 trials using oral, intravenous, or sublingual doses of the 25 milligrams a day or topical NADH 1 percent for other reasons for use. Of these 12 trials, 5 did not report on safety information and 7 reported that the patients did not experience an adverse event.

Finally, although there was limited clinical safety information, the safety of exposure to NADH can be informed by the safety from related compounds as Dr. Chan mentioned in the NAD lecture.

The nominated dose of 5 to 20 milligrams of NADH is comparable to the 15-milligram daily dietary requirement for niacin, which includes both nicotinamide and nicotinic acid. However, niacin,

nicotinic acid in therapeutic doses for hyperlipidemia, is associated with adverse events.

The second point is relevant because once a substance in included on the list of bulk drug substances that can be used to compound under Section 503A, the substance can be used to compound drug products for any use and without any limits on dosing.

In conclusion, a summary of the available safety information shows that there's insufficient, nonclinical toxicity data for NADH to fully assess the safety profile. There's limited clinical safety data available on NADH, and data from related compounds may provide some assurance of safety of NADH at the nominated dose.

Chronic fatigue syndrome is a serious disease, characterized by persistent fatigue, accompanied by additional diverse symptoms. The disease is known by various names, such as myalgic encephalomyelitis and systemic exertion intolerance disease, and various diagnostic criteria are utilized to make the diagnosis.

FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for chronic fatigue syndrome. The etiology of CFS is unknown, and there are no FDA-approved treatments for chronic fatigue syndrome.

With regard to clinical trials and the efficacy of NADH for the treatment of chronic fatigue syndrome, we identified two U.S. clinical trials using only oral NADH. The first, by Forsyth, was a placebo-controlled crossover study in 26 evaluable patients receiving oral NADH 10 milligrams per day in the form of ENADA tablets.

The investigators employed a subgenerated subjective 50-item symptom questionnaire that scored symptom severity on a scale of 1, none of the time, to 4, all of the time.

The investigators considered the patients improved if patients demonstrated 10 percent improvement as determined by an arbitrary scoring system. Based on the investigators' arbitrary scoring system used to determine improvement, at

12 weeks, 8 of 26, or 31 percent, of the subjects showed a 10 percent improvement while on NADH in contrast to 2 of 26, or 8 percent, who received placebo. The investigator reports a success rate for NADH is 31 percent, and for the placebo, 8 percent, with a p-value of less than 0.5.

The second efficacy trial by Santaella was a randomized trial in 20 evaluable patients comparing oral NADH 5 to 10 milligrams per day, and in this case, the formulation was not provided. They compared it to nutritional or psychological therapy.

The investigators employed an undisclosed subjective symptom scoring questionnaire that scored severity on a variety of symptoms on a scale of 1, minimum, to 4, maximum. A decrease in severity of symptoms relative to baseline was observed in both groups, but no statistically significant differences between groups were identified at any time points.

In conclusion, the two clinical studies we identified that compared NADH to placebo or other

therapeutic measures do not establish efficacy of NADH in chronic fatigue syndrome. The stability of NADH in study formulations is unknown and may affect the study outcomes in these trials.

With regard to historical use of NADH, there's insufficient information available to determine how long NADH has been used in pharmacy compounding. NADH has been compounded in oral, topical, and injectable formulations and used in Parkinson's disease, Alzheimer's disease, depression, jet lag, physical and mental performance enhancement, rosacea, and contact dermatitis. However, the extent of NADH use in compounded drug products cannot be determined.

NADH is not listed in the British, European, or Japanese pharmacopeias. NADH is currently marketed as a dietary ingredient in dietary supplement products.

In summary, with regard to the four evaluation criteria, we find that NADH is a well-characterized substance that is likely to be unstable when compounded in a nominated oral

capsule dosage form under ordinary storage conditions. The available nonclinical data suggest that NADH is not stable in acidic medium and is likely to degrade before absorption after oral dosing.

The available nonclinical safety data are insufficient to characterize the potential toxicity profile for NADH, particularly for use in chronic diseases such as chronic fatigue syndrome.

We found no reports of serious adverse events in the minimal clinical safety information available. The available clinical efficacy data regarding administration of NADH to patients with chronic fatigue syndrome is insufficient. The publicly available information on the use of NADH in pharmacy compounding is insufficient to determine the historical use.

In conclusion, a balancing of the four evaluation criteria weighs against NADH being added to the list of bulk drug substances that can be used in compounding under 503A of the Food, Drug, and Cosmetic Act. This concludes the FDA's

presentation on NADH.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Kulick. At this time, we will accept clarifying questions by any of the committee members.

Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. Am I correct that regardless of the vote, the dietary supplements would be unaffected and still be available?

CAPT KULICK: I'll defer that to Dr. Dohm.

DR. DOHM: That's correct. This is only putting on a list for use for compounding, so dietary supplements are unaffected.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. Are the stability concerns seen with NADH identical to the one seen with NAD, or are they different?

CAPT KULICK: I can let Dr. Zhang speak to that question.

DR. ZHANG: This is Ben Zhang from OPQ. NADH is much more reactive than NAD. This

compound, if not isolated from oxygen or without any other formulation techniques, it will degrade under ordinary storage conditions within one week. And in aqueous solutions or especially in acidic conditions, this process can be accelerated like within one hour.

DR. VENITZ: Any other questions? Dr. Unger?

DR. UNGER: I have a question of does this request relate to that special formula that's in a capsule and enteric coated? Is it all part of the same request, or is this -- I don't understand the relationship.

CAPT KULICK: I'll refer that to Dr. Dohm. I don't believe it was related to this specific formulation.

DR. DOHM: I think you're referring to the ENADA formulation. That formulation, I believe, was used for purposes of a study, but that is not -- so I think it was a dietary supplement. If I'm correct, it was used in the study. So what is being considered here isn't that specific

formulation but just the NADH for use of compounding more generally.

DR. VENITZ: Any other clarifying questions?

(No response.)

DR. VENITZ: Okay. Then let's move to the nominator speaker. We will now proceed with the nominator's presentation. We have one presentation, Mr. Tom Wynn from Fagron.

Nominator Presentation - Tom Wynn

MR. WYNN: Hello. Thank you for having me here today. First off, I'd like to say thanks for the sunshine. It was so stoic in here the last time, it's nice to have a little brightness in here for our talks today.

My name is Tom Wynn, and I'm a consultant with Fagron, and I'm here today to talk a little bit about NADH.

NADH, or nicotinamide adenine dinucleotide disodium reduced, the reduced form of NAD, is a coenzyme that is found in all living cells, so it's within our bodies at all times; we're utilizing it.

It's synthesized in the body from vitamin B3

or niacinamide or nicotinamide. It's an important pyridine nucleotide that functions as an oxidative co-factor in all eukaryotic cells, and it plays a role in the production of energy through ATP generation. So we know that it's there in the Krebs cycle, which we have a portion of it here.

Going back to our days in school, we realize that it is used in the formation of energy or the production of ATP, so it's very important in the body and can be utilized then in muscle cells and other cells to help form energy. And I think that's important further through our talk.

As far as safety goes, this particular study -- and I think it was mentioned by the FDA as well -- it was a 26-week oral tablet administration of that ENADA formulation of NAD, and the safety of the stabilized oral absorbable form of nicotinamide or NADH over 26 weeks, they actually used 1 tablet of 5 milligrams a day. It was administered into 80 rats; it was 40 males and 40 females.

The main thing I wanted to get out of this was that if you look at the daily dose of the rat,

it corresponds to 175 milligrams a day in a 70-kilogram human. I think this will become important as we go through the talk because most of the studies we're talking about were five 20-milligrams. But if you try to correlate that in the animal studies, really, what we're looking is maybe we need higher dosing; 175 milligrams here is correlated through with the study based on what they actually did on rats. And they did find it to be generally regarded as safe within the study.

The next study, this one here, we actually looked at the stabilized oral absorbable tablet again, and it was administered to dogs. And this was at levels of 20, 100, and 150 milligrams per kilogram.

Over that 14-day period, they showed no signs of toxicological effects in those animals. There were no deaths. At doses of even 500 milligrams per kilogram a day, they also found in intravenous dose into beagles, that also there were no gross histological findings indicative of toxicity of any organ system.

In the study with the dogs, we showed much higher dosing, but still found no signs of toxicity or any kind of issues. Again, it's regarded to be safe to be dosed that way as an oral dosing.

We talk about chronic fatigue and NADH. This particular study, the purpose was to look at the efficacy of NADH. Again, that ENADA was used. Again, this was a double-blind, placebo-controlled, crossover study. And what we saw in the clinical symptoms presenting was that the number of patients, 26 percent had fatigue. There was some neurocognitive difficulties.

We did find that over the course of this particular study that we did have improvement in these particular symptoms based on the addition of the NADH to those patients.

Looking further into that study, we see here that, again, there were 26 eligible CFS patients. It was a 4-week randomized, double-blinded, placebo-controlled. The participants were either given the two 5-milligrams, again, that 10-milligram dose. And I mentioned before that

some of the other animal studies, they were actually correlating a much higher dose could be recommended to get the different results that we wanted.

Even at that dose, we showed 10 percent improvement, which I know the FDA mentioned, compared to 8 percent with placebo. And the subjects were -- 35 were able to correctly evaluate the treatment, and 72 percent of the studies thus far enrolled in a longer, open-label, controlled study.

So what we found was even the patients who were in the study, 72 percent of them went on to another study because they were actually happy or saw positive effects with the results of the study that they were in, and there were no severe adverse effects observed related to this study as well.

This one I put up because there currently is a clinical trial going on with NADH in combination with coenzyme Q10. And this particular study was started in 2015. I didn't have results from it that I could look at. I know it's a combination.

But again, they're looking at supplementation against placebo with a product they're calling ReConnect, which again is a combination of the two.

I believe it's 20 milligrams of the NADH, along with, I believe, 300 milligrams of the coenzyme Q10. And they're looking at, again, treatments for chronic fatigue.

There was another study, and I believe the FDA brought it up. It was back in 1996 where they also did a placebo-controlled clinical trial. At that point, they were using the 10 milligrams of NADH, and they found no adverse effects at all from that study in humans.

Does oral coenzyme Q10 plus NADH supplementation improve fatigue? At an 8-week study, randomized, placebo-controlled of doing 200 milligrams a day of coenzyme Q10 and then 20 milligrams a day of NADH, they did find that fatigue and biochemical parameters were changed. The study is registered in the clinical trials. I believe that this one showed -- or is showing that we're having some promise in the effects of chronic

fatigue.

Getting more into that particular study, here we have 73 eligible female patients that were involved in this study. It's an 8-week randomized, double-blind, placebo-controlled. They received, again, the 200 milligrams of coenzyme Q10 or 20 milligrams of NADH. It was in a gelatin capsule, and it was divided into 2 doses.

They did see a significant reduction in total score as far as fatigue impact. They also looked at the biochemical parameters and found that NADH was definitely significantly higher. There were significantly lower blood mononuclear cells in the treated group, and there were no adverse effects reported in this trial either.

Here, again, we're seeing -- now, this is the combination, I realize, with the coenzyme Q10 and the NADH, but we are finding that we're looking at parameters of NADH study, and we are seeing improvement in the chronic fatigue from this particular study as well.

As far as the effect of coenzyme Q10 plus

nicotinamide, this, again, 8-week study, another one that was double-blind, placebo-controlled. It's NAD supplementation improved significantly through reducing max HR during the ergometer stress test and also perceived fatigue.

A lot of times, what they're looking at, too, is they're looking at heart rate. That's what they mean by HR. That's how they're determining if we're getting a change in chronic fatigue, changes in the heart rate.

In this particular one, they also saw that there were changes in the heart rates, which they were using that as a parameter to decide how it was affecting chronic fatigue and saw positive results in this study as well.

We get a little more into it. Again, they used 80 eligible females in this particular study, another 8-week randomized placebo, double-blind, controlled. They received 100 milligrams of coenzyme Q10 with 10 milligrams of NADH. So it's another combo study again, but they did look at and see that the combo showed a significant reduction

in the HR, or the heart rate, during the cycle of the 8 weeks.

Their perception of fatigue also decreased through follow-up visits, and pain and sleep did not improve in the active group. They saw it was still generally well, safe, and well-tolerated, but they were seeing pain in sleep in the active group. There wasn't as big of a change. But they were seeing definite changes in the perception of fatigue.

As far as FDA-approved therapies for chronic fatigue, there currently are not any FDA-approved therapies for that. Typically, they're managed with psychological counseling, NSAIDs, antidepressants, stimulants. And I have seen stimulants used. I've actually seen sometimes patients be put on drugs for narcolepsy for chronic fatigue. They're treating it as something to where just -- they will get that stimulant effect at the times to take it, but it's more something to where it still doesn't fix the entire course of their fatigue. It more or less gives them a boost at a

couple of times when they're taking that particular stimulant, but again, not taking care of the true symptom or cause of the chronic fatigue.

Something else that NADH can be used for -- and I put this on there, too, because it can also be used to help treat chronic dermatitis. Currently, right now, this particular study, they were looking at NADH, and it was able to be stabilized in the suspension of hydrophobic ointments.

It's basically an anhydrous type system that they put this in, and they found that a 1 percent NADH diluted in just Vaseline can be very effective in helping to treat rosacea and contact dermatitis. So it's another avenue for the NADH.

I realize the chronic fatigue was particularly on the form that was sent in. But again, there are other indications that are out there, and I wanted to make sure -- this goes to the point that it can be made into a stable product, that the idea that it's completely unstable -- as long as you can get it into a system

that is anhydrous and a system that is going to help prevent water or oxygen from getting to it, that you can create a stable product for the length of time that we would need to anyway in a compounding pharmacy.

If we look a little bit into this study, we see that it was 10 women, ages 21 to 61, with persistent disease for 1 to 4 years. They used 2 to 3 grams twice a day. The length of study was 14 days. They showed 75 percent reduction in papules and erythema.

So you can kind of go through all that, and I realize again that my main point of putting this in there was, yes, it is effective or showing effectiveness for rosacea and dermatitis. But again, they were able to make a stable product by getting it into an anhydrous system, which is what they've done here by putting it in that Vaseline-type ointment.

Look at it a little bit more, these are just some pictures from the study showing one particular patient and how well they did from that topical

application. Again, there were no adverse effects observed in this study as well.

If we look at the different things that are available as far as FDA-approved therapies for rosacea, metronidazole, azelaic acid, also I think that Accutane is used quite a bit. I've had colleagues and friends that they've been putting Accutane for rosacea as well, which is a little bit -- it tends to have a little more side effects than some of the topical preparations.

In conclusion, we know -- and even with the FDA speech, they've pretty much talked about how NADH can be used as far as efficacy. We've talked about what it can be -- how it affects -- or the studies that show improvement in chronic fatigue.

I think the main issue might be that the studies that were out there, the dosing may have been too low because in that first study, we noticed that it talked about how it correlates up to probably 175 milligrams per kilogram or for a 70-kilogram adult. And I think definitely if we look at that, we would see probably even greater

efficacy.

As far as the instability, which was another thing that the FDA talked about a lot, I think definitely it's something to where if you put it into a capsule, you're in an anhydrous system, you are protecting it from oxygen, from water. The question then becomes, can you get it past the stomach easily?

There are options available for compounding pharmacists. Many suppliers will provide options for DR capsules, capsules that are coated that will actually allow them to bypass the stomach and open up in the small intestine, and then thereby bypassing the instability of the stomach acids as well.

So I believe definitely capsules can be an option that can be stable, much like the enteric coating that they had on those ENADA tablets.

The animal studies do suggest a lot of safety, and even those placebo-controlled studies that were FDA-approved back in 1996, and the one that they're doing the combo now in 2015, I think

we're definitely seeing that these studies are showing that it can be definitely safe.

In the human trials reviewed, I mentioned that NAD was well-tolerated in those studies and no adverse effects. So I think, in general, that NADH does have a place for chronic fatigue syndrome because there's not really another option. We as clinicians need to realize we have to have something to help these patients.

It is something that's growing more and more in our society based on our activities and our stress levels. And I think we need some type of option available to help treat that particular fatigue syndrome. I believe that's all I have.

DR. VENITZ: Okay. Thank you, Mr. Wynn.

Any clarifying questions by committee members? Dr. Gulur?

DR. GULUR: Thank you for your presentation. Would you be able to clarify the benefit -- as you pointed out, ENADA is available as a dietary supplement. What is the benefit? What are the benefits with compounding?

MR. WYNN: Absolutely.

DR. GULUR: Are there doses you're particularly using?

MR. WYNN: Sure. Let's say that you go into any retail chain -- or that's probably where someone is going to get a dietary supplement. Most of them won't order off line. They're going to go into a chain grocery store, a chain pharmacy.

If you ever go in and just look at those particular preparations and you take a look at how they're actually put together, sometimes it's not necessarily looked at as far as water content. Maybe they've done an oil-filled capsule, but yet there's 70 percent water in that capsule. And they may do some type of combination of oil and water with a surfactant, which I'll bring up in the next talk a little bit that I saw. But my main concern is that, really, when you go and get something over the counter, you're not 100 percent sure necessarily that it is effective what you're getting.

It was brought up by the FDA earlier that,

basically, safety, we know that the over-the-counter stuff is safe, but it's not really looked at as far as the BUDs. Then the efficacy of it, they don't really necessarily have to show that because they're not doing an indication. They're just putting it out there as a nutritional supplement, whereas when you go to and you have a relationship with a pharmacy that's helping you and putting together that for you, I believe you have more confidence in that what they're going to provide is going to be more a potent and stable product because they have protocols in place that they're looking at.

I'm doing lot testing as far as potency testing on my preparations to be sure that it is potent for as long as I say that it is. I really only need it to be 30 days. I don't need to be a year, but in my own pharmacy, we have a program of skip-lot testing where I was checking various products at all times. And ones that I did more often, I test them more often to be sure that I had exactly what I wanted in there and that it

maintained that particular strength by testing it at at least the 30-day point to see if I kept it under normal storage conditions after I made it, and I tested it at 30 days, did it remain true to what I thought it should be at that point.

So I feel more confident in the pharmacy who's going to be checking that more often than maybe over-the-counter preparations, which definitely are safe, but I don't know that they are necessarily looked at all the time for efficacy because they're not an indication.

Here, we have a physician who has a particular indication they want, so we are held to a higher standard to check our particular preparations. That's what we're going to do. We're going to make sure that you're getting the strength that you want by doing some type of testing.

DR. GULUR: Could I just ask for some clarification of that? You said you're looking for efficacy, but it sounds like it's mostly stability.

MR. WYNN: Well, it's potency. Potency and

stability is really what we're looking at because when you ask for something and you want it to be effective, then I need to make sure it's the strength that you want. That's kind of what I'm getting it.

If you ask for prescription for 5 milligrams, and if I'm no way checking on that to be sure it's 5 milligrams, then it could be 4 or 3. But compounding pharmacies, we will actually go through -- the majority of us are going to have that program where we're going to check particularly different formulations that we make, and make sure that you're receiving what you want.

I don't know that in the process of over-the-counter, if that's going to be so much true. Also, when you're taking an over-the-counter product per se, where you get it from and how you get it can change because I've seen variations myself in different over-the-counter products from different companies, getting varying results based on dosing that a physician wanted.

If I intended to use that product, maybe I

didn't have that API that there were actual differences at times. And I felt that, myself, I had more control over what I was doing, and I could assure you more that you're going to get the strength that you want. And then that's going to give you the efficacy that you want based on that particular strength.

Does that answer?

DR. VENITZ: Dr. Pham?

DR. PHAM: I appreciate the description of your quality control processes for potency. My question goes to if any pharmacy compounder can acquire the bulk substance under 503A, if we put it on the list, what other resources are available, or how do compounders know that it is unstable and has to go through processes like what you're describing? How do they know that there is an issue with trying to make sure it goes into an anhydrous vehicle?

MR. WYNN: That's going to actually come through with a lot of times the supplier that you're going to get it through, that's going to

help you out with that because they have that available to you.

We have services where you can call in, look, you know, a doctor has -- a physician or a clinician has asked me about a particular substance. They want me to put this in to this particular vehicle, whatever. What can you tell me about it? We can then provide to them the information of, okay, this one is highly unstable, so you want to make sure that you do an anhydrous system.

Then also, just the guidelines of the research. Most of us, I, myself, would've gone ahead and looked it up. I would've gone and said this is the first time I've seen this. I want to take a look at it. It's going to come out of the literature and talk about some instability, and it's going to clue you in, okay, I might have to do something special to make sure when I make this, I give you exactly what you want.

So I think it's ingrained in the pharmacist in general that that's what we're going to do. But

there are services available to us through our suppliers and support groups that we sign up for. As being compounders, we're always in touch with other colleagues that will help through that process.

So I think that it's more or less kind of what we do as pharmacists. Anything that you, as a clinician, would prescribe, I always tell the students that I -- I help teach a class, and I would tell them, don't take anything for granted that you see. It's up to you when you get it to make sure that you want to fill that prescription no matter what it is.

So you should always look it up. You should always research, you'd always, unless it's perhaps something that's commercially available, that you point out anything that is going to be compounded is something that needs to be reviewed before you do it, if you haven't done it before.

So I think, in general, that's what we're going to do.

DR. UNGER: Just a couple. Starting out, I

would just ask you to be very careful not to just call it chronic fatigue because it's very different from just chronic fatigue. You're talking about chronic fatigue syndrome. You're talking about one of the symptoms of chronic fatigue syndrome.

That's just a point to keep in mind when talking about it. It sounds like the studies were designed to address chronic fatigue syndrome or what some people call myalgic encephalomyelitis chronic fatigue syndrome.

All the ones that you've shown appear to use both co-Q and NADH. Coenzyme Q has been used by expert clinicians. There's been no clinical trials on it, but it is among the recommendations that expert clinicians have made for helping people living with MECFS.

I just have a question. Are you aware of any NADH-alone studies or any differential effect that NADH is adding on to the coenzyme Q?

MR. WYNN: Yes. Good question. I did mention that there was a clinical trial in 1996 on NADH alone where they did show no adverse effects,

and they saw significant improvement in those parameters of chronic fatigue syndrome.

I think now what's happening is because we know that -- like you said coenzyme Q10 has evolved in muscle weakness as well, that it's the next best thing, is let's put them together and see if they don't potentiate.

I think that's the way things are rolling with those particular studies. Why not take two good things and put them together? But I did have -- was aware of one study, anyway, in 1996 where they did it just by itself and found improvement with some of the symptoms of chronic fatigue.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. So I gather that there's a preparation, this ENADA preparation that's available as a supplement that is in some sort of proprietary stabilized vehicle or system that is protected by some patents.

Dr. Pham had originally asked you about this. I'm not a compounding pharmacist, so if

someone were to ask a compounding pharmacist, unfamiliar with this, to prepare it, would there be some information that automatically comes with the raw material, that they would order, instructing how to prepare it so it's stable? And what is the variety of different ways of making it stable?

I notice that the topical study that you mentioned that was out of Poland used Vaseline, and that apparently was acceptable for whatever reason. I didn't see what they did to document that it remained stable.

How many different ways are there to get a stable product, and how would actually it happen that someone would have it compounded, dispense it to the patient? And then when would they actually be able to determine its length of use?

I hope I didn't put too much.

MR. WYNN: No, it's all right. You had a couple of questions. You also mentioned about the ENADA being available. One issue that might come up with that is going to the strength; I believe they're 5-milligram tablets. Very similarly, when

physicians sometimes want to use dexamethasone and they want to use higher dosing, they may do 200 milligrams short burst for different -- I don't know if it was -- I don't know if it was MS, but there were a couple of times I got a request for that.

There is available dexamethasone tablets. They're available, I believe, in a 4-milligram. The problem is they have to take 30 tablets at once, and it becomes cumbersome. And then you wonder, are they really going to absorb all of the medicine that they need from all those individual tablets?

So that opens the idea that compounding it should be done because it's a burden on the patient. Not only is it a burden, but it also might change how well or effective it may work. So being able to do that 200 milligrams in a capsule I think would be better.

Now, to keep it stable, let's say, when you get it from the manufacturer, they don't necessarily send formulas out. We don't like to do

that because we want to be able to discuss with them exactly what they're doing. Most of them -- wouldn't say all, but a lot of who we deal with are signed up with our program, and so they would then call us a lot of times as soon as they get something new, if they haven't looked it up on their own already, and discuss with us, okay, what needs to be done to make this a stable product.

In general, pharmacists are going to think, well, if I don't have good stability information like a study that says, yes, I can do this, and it's good for this long, or something of that nature, we're going to be thinking anhydrous.

That's why I brought up that particular study. It's nice, because actually what they did on the topical, they went to Vaseline, which is an anhydrous product. So we're going to think that we need to do some type of anhydrous preparation.

A capsule is going to be a good option. Now, we could think about different fillers, and there's a lot of different fillers that we can put into a capsule, some of which can help with

moisture, some of which -- there are some proprietary capsule excipient powders that are out there that will address flowability, will address water, address it being hydroscopic and pulling water in from the air at times.

There are things that can be done in that nature, and there's a multitude of them out there. And I also mentioned if it's a matter of its instability in stomach acids, there are capsules available that will bypass the stomach for you.

It used to be you had to spray the coating on it; you don't have to do that anymore. They're commercially available, that then they just slow down the transport, so then it just is designed to open up in the small intestine and bypass the stomach. It doesn't breakdown as quickly.

To answer your question, we don't necessarily send it with the particular powder. Now, they can look at the COA; that might give them some information, but it's not really going to give them stability information. It's just going to give them overall.

In general, it's more or less -- compounders, you have to remember, the way that we think, the way the pharmacists think is I'm not going to do anything that I'm not comfortable with at first until I asked the question or reviewed it myself in some form or fashion to the literature.

DR. VENITZ: Okay, thank you, Mr. Wynn.

Any final questions? Dr. Braunstein?

DR. BRAUNSTEIN: I don't have any --

DR. VENITZ: Okay. Then, thank you again.

DR. GANLEY: I have a question.

DR. VENITZ: Oh, I'm sorry. Go ahead.

DR. GANLEY: Can we see slide 10?

DR. VENITZ: Just a reminder, please state your name for the record when you --

DR. GANLEY: Okay.

MR. WYNN: Mine isn't numbered.

DR. GANLEY: It's the slide -- it's a table that presents -- it's a table presenting the results from that trial -- right there, yes.

It's Charlie Ganley. I just wanted to point

out that under the results section where it has a perception of fatigue being a p-value 0.03, actually, that's a p-value comparing the -- so within group treatment at baseline versus 8 weeks for the NADH group, when you compare it to placebo, there's no significant difference between the two treatment groups.

DR. VENITZ: Mr. Wynn, thank you again. I think we are now ready to start our panel discussion. Yes, go ahead.

DR. DOHM: Very quickly. It was a question though, so I don't know if that's a problem, but I can save it.

DR. VENITZ: Go ahead.

DR. DOHM: The thing that I was going to mention is that enteric coated systems are a topic for tomorrow during the difficult to compound discussion. And I was just going to mention that there are certain complexities that will be discussed with respect to that process for making that type of product.

DR. VENITZ: Okay. Mr. Wynn, I'll give you

a chance to rebuke.

MR. WYNN: The actual enteric coated system I was speaking of is not something that I'm going to compound. It's actually a manufactured product that's available to me to utilize. So it's more a device than it is anything I'm going to make. I'm not creating that device. It's already created for me.

DR. DOHM: I'm sorry. I think I misunderstood your presentation to be suggesting that you needed to be able to compound that type of product in order to ensure the stability of the NADH.

MR. WYNN: Right. What I was saying was there are capsules available already that have that particular system set up that is designed to be DR. So it will actually go ahead and release into the small intestine.

I'm not created -- I mentioned before that in the old days, they used to do a spray coating, and pharmacists would actually spray coat the capsules to make that happen. We don't have to do

that anymore because now, it's available. There are companies out there that create these capsules that are designed to bypass the stomach.

DR. VENITZ: Okay. Dr. Braunstein, last question.

DR. BRAUNSTEIN: Yes. Well, if we're going down this path, have you tested the compatibility of this product with this specific drug? Do we actually know that the pharmacokinetics of this drug, when encapsulated with this product, actually performs the way you're saying it does? I'd ask that question.

MR. WYNN: Sure. I mean the capsules themselves are designed to perform the way that they are, and what you put in them is just going to be released. So as far as compatibility, you're putting it into a capsule system, and thereby the capsule, you're relying on the capsule technology then to deliver it where you want it to be, which is bypassing the stomach.

Committee Discussion and Vote

DR. VENITZ: Okay. Thank you for good now,

Mr. Wynn. We appreciate your presentation.

Let me just make an announcement that we don't have an open public hearing, so we are now starting our discussion.

Dr. Braunstein?

DR. BRAUNSTEIN: Ned Braunstein, speaking for industry. I'm very troubled by this, speaking for industry. We don't have a system, I'm hoping, in this country where people can -- that a physician, based on low level of evidence, can just ask for a compounding of a product, or we can put something on a list and then have prescription use of a product based on the level of evidence that we're seeing here.

Generally speaking, prescription products have a standard that manufacturers have to demonstrate of safety and efficacy, and of manufacture, in that the FDA then approves.

A product that might be available as a nutraceutical or in some other space that's available for use, people can do what they want with that. But when it comes to prescription

drugs, we have a standard in this country. And what I'm seeing here is request to add things on the list so that prescriptions can be written, and basically bypass, in my view, the entire system that we've set up for prescription drug usage in this country.

So I have to say this kind of stuff troubles me.

DR. VENITZ: Any further discussion? Dr. DiGiovanna?

DR. DiGIOVANNA: Just to play the devil's advocate, dermatology has a long history of compounding, as do other areas of medicine that probably may predate some of the more structured prescription pharmaceutical development that you're talking about.

I think our job is, in some way, to balance what has happened in the past and maybe bring it up to date in some way. I think many prescribers consider compounding to be a reasonable solution for scenarios where there are either rare diseases or patients who are unable to use a standard

branded preparation. So I wouldn't throw it all out so fast.

DR. VENITZ: Dr. Carome?

DR. BRAUNSTEIN: Yes, oftentimes, we've acknowledged that those products should be on the list. The level of evidence is much greater. And I think it really depends on the level of evidence. We've seen some products here where there's a very high level of evidence based on years and years of usage and acceptance by the broader community that the product does work.

One might even imagine that if one were to submit such a product to the FDA, they'd have a striking chance of getting approved, right, if somebody were interested in doing something like that.

So I agree with you in principle. It's just that with products that we're looking at here, we're nowhere close to that level of evidence.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. Question for the FDA. Is the FDA familiar with this enteric capsule

that the nominator spoke about. Is there such an enteric coated capsule that could be just used with any type of drug, and we could judge it to be sufficient to protect any drug from stomach acid, and have pharmacokinetics in terms of bioavailability?

DR. SOOD: I'm Ramesh Sood from OPQ. There probably are enteric coated off the market you can buy, but again, somebody mentioned you have to look at the compatibility of your drug, your formulation with the capsule, and then how impermeable it is to moisture, oxygen, what is the moisture content.

It's just not that you get the capsule and put any formulation into it. So you've got to be careful about those things.

DR. VENITZ: Dr. Hoag?

DR. HOAG: I was going to say, yes, there are capsules like that in the market. They're a relatively new development. And there are two issues here. One is the drug substance stability, which they talk about, and then the other is the drug product stability. They are sometimes the

same and sometimes not. So that's where some of these issues of -- you may be able to buy this and have this, but then when you combine it -- like you mentioned what is the oxygen permeability was, what is the moisture permeability, what's the moisture content of the capsule and things.

Also, when you look at this drug, they mention protecting it in an ointment. When I look at this, it's such a polar drug, that it would seem very hard to incorporate it in a petrolatum base that would have any reasonable release rate from that base, but maybe it could happen.

DR. VENITZ: Go ahead.

DR. JOHNSON: Sue Johnson, FDA. I'd just like to add that we looked for information about the ENADA tablet in order to determine whether an enteric coating would suffice to provide an NADH stable product, and we were unable to find any pharmacokinetics associated with that product. So we couldn't determine whether enteric coating was adequate.

DR. VENITZ: Thank you. Dr. Gulur?

DR. GULUR: Since we've had many comparisons to dietary supplements and questions on that, and I believe we appear to have an expert on that, could we be educated on how that is regulated or any key pertinent points?

DR. WELCH: Cara Welch with CFSAN's Office of Dietary Supplement Programs. You're talking generically about dietary supplements?

DR. GULUR: Yes, and if you could be specific about -- you know, there were concerns about the dose, whether that was actually what was being delivered, things along those lines.

DR. WELCH: Dietary supplements are, first and foremost, a category of foods. As I mentioned before, it's largely a postmarket regulatory environment. There is very little barrier to entry into the market. If they are using old dietary ingredients, which I can define here in a second -- if they're using dietary ingredients that were on the market prior to 1994, there's no pre-market opportunity for FDA to review the formulation.

There are current good manufacturing practice requirements for the manufacturing of dietary supplements, and that is confirmed by facility inspection. That would be an opportunity to dig into the documentation supporting the manufacturing of the product.

As I mentioned before, manufacturers have the requirements to, of course, put safe dietary supplements on the market. However, there is no pre-market review by FDA as to the dosing, the serving size for foods, and whether that provides an efficacious amount.

If they are making claims about their product, they do have to have substantiation to support that the claims are truthful and not misleading. But that substantiation is not reviewed by FDA. It's not even required to be submitted to FDA. They are required to have it. They review it on their own, and then they make the claims.

So the burden is largely on manufacturers when they're putting together their product. They

don't proactively submit much of that information to FDA.

DR. GULUR: To be specific to the ENADA tablet, the fact that they are making a claim that it is stable, is that something that the FDA could ask for substantiating?

DR. WELCH: That's a good question, and that's what Dr. Ganley was just mentioning. Expiration dating, they are not required to have an expiration date or a best buy date on the products. If they have a best buy date or an expiration date, they do, of course, need to have the substantiation that that date is truthful and not misleading.

They don't need to provide that to FDA, but they should have scientific studies to support that date. And that would be something that we could look at during the facility inspections during the CGMP inspections.

DR. GULUR: Thank you.

DR. VENITZ: Thank you.

Any further -- yes, Dr. Pham?

DR. PHAM: In looking at the commercially

available alternative, one of the claims on their own website is that it went through trials through Georgetown, and in looking further, it looked like there was notation on a previous study that FDA approved in 1996.

I don't know if FDA is familiar with that history. Was that like an IND?

DR. JOHNSON: We cannot confirm or deny the existence of an IND without the sponsor's admission. But we did go through the information in the literature that's available about ENADA. And again, we didn't find any pharmacokinetics to determine whether or not the NADH was actually delivered.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: I'm going to ask the same question I asked in the last presentation. Considering that the application for this distinct substance is for oral use, considering that niacinamide is substantially monographed as both a drug and a food by USP, I still don't understand the advantage of this distinct substance, NADH, as

well as NAD. I understand a little bit better for NAD as an intravenous application, but for an oral application, why is NADH better, different, more justifiable than niacinamide, nicotinic acid, which are monograph substances?

DR. VENITZ: Okay. It looks like you're not going to get an answer today.

(Laughter.)

DR. VENITZ: Any other discussion questions before I will call for the vote?

(No response.)

DR. VENITZ: Okay. Then let me call for the vote, and let me go through the preliminaries.

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

If there's no further discussion, we will now begin the voting process. Please press the

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

Go ahead.

(Vote taken.)

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

DR. VENITZ: As usual, we'll go around the table. Please announce yourself, your vote, and your reasoning. Let's start with Dr. Unger.

DR. UNGER: I voted no because I thought there was no -- while there was no clear safety problems, it wasn't clear what product really was being delivered or if a product was being delivered. And I think a lot more study is needed and worthy to understand if there is an efficacy in the setting of MECFS.

DR. GULUR: Dr. Gulur from Duke University. I also voted no for similar reasons, questions on

the stability, on the delivery, and the need for further research on safety and efficacy of this formulation.

DR. VENITZ: Jurgen Venitz. I voted no. My main hang-up was the formulation issue.

MS. DAVIDSON: Gigi Davidson. I voted no. Again, I'm not sure this is a distinct enough substance to justify putting it on the list. I have concerns about the stability, but I also have a little bit of concern about the safety signal with ocular lesions. We did see that in dogs; we did see that in rats; we see redness of the eyes in many of the studies. So that concerns me just a little bit.

DR. DiGIOVANNA: John DiGiovanna. I also voted no for most of the same reasons, particularly the stability and the formulation issues.

DR. PHAM: Kathy Pham. I voted no for similar reasons. I struggled with this because whenever we do talk about a potential dietary supplement taking its place as the commercially available form, there still is the claims issue

from the USP perspective of the USP food monograph versus the USP drug monograph, and the difference in the ability to make claims.

So I am a little hesitant about that as this would fall under USP food monograph; I'm looking at Gigi. But if this was to come back as a renomination for topical use, there would still be many questions about stability in that formulation as well.

DR. WALL: Donna Wall. I voted no for the reasons that the committee has mentioned.

DR. HOAG: Steve Hoag. I voted no for the reasons the committee mentioned, and also the main thing was the stability in the formulations.

DR. CAROME: Mike Carome. I voted no for many of the same reasons already discussed.

Adjournment

DR. VENITZ: Okay. Thank you. I think we have taken care of two orders of business, so we will now break for lunch. And we'll reconvene again in this room in one hour from now at exactly 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 there should be no discussion of the meeting during lunch amongst yourselves, FDA, or with any member of the audience. Thank you, and I'll see you in 57 minutes.

(Whereupon, at 12:03 p.m., the morning session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Monday, May 8, 2017

1:00 p.m. to 3:33 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Hong, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Michael A. Carome, MD, FACP

(Participation in May 8th session and artemisinin discussion)

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director, Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

John J. DiGiovanna, MD

Senior Research Physician

Laboratory of Cancer Biology and Genetics

Dermatology Branch

Center for Cancer Research

National Cancer Institute

National Institutes of Health

Bethesda, Maryland

Padma Gulur, MD

(Participation in May 8th session)

Vice Chair, Operations and Performance

Duke University School of Medicine

Department of Anesthesiology

Duke University Medical Center

Durham, North Carolina

Stephen W. Hoag, PhD

(Participation in nicotinamide adenine dinucleotide disodium reduced, nettle, ubiquinol, and vanadyl sulfate session)

Professor

Department of Pharmaceutical Science

University of Maryland, Baltimore

Baltimore, Maryland

Katherine Pham, PharmD, BCPS

Senior Officer

Drug Safety Project

The Pew Charitable Trusts

Washington, District of Columbia

Jurgen Venitz, MD, PhD

(Chairperson)

Professor and Vice Chairman

Virginia Commonwealth University

School of Pharmacy, Department of Pharmaceutics

Richmond, Virginia

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

TEMPORARY MEMBERS (Voting)

Robert J. Smith, MD

(Participation in May 8th nettle, ubiquinol, and vanadyl sulfate session)

Professor of Medicine and Health Services, Policy, and Practice

Brown University

Providence, Rhode Island

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

DR. VENITZ: Okay. Welcome back from lunch break. This will start our afternoon session of the first day of the PCAC meeting. Before we begin, I will introduce one new voting special government employee who will be participating in this afternoon's topics.

Dr. Robert Smith, will you please introduce yourself?

DR. SMITH: Yes, I'm Robert Smith. I am professor of medicine and professor in the School of Public Health at Brown University. My specialty area is endocrinology with a focus in diabetes, both clinical and research.

DR. VENITZ: Thank you, and welcome, Dr. Smith. Now, we are starting off the third bulk substance to discuss, and I'm going to ask Dr. Shiang to give us the FDA presentation.

Dr. Shiang?

FDA Presentation - Jennifer Shiang

DR. SHIANG: Good afternoon. My name is

Jennifer Shiang, and I'm an ORISE fellow in the Office of Drug Evaluation IV. Thank you to the team who reviewed nettle, including members of the botanical review team.

Nettle or Urtica dioica, referred to in this presentation as UD, has been nominated for inclusion on the list of bulk drug substances for glycemic control. Although no route of administration was proposed, we've reviewed the available data and only the oral route was found.

Urtica dioica is a herbaceous perennial flowering plant, known as common nettle or stinging nettle. The name, "stinging nettle," refers to the hairs on the leaves and stems that produce a stinging sensation and inflammatory response when in contact with the skin.

The physicochemical profile of UD is not well-characterized. As with any botanical, UD is a complex mixture of compounds. In particular, UD has low percentages of fully characterized compounds and can vary from batch to batch.

Even if the plant is correctly identified,

the chemical profiles of the botanical raw material may vary significantly due to different cultivation conditions and different parts of the plant being used.

Examples of plant parts could be the leaf, stem, aerial parts, which are the parts of the plant that are above ground and may include left, stem, and flowers, and roots. We did not identify a specific method to assure quality control for UD in compounded formulations.

According to the WHO monograph on medicinal plants of Radix Urticae, here are some categories of chemicals identified in nettle extract and some specific examples. Classes of compounds include terpenoids, ceramides, fatty acids, lignans, coumarins, and other chemicals shown here.

In addition to the complex mixture of compounds, a number of impurities may be present in an extract of UD. Some impurities include various Urtica dioica subspecies, other related species in the Urtica genus, or even other botanicals.

As with any botanical, impurities may arise

from growing conditions such as heavy metal impurities found naturally in the soil or pesticide residue. Moreover, impurities may result from the manufacturing process such as amino acids, residual organic solvents, heavy metals, bioburden such as microbial content or mold, or inorganic impurities.

In conclusion, for the physical and chemical characterization, Urtica dioica is not well-characterized. Chemical components may vary due to cultivation conditions and depending on which plant parts are used.

Moving on to the safety section, there are limited pharmacologic data available for specific components or formulations of nettle that may produce the intended pharmacologic effects.

In addition to variability and plant materials, as I just mentioned, there are likely differences in the content of active components associated with preparation methods such as aqueous, oil, alcoholic, or hydro alcoholic extracts.

Many potential pharmacologic actions for

nettle have been investigated, which include its properties as an antioxidant, immunomodulator, anti-nociceptive, muscle relaxant, diuretic, and other actions listed here.

Regarding the nominated use in glycemic control, varied physiological responses have been observed in animal models of diabetes, including decreases, increases, or no change in blood glucose levels.

Two studies were found that are related to nettle pharmacokinetics. In the first study, oral PK data was obtained from rats dosed with a single component of nettle root called DVTF. The maximum plasma concentration was reached within 2 hours, and then DVTF was undetectable after 24 hours of dosing.

In the second study related to pharmacokinetics, oral exposure to nettle showed a change in the activity of several drug-metabolizing enzymes, CYP450s, and antioxidant enzymes.

Although several changes were observed, it is unknown whether these changes may affect the

metabolism of nettle in animals or humans or whether these changes might impact the metabolism of other drugs or substances sharing metabolic pathways.

In summary, for pharmacokinetics, no standard, nonclinical pharmacokinetic, toxicokinetic, or clinical pharmacokinetic data were found in the literature.

Now, turning to nonclinical safety studies, acute toxicity of various extract preparations was reported in rodents. From intraperitoneal injection of aqueous extract in mice, an LD50 of about 3.5 grams per kilogram was determined, with doses above 750 milligrams per kilogram associated with decrease in spontaneous activity, loss of muscle tone, and hypothermia.

Other studies reported an oral LD50 of aqueous extract to be 1.7 grams per kilogram and an LD50 of ethanoic extract of about 2 grams of dried herbal substance per kilogram.

For repeat-dose toxicity, we located one 14-day study in rats, which fed hexane UD extract

by oral gavage. Minor clinical chemistry findings in the blood included decrease in lymphocytes, increases in packed cell volume in corpuscular hemoglobin, and decrease in alkaline phosphatase.

No major signs of toxicity were observed such as changes in survival behavior in histopathological findings, and there was no association between clinical chemistry changes in overall health of treated rats.

A number of studies have been conducted to assess the potential of nettle extracts to cause genotoxicity, but no conclusion could be drawn due to inadequate study design or incomplete data reporting.

For developmental and reproductive toxicity, we identified a single study in the literature, which observed decrease of implantation sites in pregnant rats exposed to nettle, but this study was not considered adequate. Other developmental and reproductive toxicity data such as embryofetal or pre- or post-natal toxicity were not found.

For carcinogenicity, no studies were found

in the literature.

In terms of human safety, the FAERS voluntary reporting system was searched and 48 reports retrieved for UD. However, causation cannot be established in any of these cases due to confounding concomitant medication or multi-ingredient products.

For the CAERS reporting system, 117 reports of adverse events were retrieved from individuals using products containing nettle; 113 of these reports involved use of products containing multiple herbal ingredients.

Four of these reports had UD as a primary active ingredient ingested, but these cases were attributed to other factors such as inactive ingredients, capsule-chewing, or other health issues.

Other information about the human safety of nettle was obtained from recalls and case reports. As documented by a publication, 4 lots of nettle capsules were recalled by a major commercial supplier of U.S. herbal dietary supplements due to

excessive lead. These lots were traced back to a single batch of raw material, and no adverse events were reported in the publication.

Adverse events have also been described in case reports and include diffuse edematous gingivostomatitis, with a positive allergy test, unilateral gynecomastia, galactorrhea, and urticarial rash.

Adverse event data were not reported in any of the seven publications we found that investigated nettle for the treatment of diabetes. I'll discuss these studies shortly in the effectiveness section.

To evaluate possible nettle efficacy for the treatment of other diseases, clinical trials have been conducted using oral dosing of UD aerial part formulations for peripheral edema, arthritis, and allergic rhinitis.

A published review of over 10,000 patients included 10 studies. However, adverse event data were not collected or reported in each study. The review concluded that the risk of adverse events

was low and included mild gastrointestinal or allergic skin reactions.

For the treatment of benign prostatic hypertrophy, a review assessed approximately 40,000 patients from 34 clinical studies and also found that adverse event data were not collected in each study. And it was not reported whether patients who experienced adverse events were receiving UD or placebo.

The most common adverse events were impotence and decreased libido, as well as mild gastrointestinal and allergic skin reactions.

In summary, for the safety of nettle, insufficient nonclinical toxicology and pharmacokinetic data were found. There is limited systematically collected safety information regarding UD despite the large number of patients that have been observed in clinical studies.

Of note, the information that is available is based on formulations of UD with an uncharacterized composition. Taken together, the safety profile of UD is not adequately established.

Moving on to the effectiveness section, we identified seven publications that reported outcomes associated with glycemic control. Three of the seven publications appear to be derived from the same study with a different set of endpoints reported in each publication.

These three papers described a randomized, blinded study of type 2 diabetic patients. The patients received a UD formulation in a glass of water, after each of three main meals or colored placebo for 8 weeks.

The extracts of UD aerial parts were prepared with 60 percent ethanol, which was associated with a final concentration of 45 percent ethanol. Of note, patients continued their pre-study oral antidiabetic medication so the participants were not on the same regimen.

The results showed that there was a possible treatment-related decrease in fasting blood glucose and percent HbA1c at the end of the study compared to controls. But the details of the statistical analysis are unclear.

Another two publications were from studies that were apparently related. The articles describe blinded, randomized, placebo-controlled studies in type 2 diabetics.

Pre-study antidiabetic medication was continued with addition of UD for 12 weeks. Minor improvements in fasting glucose in HbA1c were reported but cannot be relied on because of apparent errors in data reporting. Briefly, data is duplicated in the 2012 and 2013 reports even though the studies included different numbers of patients.

Of potential interest, the UD components from the same extraction procedure, but performed in separate occasions, were assayed for each study and found to be substantially different. This is potentially indicative of variable dosing.

A sixth publication reported a double-blind, randomized, placebo-controlled study in type 2 diabetics. Patients received 8 weeks of UD extract or placebo after daily meals. No statistical difference was noted between treatment and placebo

groups in mean-fasting blood glucose.

Lastly, we reviewed an unblinded parallel group study with 4 groups of male participants. This study assessed changes in fasting blood sugar that occurred after an 8-week study period with 4 arms: 1) aerobic exercise alone; 2) UD, in the form of dried leaf powder mixed in yogurt for daily administration before breakfast; 3) the combination of exercise and daily UD powder; and 4) placebo, which was yogurt alone.

The results of this study were that the mean-fasting blood sugar decrease was statistically greater for all active treatments, including exercise alone compared to placebo. In addition, the mean-fasting blood sugar change of the combination treatment, which was exercise and UD, was statistically greater than for UD alone.

To summarize the effectiveness section, published studies provide some suggestion that UD may affect glycemic control, but they do not provide substantive evidence of UD's effectiveness. All available studies lack information regarding

composition of the UD formulation utilized. Furthermore, there are many FDA-approved products for the treatment of diabetes.

Historically, nettle has been used as a medicinal agent since ancient times. According to the literature, nettle has been used in pharmacy compounding for at least seven years. As a compounded product, nettle leaf currently appears to be compounded in combination with other ingredients as a capsule. However, the extent of use cannot be determined.

Nettle leaf, nettle root, and UD as a whole plant are listed under botanical or homeopathic chapters of the European and British Pharmacopeias and not in drug monographs. In the U.S., nettle is available as a dietary ingredient in dietary supplement products.

To recapitulate the main points from the four evaluation criteria, first, for the physical and chemical characterization, nettle is not well-characterized. Therefore, without strict controls on the manufacture and testing of a

nettle-containing drug product, there can be no assurance that its properties and toxicity would be consistent.

Second, the safety of nettle has not been adequately assessed with well-characterized formulations. This does not allow for an adequate assessment of the safety for use in a chronic disease such diabetes.

Third, the effectiveness of nettle has not been adequately assessed with well-characterized formulations. Although UD may have some effect in reducing fasting blood sugar, the data do not provide sufficient evidence for effectiveness in providing glycemic control.

Fourth, historically, nettle has been used for centuries and appears to be compounded with other ingredients as a capsule.

To sum up, a balancing of the four evaluation criteria weighs against nettle being added to the list of bulk drug substances that can be used in compounding under Section 503 of FD&C Act.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Shiang. Any clarifying questions?

Let me go ahead and start. You mentioned that there are studies with aqueous extract, ethanolic extract, dried leaves, and now we have capsules. Do we know anything about how they compare in terms of content, at least of one of the ingredients? Do they have a common ingredient?

DR. SHIANG: I guess we don't know.

Dr. Johnson, do you want to comment on that?

DR. JOHNSON: As Dr. Shiang's presentation mentioned, the studies are very vague with regard to exactly what the content is. For the majority of them, they extracted a leaf or some part of the plant, part or parts of the plant, with alcohol, or water, or something. And what was resultant, we don't have a good understanding of because they weren't assays and there wasn't a description of --

DR. VENITZ: There's no standard that would allow us some kind of a comparison across those

various extracts?

DR. JOHNSON: No, and our botanicals expert may want to comment on the standard or lack of existence of a standard.

DR. TAYLOR: Hi. I'm Cassie Taylor. I'm from the botanical review team. And as Dr. Johnson mentioned, there actually is really no standard preparation for nettle. We did review the available literature and some monographs, which are mainly for our supplement series, but it didn't allow you to characterize them well enough.

As Dr. Johnson mentioned, most of the literature is very vague about these preparations, so there really is no standard protocol.

DR. VENITZ: Thank you. Dr. Davidson?

MS. DAVIDSON: The USP dietary supplement monograph for stinging nettle kind of suggests that it's all below-the-ground parts that are standardized, which are roots and risomes. And it sounded like the nominators were requesting whole leaf, and maybe these studies were conducted with leaves and aerial parts.

So I agree with you, there appears to be no standardization for what might've been used in the studies.

DR. TAYLOR: I concur.

DR. VENITZ: Other questions?

MS. DAVIDSON: I have one more question.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: Also, in the safety studies, I know one herbalist used nettle. They recommend caution in patients that are concurrent blood thinners or anticoagulants. Did you find any safety signals with regard to antiplatelet effect or anticoagulation?

DR. SHIANG: I'll defer that question to Dr. Johnson.

DR. JOHNSON: I'm sorry. I didn't hear the question.

MS. DAVIDSON: I know when herbalists use nettle, the recommend that they not be taken by patients that are on blood thinners. Did you find any -- it seems like there was something in the briefing material to that effect where there was a

suggestion of an anticoagulant effect, and that did peak my interest as a potential safety signal.

DR. GANLEY: Hi. This is Charley Ganley. The only thing I can think of as you recall in the one slide, coumarins are one of the potential ingredients. Coumadin is a derivative of a coumarins. And coumarin itself does not have an anticoagulant effect.

DR. VENITZ: Any further clarifying questions?

(No response.)

DR. VENITZ: Okay. We do not have a nomination presentation. We do not have an open public hearing; is that correct?

Okay. I'll take that back. We do have an open public hearing speaker, so let's move right into open public hearing.

Can I ask the open public hearing speaker to proceed to the podium, please?

Open Public Hearing

DR. HAUSER: Good afternoon. Thank you for allowing me this opportunity to share Community

Pharmacy's perspective regarding discrepancies that we have noticed related to FDA inspections of manufacturers and compounding pharmacies.

I'm Ronna Hauser, vice-president of Pharmacy Affairs at the National Community Pharmacists Association. NCPA represents America's community pharmacists, including the owners of more than 22,000 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 503(b) 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.

When inspected by the FDA, our members potentially receive an FDA Form 483. This form is issued at the conclusion of an inspection when an investigator has observed any conditions that in their judgment may constitute violations of the Food, Drug, and Cosmetic Act and related acts.

It is important to note that the compounding inspections that have been conducted to date by the FDA are focused on community-based compounding pharmacies. As discussed earlier this morning, FDA has inspected only one physician compounder and no federal facilities to our knowledge.

We are unsure how many compounding pharmacies residing in health systems have been conducted, but believe this number to be very small or none at all.

NCPA feels strongly about the quality of compounded medications, and after learning of several of our members' experiences with FDA inspections and subsequent public posting of Form 483s, we sought information on how the inspections were similar to those of FDA registered manufacturers.

I will discuss what information we were able to find. I will also discuss how similar the observations being documented at FDA registered facilities are to those that FDA publicly reports as unsafe in a compounding environment. When a

Form 483 is presented to a compounding pharmacy, it is also posted by the FDA to the FDA website. See slide 2 for all postings, and slide 3 is an individual Form 483.

I also wanted to point out there have been multiple observations of publicly posted Form 483s related to veterinary compounding, even though veterinary compounding is not under the purview of the Drug Quality and Security Act.

Conversely, when perusing the FDA website to search for any Form 483s given to FDA-registered manufacturers, all that can be found are inspection citations and inspectional observation summaries. I've been unable to find any Form 483 for FDA-registered manufacturer facility posted to the FDA website.

The manufacture inspection citations are on an Excel spreadsheet and list a brief description of the general nature of the violation. The inspectional observational summaries summarize a number of Form 483s in various fields, and you can expand a specific field to see the frequency of the

violation. See slide 4 where you can download FDA inspection citation spreadsheets, and slide 5, which is a snapshot of the FY2016 spreadsheet.

It is our understanding that software utilizing consistent language is able to summarize in spreadsheet format observations for FDA-registered manufacturers. The manufacturers found on these spreadsheets are well-known. Slide 6 is a snapshot of the observation summaries.

As you can see, the information posted to the website pertaining to inspections of compounding pharmacies are much more detailed and in-depth than those posted for FDA-registered manufacturers.

As you can also see, many of the same observations found in compounding pharmacies are the exact same ones found in FDA-registered manufacturing facilities. See slide 7, which are citations pulled directly from the FY2016 inspection citation spreadsheet.

However, FDA presents the findings of inspections of compounding pharmacies in a much

more intense manner than those of registered manufacturers. This is evidenced by discussions at Pharmacy Compounding Advisory Committee meetings and reports to Congress, for example.

While FDA publicizes Form 483s and photographs from compounding pharmacy inspections, we do have evidence of several of the same observations from CGMP manufacturers with no corresponding publicity.

It seems like there is intent to sway the public to be afraid of compounding. The observations from inspections of compounding pharmacies have been over-generalized as applying to the entire profession.

This has led some to believe the majority of compounding is done in substandard conditions, which in reality, this is not the case. These over-generalizations are detrimental to pharmacies and patients.

I would like to show you pictures of compounding labs and encourage you to visit a compounding pharmacy. See slide 8, which includes

pictures of nonsterile, nonhazardous drug compounding labs. If you have not visited a compounding pharmacy, I'm happy to personally set up a visit for you with one of our members.

In summary, violations do occur in even the most advanced manufacturing processes. Unfortunately, the public is unable to see more details of violations found in FDA-registered facilities as manufacture 483s are not public information, to my knowledge. At the same time, 483s from compounding pharmacies are publicized.

I appreciate the opportunity to point out today these discrepancies, and I want to make clear that in whatever environment deficiencies were cited, they should immediately be addressed. However, we must always keep all findings in context.

NCPA is committed to working with the FDA, the committee, and other stakeholders regarding these important matters. We appreciate your consideration, and we thank you for allowing us to make our remarks today. Thank you.

DR. VENITZ: Thank you. Dr. Hauser.

Any questions for Dr. Hauser?

(No response.)

DR. VENITZ: Then thank you, again. We appreciate it.

DR. HAUSER: Thank you for the opportunity. Thanks.

DR. VENITZ: I have a follow-up question for our colleagues at FDA. What is your response about this apparent discrepancy in the reporting between compounding and FDA-regulated manufacturers?

DR. DOHM: I cannot speak to the rationale behind not posting 483s that are sent to conventional manufacturers, but I can speak to why we post them for compounders.

This was largely an initiative that was taken in response to the 2012 fungal meningitis outbreak, and we thought it was important to be quite transparent about what kind of compounding initiatives we were taking in response to that outbreak and also to be transparent about what we were finding during inspections of these

facilities.

So we made an effort to be more perhaps transparent than in other programs and to post documents that include 483s, warning letters, and untitled letters, warning letter responses if requested, replies, closeout, state referral letters, and all of those types of documents. That's why those are posted.

Then as for the similarities in the observations between what you might find on a 483 for a conventional manufacturer and what you might find on a 483 for a compounder, that just pertains to whether or not the citations are -- if the compounder is subject to CGMP requirements.

If it is, then you would expect that the citations on the 483, with respect to that firm, might look very similar to that of a conventional manufacturer who is also subject to GMPs.

DR. VENITZ: Thank you. Any further discussion before we move back to our bulk substances of interest?

(No response.)

Committee Discussion and Vote

DR. VENITZ: Okay. Then let's move to the discussion of nettle. Any further discussion items that somebody would like to put forward?

Yes, Dr. Smith?

DR. SMITH: I'll just make a couple comments as someone who specializes in diabetes and endocrinology. I think in considering the data that are available on nettle, it's important in looking at the animal data, to acknowledge the limitations in extending animal model data to human diabetes.

There are some data with streptozotocin diabetes. They are limited, but strep diabetes itself is, in some ways, informative but a problematic model to extend directly to humans.

The drug itself, streptozotocin, is not totally specific to beta cells. It creates an insulin deficiency state in animals, but there are other injuries to animal tissues, so there are other processes that characterizes diabetes.

In terms of the available human studies,

some of the problems were pointed out in the FDA presentation. I think it's just worth noting -- I'm familiar with these articles, and I've looked at other data in the past on nettle and diabetes.

In terms of the studies that have produced some data on hemoglobin A1c levels, which is really the accepted and most essential marker to understand diabetes control and really understand what's happening with mean glucose levels throughout a 24-hour cycle, if we look at those studies, within the summary sections of those articles, I think the authors acknowledge limitations.

If I took the one from Namazi, the authors in their conclusion state that -- just to be really brief about it -- that longer duration studies are needed, and that was an 8-week study, which, again, for a life-long illness and potentially chronic treatment, we need to know more of than what happens with an 8-week timeframe to really judge efficacy, as well as adverse events.

In terms of the Kianbakht article that also was noted with some problems in the data, this is a study where they took some effort to analyze some of the components, acknowledging the incompleteness of that. So again, some of their summary remarks were that -- let's see if I can find the right little section of this -- the bioactives and mechanisms involved in the antidiabetic effects of the extract were not examined in the present trial.

Thus, considering the results of this study, further trials with a larger number of patients assessing the efficacy and safety of nettle in the treatment of type 2 diabetes, as well as more studies addressing the mechanisms and the bioactives involved, seem necessary.

So even the authors of some of the more positive studies, limited though those studies are, have acknowledged limitations in their own concluding remarks.

DR. VENITZ: Thank you, Dr. Smith.

Any further comments? Dr. Wall?

DR. WALL: The only time that I have run

into nettle in the hospital -- and this was a patient that I went in to see to talk about her home meds, and she told me she was on nettle. And she said, "It is the only thing has ever controlled my blood sugar." And she wanted to know if we were going to get her off the insulin and back on her nettle. This was her devotion or her belief that this product -- which just made me think about it. And certain patient populations, as we know, have certain beliefs about medications. But that's just sort of a side story.

The thing that concerns me as looking at this product when we're trying to put it into a complex medical situation is the complexity of the product. It has 5 or 6 different ingredients at varying concentrations. And to try to figure out the drug interactions and everything associated with it is extremely difficult.

It would also be just difficult to figure out the dose. We say, okay, you give however many milligrams, but you don't know milligrams of what.

Those are the things that I sort of struggle

with, is an individual patient who swears to me that it's the only thing that works as compared to looking at the product and trying to figure out how do you deal with it with multiple patients.

DR. VENITZ: Any further comments? Yes, Dr. Davidson?

MS. DAVIDSON: I'm a nettle grower and a nettle user for nutrition reasons. I do eat nettle seasonally. I learned that from my family, and I do love nettle.

I've never encountered it for use medically, and it does seem, to me, after reading the briefing book and hearing the presentation that at best, nettle could only be an adjunct in managing diabetic therapy and that maybe the best role for that would be as a dietary change and not as a prescribed medical therapy.

One thing that concerns me about nettle, as a person who handles nettle, if you don't harvest it correctly, you can get a really good sting from any resultant product. The formic acid in that, it can cause considerable irritation. So it does

concern me about the lack of standardization of sources and products and harvesting and all the heavy metals that certainly has been held with a couple of recalls that can accumulate in the product.

I think that it probably is best treated as maybe an individual dietary preference and not as a prescription drug.

DR. VENITZ: Dr. Smith?

DR. SMITH: Yes, I might just briefly respond to Donna Wall's comments. It certainly touches on one of the challenges in treating disease, which is how does one deal with patient-based reports of remarkable success that may differ from the expectations or differ from the norm. That's always a difficult challenge.

One can understand the various ways that that could be misunderstood. For example, if an agent that doesn't really have a direct action, it might relate to an effect being measured, such as an improvement in blood glucose, but if either from an action of an agent within that compound, within

that mix of compounds, or just from a behavioral change associated with using it, if something happened like a significant change in dietary intake patterns, that could have an effect. And then we could debate whether that's something that is reliable and repeatable and likely one something we might endorse.

There is a lot of interest in type 2 diabetes and the heterogeneity of that disorder. There has been a lot of work and a lot of thought on that, with the concept that we might do better if we targeted drugs or selected drugs for subpopulations that might be definable within the mix of what is type 2 diabetes, which is heterogeneous for many reasons, environmental and genetic predisposing reasons.

There certainly, to my knowledge, are no data regarding nettle that would support the notion that there might be a subset of type 2 diabetes patients who would respond differently than what's seen in the -- that doesn't mean it's not the case, but I'll just point out that there really no data

in that regard.

DR. VENITZ: Any further discussion?

(No response.)

DR. VENITZ: It looks like everybody is ready for the vote, so let me go through the preliminaries.

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 component of an FDA-approved drug.

If there is no further discussion, which I think there is none, we will now begin the voting process.

Please press the button firmly on the microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you make your selection, the light will continue to flash. If you're unsure of your vote, please press the corresponding button again.

(Vote taken.)

DR. HONG: For nettle, we have zero yeses, 9 nos, and zero abstain.

DR. VENITZ: Okay. Let's go around the table. Again, please indicate your name, your vote, and the reason why you voted. Let's start with Dr. Carome.

DR. CAROME: Mike Carome. I voted no, first, because of the concerns about the variability in quality of the formulations and that not being well-defined, the lack of a well-established safety profile for the drug, and finally a lack of evidence that the drug is effective for treating diabetes.

DR. HOAG: Steve Hoag. I voted no for mainly the reasons mentioned. Probably the most important was the lack of a consistent phytochemical protocol and the lack of understanding of what this product actually is.

DR. WALL: Donna Wall. I voted no for the reasons that my colleagues have mentioned.

DR. PHAM: Kathy Pham. I voted no based on

concerns of product variability that could affect both its safety and effectiveness, as well as the number of well-studied available alternatives for glycemic control.

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

MS. DAVIDSON: Gigi Davidson. I voted no because of the complexity of the substance and potential safety signal from unknown components at this point.

DR. VENITZ: Jurgen Venitz. I voted no primarily based on the complexity of the formulation and all the other reasons we've heard before.

DR. GULUR: Padma Gulur. I voted no for the reasons already stated.

DR. SMITH: I'm Robert Smith. I voted no for the same cluster of reasons that we've heard stated, concerns about the product itself and its limited definition, concerns about safety issues and the lack of adequate demonstration of efficacy.

DR. VENITZ: Okay. Thank you. That takes

us to our next bulk substance. We now have Dr. Susan Johnson who is going to give us the FDA presentation on ubiquinol.

FDA Presentation - Susan Johnson

DR. JOHNSON: Good afternoon. My name is Susan Johnson, and I'm an associate director in the Office of Drug Evaluation IV. This afternoon, I'll be presenting FDA's review of ubiquinol.

I want to say thank you to the ubiquinol review team and recognize and thank the subject matter experts from the Division of Metabolic and Endocrine Products. I'd also like to thank the other speakers for the various substances that are nominated that spoke today and will speak tomorrow so that you guys didn't have to listen to me talk for two days.

Ubiquinol has been nominated as a 30 percent powder for use in compounding under Section 503A of the FD&C Act in oral capsules as adjunctive therapy in glycemic control.

As in the review that you received, I'll be referring to both ubiquinol and coenzyme Q10 during

this presentation. Eligibility of coenzyme Q10 or CoQ10 is not being considered at this time. In addition, uses for chronic fatigue, treatment of adverse events associated with statins, and athletic performance are not considered nominated uses at this time.

Ubiquinol has a well-characterized structure and is minimally soluble in water. It is not likely to be stable under ordinary storage conditions but may be stable if formulated with antioxidants.

Ubiquinol is the reduced form of coenzyme Q10, and the structures are very similar. In fact, ubiquinol is usually prepared by reducing CoQ10 obtained from yeast fermentation.

Ubiquinol and CoQ10 are endogenously synthesized in humans and are also ingested in our diet in meats and produce. Ubiquinol is an antioxidant in cells and is key in mitochondrial energy and ATP production. The nominator will be presenting in vitro information regarding potential mechanisms of action later in this regard.

In humans and most other mammals, CoQ10 is the most common coenzyme serving these functions. However, in rodents, CoQ9 is the most common coenzyme, and there are numerous others in the series serving similar functions in other living systems. But there is lack of clarity about how to relate data from one system to another.

Having said that we don't know how to interpret it, let's discuss nonclinical studies in CoQ9-based rats. As Dr. Smith has said, streptozotocin or STZ-induced diabetic rat models may be not ideal and have limitations with regard to extrapolations to humans.

Ubiquinol-treated rats in this study were associated with a greater decrease in blood glucose than placebo, treated rats at the 2-week assessment. This difference between groups did not persist between weeks 3 and 4 of the study.

In the same study, a different group of rats were treated with CoQ10. They also demonstrated a larger decline in blood glucose than placebo-treated rats at week 2. The difference

between the groups did persist through weeks 3 and 4 of the study.

In a nonclinical pharmacokinetic study, oral ubiquinol was shown to be bioavailable in dogs throughout 13 weeks. In humans, we found three single-dose and two multiple-dose oral pharmacokinetic studies.

Ubiquinol is readily absorbed, achieve steady state after approximately 2 weeks, and does not appear to accumulate in the body.

In nonclinical safety studies, no adverse effects were seen in rats following a 5-gram per kilogram oral dose. However, in the 13-week oral gavage study, rat showed signs of hepatic toxicity at doses as low as 200 milligrams per kilogram per day.

This finding was more pronounced in females than males, so a second study of female rats was under taken. The hepatotoxicity findings from the prior study were not observed with doses up to 300 milligrams per kilogram per day.

In a 13-week oral gavage study in dogs with

doses up to 600 milligrams per kilogram per day, no abnormalities were shown with the exception of a decreased heart rate immediately following dosing.

A standard panel of assays did not show genetic toxicity, but we found that no developmental or reproductive toxicity or carcinogenicity studies for ubiquinol.

In the FAERS voluntary reporting system, there were 39 serious adverse event cases found, but there was insufficient information in each to establish whether ubiquinol was related to the events.

In the CAERS database, there were 112 cases identified. In 2 cases, other dietary supplement use was not reported, and those two individuals were reported to have had difficulty breathing. Both individuals recovered following treatment and discontinuation of ubiquinol.

We found 23 clinical studies of ubiquinol in which doses of up 1200 milligrams per day were used. For 11 of these studies, no safety data were reported, and this includes the single study in

type 2 diabetes.

One of the 23 trials was in sepsis patients. Four ubiquinol-treated patients died during this study, and an independent safety review board ruled the deaths unrelated to ubiquinol.

Among the other studies, there were various adverse events reported including three potentially serious adverse events. The first was an enterocolitis, which was reported in one volunteer and believed to have been a preexisting condition. Deconditioning was reported in one chronic fatigue syndrome patient, and worsening asthma was reported in one autistic child.

Overall, the existing nonclinical data are insufficient to determine the safety of ubiquinol for the treatment of a chronic disease like diabetes. And the clinical safety profile also lacks information on which ubiquinol safety can be adequately assessed.

In a 4-week pharmacokinetic trial in which glucose HbA1c and insulin levels were measured as safety parameters, no clinically significant

changes were seen. We found one open label, uncontrolled pilot study of a total of 9 type 2 diabetics.

Using 200 milligrams ubiquinol daily for 12 weeks, it was reported that HbA1c was reduced. However, 7 of the 9 patients continued on pretrial antidiabetic drugs, and there was no diabetic patient control group. Only intragroup statistical comparisons were made. This trial was inadequate to assess ubiquinol as a primary or as an adjunctive treatment.

As we discussed earlier, there's a close structural relationship between ubiquinol and CoQ10. In addition, we found considerably more literature regarding the use of CoQ10 in diabetes than we did with ubiquinol.

Although we don't fully understand the relevance of CoQ10 studies to ubiquinol, we're sharing this information so as not to overlook potentially related evidence of efficacy.

In 7 studies of CoQ10, in type 2 diabetic patients, 5 studies failed to show improvement in

CoQ10-treated patients compared to placebo. In 2 studies, HbA1c or fasting plasma glucose was reported to have been improved, but the study designs were inadequate to associate the improvements with CoQ10. I think Dr. Smith has mentioned some of the other elements such as diet that were not reported on in the study write-up.

No improvement was seen among type 1 diabetics treated with CoQ10 in 2 studies.

In conclusion, there are insufficient data to support the use of ubiquinol as a primary or adjunctive treatment in glycemic control, and there are many FDA-approved treatments available for use.

Based on the single retrospective claim study, it appears that ubiquinol has been used in compounded medications, but there is insufficient information to determine the duration or extent of use. Ubiquinol is marketed as a dietary ingredient in dietary supplement products.

In summary, ubiquinol is well-characterized and may be stable as a powder in oral capsules if formulated with antioxidants. The existing

nonclinical data are insufficient to characterize the safety of ubiquinol, particularly for chronic use in a disease such as diabetes.

The clinical safety data are also insufficient to adequately assess ubiquinol. There are minimal data regarding the effectiveness of ubiquinol as an adjunct or primary treatment in glycemic control or diabetes.

It appears that ubiquinol has been used in compounded medications, but the extent in duration of its use are unknown. A balancing of the four evaluation criteria weighs against ubiquinol being added to the list of bulk drug substances that can be used in compounding under Section 503A. Happy to take questions.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Johnson.

Any clarifying questions at this time? Dr. Smith?

DR. SMITH: I had a question about the heart rate changes in the humans. I was a little surprised when I read your summary that that was

not a concern. I just was curious about the FDA's considerations about any evidence of an effect on the cardiovascular -- or an effect on the heart of that nature.

DR. JOHNSON: I'll ask the DMEP folks to comment if they would like. But in general, I would say that because our reviews are limited to the published literature, sometimes it's difficult to assess what the extent or the meaning, the clinical meaning of a certain reported event is. And that probably skewed our interpretation.

If we had seen replicate studies with the same events or had more information about the seriousness, we may have placed more emphasis on that. But we hear you that that's something to be a consideration.

DR. SMITH: Yes, I was responding in part because I'd noticed that there was some degree of rate change in the dog as well. You had two species, heart rate change. It doesn't mean that's a real problem, but certainly my antenna went up about, hey, what's is the mechanism of this change

in an essential system, the beat of the heart.

DR. JOHNSON: I don't think DMEP has any additional information about this study. Thanks.

DR. VENITZ: Any other clarifying questions?

(No response.)

DR. VENITZ: Thank you again, Dr. Johnson.

Then we are moving to the nominator's presentation. Mr. Wynn is going to nominate ubiquinol.

Nominator Presentation – Tom Wynn

MR. WYNN: Thank you again for having us. My name is Tom Wynn. I said before I'm a consultant for Fagron, and I'm going to talk a little bit about ubiquinol.

Ubiquinol, we've already mentioned, it's a reduced form of coenzyme Q10. It does have greater bioavailability over coenzyme Q10. And in the reading that I was doing, I found that -- they say that in the tissue, it's probably more -- 80 percent of the coenzyme Q10 you take in is going to go to that ubiquinol form when it's going to be used in the tissue.

It is found in oily fish, organ meats, peanuts, avocado, spinach, and whole grains, but there is not a lot in there. So dietary-wise, you can't get that much ubiquinol from those types of sources, but it is available there. It does have a low-water solubility.

As I mentioned, it's found naturally in the body, and again, it's the most common form, I mentioned about, probably 80 percent in the tissue at least; involved in many biological processes pertaining to antioxidative abilities, including production of ATP.

In this slide, just to show what one looks like, there is a dietary supplement monograph. I know that when we do these reviews, we often talk about USP monographs and that they didn't necessarily include the dietary monographs.

To give you an idea of maybe what one looks like, I wanted to put this slide up there. There is a lot of good detailed information in that monograph that USP puts together.

You can get a lot of information about the

ubiquinol from those monographs that they put out. I thought it was important just to see one since we're talking about a dietary supplement today.

As far as ubiquinol in low density lipoproteins in the body, I think it's important to talk about, first off, LDL, it's a molecule that's a combination of lipid and fat -- excuse me -- lipid and proteins.

Lipoproteins are the form in which lipids are transported in the blood. The LDL transport of cholesterol from the liver to the tissues, LDL is therefore considered to be the bad cholesterol. It's the one we all know about that that's the level we want to watch; we don't want it to get too high.

A decrease in cholesterol can lead to problems, like atherosclerosis, plaques on the arteries, which increases risk for a stroke and heart attack.

What we know about coenzyme Q10 is coenzyme Q10 can actually help with the stopping those plaque formations naturally in the body. It's one

of our body's ways to help control some of that that's going to on. And this particular study, they were looking at that. They were looking at ubiquinol. As an important factor, in the susceptibility of the oxidation that's suggested represents that defense against modification of human LDL.

In this data, they were looking more at its effect on LDL and that plaque formation and finding that it is beneficial in helping prevent that.

Here, we actually look at -- it rescues simvastatin suppression of mitochondrial content and implications of induced rhabdomyolysis. I know we weren't necessarily going into rhabdomyolysis, but I think it's important to consider what the ubiquinol is actually doing, and that as we deplete levels, which is what the statins can do, or HMG-CoA, that you do get effects in the muscle.

So it's showing that it is beneficial for the muscles, and we can get muscle degradation, and other things have happened with this rhabdomyolysis.

Here, getting a little bit more into that, if we look at the extent of rhabdomyolysis that can occur, it is again the breakdown of tissue into the bloodstream from the muscles.

They did a study, and they were looking at 26,000 individuals pooled, what was kind of the -- how much that actually occurred, it was about 1.8 percent, which doesn't seem like a lot, but other studies I've read, it can be up to like a million people that could have an issue with this.

Again, it's coming down to the fact of how important coenzyme Q10 is for the muscles. You can see here, as it's depleted by HMG-CoA, that you can have a reduction of muscle size.

Again, this can be a factor in why it can be good for further disease states like we're going to get on the next slide here. Well, actually, first I'm going to get stability, but we'll get into talking about chronic fatigue again.

As far as the stability goes, I know that sometimes the concerns is, how do we get a stable product of ubiquinol? Well, there is a company,

and they came out with a Kaneka QH. And here, they actually did a study on their particular combination or form of ubiquinol and showed that they were able to actually get a stable capsule product.

Within the study, they looked at multiple different things. They also looked at some clinical relevance too, but in this particular one, they did 150 to 300 milligrams oral administration for about 4 weeks.

They actually didn't see -- in this study, they observed no safety concerns, and the assessment of those 300 milligrams after treatment completion -- they looked at about 300 milligrams, no safety concerns. And they actually were testing at the time the stability of the product and found it to be quite stable in this particular form that they were putting it in.

What exactly is that? It's a stabilized powder that they make, and this is what is available to suppliers to actually let compounders use.

What they're doing is they're using gum Arabic ascorbic acid and lecithin. They're putting together like beadlets that are then dispersed throughout this -- compounded with dextrin, and it's a 30 percent dispersion.

It's allowing for greater stability than just actually putting the straight powder itself alone into a container. They're actually using this process to increase that stability so we can ensure a better product or a preparation when we're actually compounding it.

This same study, again, when I talked about before, that 4-week study, they did have no safety concerns. They had acceptable safety profile, and they were doing doses up to 300 milligrams for about 4 weeks.

Also, in another study, they actually looked at the mutagenic and genotoxic potential using the bacterial reverse mutation assays, and they didn't find any reverse mutations. They also looked at chromosomal aberrations and found it did not induce any type of chromosomal problems.

Again, this is just go along with the whole safety of ubiquinol that they weren't finding any issues, even at doses up to 2000 milligrams per kilogram per day as far as the chromosomal aberrations.

As far as efficacy goes, ubiquinol 10 supplementation can or at least was showing some improvement in autonomic nervous function and cognitive function.

In this study, they were actually given 150 milligrams for 10 days. These were patients, again, with chronic fatigue syndrome. This was actually a double-blind, placebo-controlled. They only had 20 patients, but with the supplementation, they were seeing improvement in a lot of these patients over the course of 12 weeks for the different symptoms of chronic fatigue syndrome.

This I pulled out just because looking at -- again, in that study, they were looking at the efficacy as far as changes in the actual concentrations when they were monitoring the levels in the body. And what they found was after

8 weeks, they were seeing much greater levels.

Now, they were referring to as coenzyme Q10. They went back and forth a little bit in that study, but really, what they were doing was giving ubiquinol. But the monitoring levels there did increase, showing that the product that they created in that capsule was actually changing the levels in the body over the course of that 8 weeks.

Oxidative stress is regarded also as one of the major causes of renal dysfunction. It's found that -- when we think of renal dysfunction, we think of maybe chronic kidney disease, and there's not a lot of treatments out there. I don't know if there's any necessarily specifically for chronic kidney disease. It's more or less treating it after it gets to the extreme, or maybe the kidneys are already failing, or maybe it's starting to cause blood pressure issues or other issues like that.

But we did find, in this particular study, that ubiquinol was normalizing the superoxide generation from the kidney. Supplementation can

increase that antioxidant activity, and then it was decreasing kidney injuries and salt-sensitive hypertension.

What we found was, again, because of its oxidation or ability to help with oxidative stress, that it actually was helping out with chronic kidney dysfunction, which is something again -- and I put this in there just, again, to show some efficacy that when we actually give these capsules -- and this particular one -- I'm trying to remember if they actually used -- I think they might've used Kaneka form as well. But again, showing that we can get efficacy for different disease states by the preparation that we're actually making in the capsule.

We know that it plays in role in energy production of the muscle cells. That's why, I think when I talked before a little bit of rhabdomyolysis that -- again, we know it's involved in that so it definitely can help with different things like chronic fatigue syndrome.

It's integral component of the mitochondrial

oxidation. It harnesses energy from nutrients and produce ATP. Again, all these things can be beneficial for patients that are feeling fatigued.

This one, I did have up before, and we talked about -- it proves autonomic function. They did find that supplementation is effective in improving high frequency heart rate, which I know someone mentioned before about the fact that it can affect heart rate.

That's one way that they were assessing how well it was doing for chronic fatigue symptoms just because heart rate can be some way quantifying how you're doing with in helping with that particular disease state.

That's what they were doing in this particular study. They also looked at nighttime awakenings, and they did some arithmetic task performances, and found that all these were improving by just adding ubiquinol to these patients, and it was over 12 weeks.

In conclusion, I think we know that it has strong oxidative properties. Can it be stabilized?

Well, definitely, I think that Kaneka form is probably the most stable form that we're going to have out there, and that's what's available for us to utilize.

Again, looking at -- it came up before. I know with the over-the-counter, gone and looked at some of those. The way they put those together, they have about 70 percent water with them, and we know that water is not necessarily the most stable form to put anything in any way. So I don't think having that as an option over-the-counter might be the best way to go.

It's shown to be safe and non-genotoxic, and it helps a lot of variety of oxidative stress-related chronic illnesses. The main one I'm thinking about is chronic fatigue syndrome only because this is the last one that we have as an option perhaps because we already talked about before, NADH, and that we did not want to recommend that, or you chose not to.

We're running out of options to effectively help patients with chronic fatigue syndrome. I

know from dealing with some of those patients myself, they're definitely having something that's good for oxidative stress can definitely be beneficial to help these patients.

We know it's helping with muscles because of its absence as shown with simvastatin, can lead to rhabdomyolysis. Also, studies that talk about illnesses, and chronic fatigue syndrome can be, again, an illness that puts stress in the body. You can then have depletions of things like coenzyme Q10 ubiquinol, which, again, adding those back in can only be beneficial.

Making sure that we monitor and get the right amounts based on relationship with a provider, I think would be the best way to go than trying to do this with just supplementation from over-the-counter sources.

DR. VENITZ: Okay. Thank you, Mr. Wynn. Any clarifying questions by committee members?

(No response.)

Open Public Hearing

DR. VENITZ: Okay. Thank you again. We

appreciate it.

Now, we have 2:10, and we are ready for the open hearing. Is our presenter here? Then let me move the open hearing up, if you can, and ask our speaker to step forward to the podium.

COL JOHNSON: I'm still Jeff Johnson. I'm still representing Medisca as a contractor, and I appreciate this opportunity to speak to you once more.

As far as ubiquinol, I appreciate Tom's comments and what he shared with you. My additional comments will be very brief.

I think you can see from the presentation that he gave you that the relatively safety nature of it does meet the criteria of the four. And I think that the evidence that's there that Tom has presented does show that it has some valid use.

I agree fully with Tom that we are starting to run out of options from a compounding pharmacy perspective, and ubiquinol does offer us still that opportunity to help our patients based on what the providers are asking us to do.

I think you saw with him, as he was presenting his material, that it does help stabilize that cellular energy utilization, and I think in diabetes mellitus that we can see that being used.

Right now, looking just through a couple of Google searches on my own, the average over-the-counter dosing for oral use, you can find it in 50 milligrams, 100 milligrams, and 200 milligrams. But as a compounding pharmacist, the thing that we offer for our providers and our patients is that ability to tailor that prescribed dose the way the provider has determined that will best help our patient.

Just one other thing. In 1957, Drs. Faulkner and Mosegaard started studying ubiquinol in CoQ10 to see exactly how we could utilize that. So there has been a lot of research done on ubiquinol and CoQ10.

I would strongly recommend for the committee to consider this one and approve it, and I am open for any questions from the committee.

DR. VENITZ: Thank you, Dr. Johnson.

Any questions for our open -- yes, Kathy?

DR. PHAM: Further expanding on that, I'm actually curious as to what some other strengths that might be commonly compounded could be, like in addition to what you've seen.

COL JOHNSON: If I may, I'm going to defer to Tom for that as far as -- because from a compounding pharmacist's perspective, I have not used ubiquinol myself in compounding. But I'm going to defer to Tom and let him answer that question.

MR. WYNN: I'm sorry. I didn't catch that.

DR. PHAM: In addition to what's available on the market through Google searches and whatnot, what are some of the other commonly compounded strengths of the ubiquinol that might be compounded that are different?

MR. WYNN: Sure. I mean, like he said, I think he said there was a 50, 100, and 200. I know that -- again, it's going to be patient-individualized, so it's going to be a

matter of what is best for that patient.

I did have some physicians who actually were monitoring levels of some of the different supplements that we did. I had one in particular that wanted a group of supplements that he wanted us to put together for the reduction in amount of schizophrenic medication that patient was taking.

So it was a very specific amount. It might've been 70; it might've been 65. He was actually going for a certain figure that he was looking for based on testing that he had done with that particular patient, and it turned out it worked out very well.

The whole goal wasn't, in that particular patient, to necessarily get rid of the schizophrenic medication but lower them because of the side effects that are involved with those medications. So giving the option of putting together something that's particularly for that patient is an advantage to the physician, and that's one case where that came into play.

It's hard for me to say particularly. I

just know it can vary off enough that you can't just open a capsule -- you can't have a patient open a capsule, and sprinkle out and some, and then get the right dose. We're going to have to create that specifically for that amount, whether it be 65, 75, or if it turns out to be 350 or somewhere in between. I guess 350 could get -- but somewhere in between where they couldn't actually group together those capsules and make that happen for them.

DR. VENITZ: Thank you.

DR. HONG: Mr. Wynn, could you just state your name for the record just so that --

MR. WYNN: Sorry. Tom Wynn.

DR. HONG: Great. Thank you.

DR. VENITZ: Thank you.

MS. DAVIDSON: Before you sit down, Tom, maybe you could characterize about how many patients that you're providing or you know are receiving compounded ubiquinol.

MR. WYNN: I know from my personal experience, I probably -- it was a little more

narrow of patients. I might've sold -- you know, with chronic fatigue syndrome and then also the one I was talking about, I might've had 20 or 30 that I was dealing with.

I know from dealing with my current position and being asked the questions, that it's much more than that, where I was seeing a lot more questions about it, how do I put this together, what's the best way, that I think there's more of that out there.

I also think that with there being more understanding and bringing in the limelight, which I know she's already gone -- but our other guest that was here was involved much more into chronic fatigue syndrome and probably could've said a lot about that, that it's becoming more of something that we are recognizing and trying to treat.

Rather than before, we might just think it's depression or something else. Now, we're realizing what it really is. And I think that's growing now, looking at options that we can take care of that for.

Since there aren't really commercially available options that we can pull off the shelf, having something like ubiquinol available to us, knowing how good it is at oxidative stress, and knowing it's better -- in lot of the studies I'm looking at, it's better than vitamin E, it's better than ascorbic acid at taking care of oxidative stress, and it's part of what chronic fatigue is.

DR. VENITZ: Thank you.

Any other questions for Dr. Johnson? Yes, Dr. Braunstein?

COL JOHNSON: Sir, I'm more than happy to defer to Tom, so if you have one for him, I can bring him back.

DR. BRAUNSTEIN: Well, just listening to the conversations, one is -- I mean we have CoQ10 available, so why ubiquinol?

My other question is with all this discussion about dose, I haven't seen a single-dose ranging study. I haven't seen any data that really informs us about dosing and why one dose is preferable to another. So maybe you can help us

with that information.

COL JOHNSON: Sir, that's an excellent question. I think that's part of the challenge within the dietary supplement range in itself because that's where research is still lagging for us to have more of a specific on-dosing range than what we've had in our conventional medications. So that is one of the challenges we face as compounding pharmacists.

We are trusting our providers to be looking at that as well. So there is, as I said earlier in my comments, of doing that triad of the clinician, the pharmacy clinician, the medical clinician, and the patient to make sure we are getting it nailed down to exactly where they want.

Your question is very good. I wish I could tell you that, yeah, we've got that research right here to hand to you, but I don't.

DR. BRAUNSTEIN: The first part, why ubiquinol and not just CoQ10?

COL JOHNSON: Come on, you can help me with that. I know from my experience, what I've seen

with CoQ10, especially over-the-counter versions, ubiquinol just offers a better version of that. As he was saying earlier, I think the absorption of it and the availability of it is much better than what we see in just the normal CoQ10.

MR. WYNN: That's correct. That's what I was going to say. The studies are showing that ubiquinol is the more bioavailable form. Not only that, it's the one that's used more in the body, so it's the one that -- in the tissues, it's what the body is using. Even if you gave CoQ10, it's probably being converted to ubiquinol when it gets to the tissue.

DR. VENITZ: Okay. Thank you.

COL JOHNSON: Thank you, sir.

Committee Discussion and Vote

DR. VENITZ: Thank you, both. And this concludes our open public hearing, and we are now moving into the discussion session. So I'm looking for anybody to raise issues.

DR. PHAM: Directed back to the FDA presenters on this one, I'm still also trying to

wrap my head around what is the advantage of ubiquinol over CoQ10. I appreciate the nominator's comments regarding its greater bioavailability. That's part of also why I was trying to ask about what other dosages or strengths are compounded because you can -- scientists in the room, correct me here. I think you can also overcome bioavailability if you account for that in a higher strength, as long as those strengths are still safe.

The key here, as far as I know in reading the material, is that the body can make one or the -- I mean, you can hydrolyze down to ubiquinol. So if it was something like it required a certain type of liver enzyme or liver activation, I could understand the benefit. But when it's hydrolysis, as far as I know, there aren't any organ impairments that would deter the body from being able to convert from one to the other. So that's why I'm still trying to understand the advantages either way.

But are there any scientists in the room

that can confirm whether or not bioavailability can be overcome by the commercially available product or confirm whether or not hydrolysis is a pretty easy process for the body to undergo to create the ubiquinol active form, regardless of what form they ingest?

DR. JOHNSON: I can't answer that question fully. We do know that ubiquinol is somewhat more bioavailable than coenzyme Q10. Although coenzyme Q10 is bioavailable, in the body, coenzyme Q gets reduced -- am I right on this, Ben? He's nodding. Coenzyme Q gets reduced to ubiquinol, although they do both exist in the body at the same time.

I think one of the studies that was referred to in the nominator's presentation was referring to that point. These substances are often monitored together in the body, and there's often one figure associated with the levels of both because they're both considered CoQ10 under a larger umbrella.

I don't think that we -- and I'm going to ask Yen-Ming, Dr. Chan, as well if we know of any

reason why there would be a use for ubiquinol as opposed to CoQ10. I don't think we identified anything.

They were interrelated enough for us to look at the safety and efficacy of both of the review, just to be clear, and they seem to not to have great differences.

DR. CHAN: It is known in the literature that the bioavailability is quite different. CoQ10 is much less bioavailable than ubiquinol, but that's only in the short-term though.

When the dosing lasts to up to three weeks or more, we tend to see the bioavailability actually tends to be quite equal between the two. And I do not know whether or not higher dose of CoQ10 would compensate for the fact that CoQ10 is less bioavailable than ubiquinol and how we reconcile the different bioavailability between the two in terms of dosage forms.

DR. VENITZ: Thank you. Dr. Smith?

DR. SMITH: I'd like to ask a question that maybe is for somebody else on this panel to help

with, which is that we -- and I think it spins off the discussion we were just having about the interconvertibility of ubiquinol and CoQ10, but maybe some temporal differences when one or the other is dosed.

If I understand the background data correctly, there's really no data for ubiquinol in terms of reproductive toxicity. Correct me if I'm wrong, if someone knows this, but in terms of both human and animal data, we really don't have any data that bears on that.

The question is how comfortable or uncomfortable should that situation make us? A perspective on -- we have interconvertible compounds within an organisms, and if I understand the background data, we really lack data on the reproductive system. And this obviously then becomes immediately relevant to clinical use in terms of pregnancy, in terms of women of childbearing age who may be pregnant or become pregnant without knowing it.

Does anyone have a comment on that? I'm not

trying to stick the other committee members here, but it's a little out of my area of expertise.

MS. DAVIDSON: I had a similar question about the safety signal. I also saw the decreased heart rate, and liver problems, and liver enzymes, and accumulation in the liver in some of the lab studies.

I looked at Q10 to see if those adverse events occurred more with coenzyme Q10 than with ubiquinol. And it seems to be that they're quite prevalent with coenzyme Q10, and I see them in the safety signals for ubiquinol.

It doesn't seem like a safer alternative or an alternative of less adverse events than coenzyme Q10. It doesn't answer your question, but I can't make an argument for why this is better, even based on the increased bioavailability because the safety signal is still the same, and the lack of evidence doesn't appear to be there.

DR. VENITZ: Yes?

DR. SMITH: I'll just follow-up with my own comment. I don't feel that naturally-occurring

substances are necessarily, under all circumstances, nontoxic substances. All we would have to think about -- as there are numerous examples of that.

Heavy metals are an obvious example, that are absolutely essential components of enzymatic functional systems, but also are fatal or terribly toxic if taken in inappropriate doses.

I personally have a discomfort with an absence of data. As I think about the interconvertibility of those compounds, I imagine a leveling to occur between the two of them. But I don't know what the exposures at certain sites or tissues or peak effects that are transient effects, I don't know how those might play out to adverse effects, with reproductive system effects as on possibility. So having a lack of data makes me uncomfortable.

DR. PHAM: I'm going to throw back to my pediatric pharmacy hat. Previously, there has been in the literature news of coenzyme Q10 in pregnant women to reduce risk of preeclampsia.

In that respect, because they will be hydrolyzed to ultimately the same drug, you could extrapolate, but again, legally, you can never say, well, I'm sure it -- the same thing.

I think that's why we're having these discussions. We're trying to figure out what's extrapolatable and what's not between the two products, keeping in mind that they both will hydrolyze to the same drug in the body.

When it comes to safety in pregnancy, I think it's always going to be a risk-versus-benefit conversation. On the one hand, you could say, if it is coming from a compounding pharmacy, if they are having conversations with their patients at the time that a prescription is getting filled that is written by a provider, you have the opportunity to counsel on that. But on the flipside, that doesn't always happen, even when there are known pregnancy risks. Usually, it's up to the provider, really, to have that conversation at the time of recommending to start treatment.

The risk versus benefit here is if it's

something that showing minimal clinical benefit, then it's always safer to not have to take a drug unless it's really medically necessary in that period of time. Again, it's an individual conversation.

But for something like this, there was a study; it was over 200 patients. It was used in pregnant women, obviously, if it was trying to reduce preeclampsia. So there is something to be said that there's known use in the past, but I don't know if that really answers the question.

I think you have to go back to, do I still trust that the hydrolysis of this drug, being the same drug, is the same thing?

DR. SMITH: Right, and I think that's very key that it's -- that's a key question that we don't have any direct data with ubiquinol.

DR. VENITZ: Dr. Johnson?

DR. JOHNSON: Dr. Harrouk would like to comment on -- I think principally, the absence of reproductive toxicity data and what that means to drug development.

DR. HARROUK: Thank you, Dr. Johnson. My name is Wafa Harrouk, and I'm a pharmacologist/ toxicologist who worked on ubiquinol.

Just to echo what Dr. Smith was talking about in terms of the reproductive toxicity and other aspects of toxicology, what you've seen from Dr. Johnson's presentation is that there was a 13-week toxicity study that was from a single source.

We don't have a lot of information about the general toxicity. We don't have data on carcinogenicity, as well as reproductive toxicity. So it's not like we have all this data on ubiquinol, and the only thing that's missing is one aspect.

The other thing that we don't have are data on toxicokinetics. Usually, as a toxicologist, when we're reviewing data, we look at the TK aspects, and we try to correlate the safety of a drug at a certain dose to the findings.

We didn't have that aspect for ubiquinol where we can correlate the findings in animals to a

certain dose, so we have no idea what safe dose is there because there was no TK data. There's no reproductive data. There are no carcinogenicity data. There are lots of holes for this product.

DR. VENITZ: Thank you. But then let me play the devil's advocate. How is that different from, I don't know, 20 other compounds that we looked at over the past seven meetings?

For a lot of them, a lot of information is missing, and it's basically up to the judgment of each of the individual members to figure out how important that missing information might be.

DR. HARROUK: Yes, the problem is when we don't have a specific dose and people can go as high as they want out in the compounding pharmacy -- I mean, it's a general comment for all of them. I agree.

DR. VENITZ: And I appreciate your comment. I'm just saying having sat through I don't know how many of those bulk substance nominations, it's always the question of what is the evidence and how much evidence do we not have.

DR. HARROUK: Yes.

DR. VENITZ: And even the little evidence that we have, what does it mean? Well, I think that's our job to figure out.

DR. HARROUK: Yes.

DR. VENITZ: So the fact that something in particular is missing, let's say about reproductive toxicity by itself, to me is not anything unusual. The question is, what does it mean. And would make the argument that this is an endogenous substance, but in all the other compounds we looked at were not necessarily endogenous substances.

DR. HARROUK: Right.

DR. VENITZ: So that personally gives me a little more comfort to be maybe less worried about it, even though there is no information.

DR. HARROUK: When it's endogenous, you usually have a certain level where the body functions at a level. But when you give it exogenously and you're pushing the system to handle this much -- I don't know. Your guess is as good as mine.

DR. VENITZ: That's basically the point that I'm making. There's an absence of information, and that is typical for all the compounds that we looked at. This is not an NDA package where you and I, and the rest of the committee members that do this stuff --

DR. HARROUK: I agree.

DR. VENITZ: -- can dissect every piece of empiric information and argue about it. Here, we are dealing with uncertainty.

DR. HARROUK: Agreed.

DR. VENITZ: That's the only point I'm making.

Yes, go ahead.

DR. JOHNSON: I just want to add a quick point that in this proposed nominated use, this is a chronic indication, and that may make a difference in the weighting as well.

DR. VENITZ: Agreed. Any other comments, or is the committee -- well, no, not really. We're discussing now. This is not open hearing; this is not nomination anymore.

UNIDENTIFIED MALE SPEAKER: [Inaudible -- off mic]. Dr. Venitz, if we're going to allow the FDA --

DR. VENITZ: I asked a specific question to the FDA staff. They didn't just participate on their own, and we've done that throughout any of the meetings that at least I chair.

Any questions by committee members? Yes, Dr. Pham?

DR. PHAM: One quick question. The slide that noted that ubiquinol was water soluble, I wasn't sure if that means it's like a water-soluble vitamin like CoQ10 is a fat-soluble vitamin, or the drug bulk substance itself is water-soluble and therefore makes it less stable.

Regarding water solubility of ubiquinol, can we just clarify?

DR. ZHANG: This is Ben Zhang from OPQ. Could you please restate your question?

DR. PHAM: Yes. Regarding ubiquinol, there was I believe a bullet point that spoke to its water solubility. And I wasn't sure if that was

part of its -- the stability concern versus its aspect of it being water-soluble in the body.

DR. ZHANG: The stability issue about ubiquinol, it's not about its water solubility or aqueous-related problems. It's about oxidation.

DR. PHAM: Okay. One follow-up -- I think that's good. The reason why I'm asking is because, as far as I know, CoQ10 is a fat-soluble vitamin. So as we talked about things that are used for a chronic disease state and whether or not we have good dosing data, things that are fat-soluble don't have the luxury of being excreted in the urine, so you have the potential for accumulation.

That's why I was wondering if -- trying to figure out if there's a benefit if ubiquinol is a water-soluble vitamin compared to CoQ10. So it sounds like that the water solubility was related to ubiquinol and not necessarily the -- that was the reason why I was asking.

I made the comment because I thought it was valuable to talk about fat versus water solubility on dietary supplements for chronic use.

DR. VENITZ: Any further comments or questions? Dr. Johnson?

DR. JOHNSON: I can clarify the slide. Dr. Zhang and I had a discussion about this particular point because in fact ubiquinol is minimally water-soluble.

I think he would've preferred if we had said not water-soluble, and he explained to me -- I don't know, Ben, if you want to comment -- that there are other mechanisms to help absorb ubiquinol like the formulation of micelles, which will enhance absorption without it being water-soluble. I'll just relate as well that the pharmacokinetic trials didn't suggest accumulation.

DR. ZHANG: I think that's good enough.

DR. VENITZ: Any further discussion?

(No response.)

DR. VENITZ: All right. It looks like we're ready for the vote. Okay, let me do the preliminaries.

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 the Section 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

We will now begin with the voting process. Please press the button firmly on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you've made your selection, the light will continue to flash. If you're unsure of your vote, please press the corresponding button again. Please go ahead and vote.

(Vote taken.)

DR. HONG: For ubiquinol, we have 2 yeses, 6 nos, and 1 abstain.

DR. VENITZ: We're going to go around the table, and I think we're starting this time with Dr. Carome -- oh, I'm sorry. Thank you for pointing that out.

Dr. Smith, please state your name, indicate

your vote, and explain why you vote the way you did.

DR. SMITH: I'm Robert Smith. I voted no. Often the FDA tells us that our comments are more important than our vote, and this is the case where it's worth me thinking through that because I actually found it a somewhat difficult decision to make.

I think there's inadequate safety data for ubiquinol. But there's not concerning, major concerning, safety data. I express discomfort with the heart rate change, but there's also a heart rate change with CoQ10 as I was told. I don't know those primary data. So I would like to know more about safety, but there aren't terribly concerning signals.

I find the efficacy data quite unconvincing, and I understand that there are some positive data, but it's not a database of a type that enables one to confidently conclude about the beneficial effects of the drug that may be happening.

Operating within this system of pharmacy

preparations, though, I find it was a little difficult decision for me to make, knowing that CoQ10 is available as an alternative and that there's, well, still some deficiencies in the CoQ10 data but substantially more extensive data.

Not having seen data that convinced me that -- I understand the differences, but that convinced me that ubiquinol provides something that CoQ10 could not, when I put that together, my vote is no.

DR. VENITZ: Okay. Dr. Gulur?

DR. GULUR: Dr. Gulur. I voted no and would agree with the previous speaker that this was a more challenging decision mainly because there is potential in this drug, however, again, insufficient data presented on the efficacy and some concerning signals from a safety perspective.

One other request I would make, having gone through many of these today, is when there are multiple indications for these medications that are being discussed in our presenters and nominator presentations, it would be good if these substances

were nominated for that so the review could be more comprehensive.

DR. VENITZ: Jurgen Venitz. I voted yes, and I looked at the same data that my two predecessors did, but I obviously arrived a different conclusion.

In a nutshell, as I mentioned before, I think the uncertainties are related to some of the safety information, but not to the point that I'm utterly concerned about it, in particular looking at the human dose that is used relative to the preclinical doses that were used.

I do agree, however, on the efficacy front that is not convincing, that is not compelling, but not enough to turn me off.

MS. DAVIDSON: Gigi Davidson. I voted no because of you look at the patient counseling literature that's associated with coenzyme Q10, you see the words "use cautiously, use cautiously, use cautiously" for bleeding disorders, blood thinners, liver problems, breathing problems, heart problems, et cetera, et cetera, et cetera. And I did see

hints of those in the tox and safety studies that were presented by FDA and in my own research, so that does concern me quite a bit.

Finally, I voted no because other than bioavailability, I could see no advantage to using this over coenzyme Q10.

DR. DiGIOVANNA: John DiGiovanna. In this advisory committee, this is the first time I haven't been able to come to a decision and decided to abstain. I think there's non-convincing evidence of the efficacy, and I don't see a signal for safety. I don't see an unclear -- rather, I don't see a clear unmet need that would make this drug have a strong reason to be able to be compounded.

However, I think that it's probably a natural component that probably has a wide degree of safety, yet I really have no data to get a sense as to how it would be used or what dosages it would be used in patients that may have multiple other medical problems.

So I think we really don't have the data to

make me feel comfortable to lean one way or the other.

DR. PHAM: Kathy Pham. I voted no, but also sat divided like many of my peers on this panel. Ultimately, I was looking for a reason to support it over coenzyme Q10 and really could not find that clinically advantageous benefit.

I am concerned about patient access, but if there is no clinically significant difference to coenzyme Q10, hopefully, this will help to shift some of the literature and continue studies in coenzyme Q10.

I want to note that I did not feel that the safety data warranted cutting off patient access. It's just we could not prove much benefit over coenzyme Q10.

DR. WALL: Donna Wall. I voted yes on this one. I felt like this is just -- coenzyme Q and it are basically about the same drug. It's just one is metabolized more.

If one was approved, maybe there was -- in certain patients at certain times, this could be an

advantage of those patients. But I struggled with this one, and I happened to hit the yes key.

DR. HOAG: Steve Hoag. When I looked at the risk/reward calculation in my mind, I was thinking this is similar to CoQ10 and had less data, so I took the cautious approach.

Also, I'm not sure a patient would be harmed by lack of access to this drug. That was my reasoning.

DR. CAROME: Mike Carome. I voted no primarily because of lack of evidence that the drug is effective for anything.

DR. VENITZ: Okay. Thank you. We did another round, and I think we're going to get an early break as a reward for it.

I'd like for us to reconvene at 3:00. So we're going to start the late afternoon program at 3:00. Thank you.

(Whereupon, at 2:43 p.m., a recess was taken.)

DR. VENITZ: Okay. Welcome back to the final bulk substance for discussion today. We will

now proceed with the FDA presentation for vanadyl sulfate, and Dr. Johnson is going to give that presentation.

Dr. Johnson?

FDA Presentation - Susan Johnson

DR. JOHNSON: Good afternoon again, and I'll be presenting FDA's review of vanadyl sulfate.

I want to say thank you to the vanadyl sulfate review team and recognize the folks who worked as part of the team while on detail at ODE IV.

Vanadyl sulfate has been nominated for use in compounding under Section 503A of the FD&C Act as a slow intravenous injection for the treatment of diabetes, hyperlipidemia, and heart disease, and to prevent cancer.

Vanadyl sulfate is an inorganic salt of the element, vanadium. It has a well-characterized structure. It's soluble in water and likely to be stable under ordinary conditions as an injectable solution.

Vanadyl sulfate can be synthesized from

vanadium pentoxide. It's a well-characterized substance that's likely to be stable under ordinary storage conditions.

Vanadium is a naturally-occurring element, one of the 38 transition metals. It's found in soil, and we ingest it in meats and various kinds of produce. As a transition metal, vanadium exists in various oxidation states. Vanadyl sulfate contains the most stable state, which is the tetravalent form, and this is the most common intracellular form as well.

The Institute of Medicine, or IOM, has identified a tolerable upper limit of intake for vanadium based on safety data, but IOM has not identified a functional or biological role for vanadium in humans.

The Environmental Protection Agency, or EPA, has considered vanadium extensively, and based on safety concerns has set a limit on vanadium pentoxide in drinking water. However, EPA has found that they are unable to make a complete regulatory determination regarding the safety of

vanadium in drinking water.

To provide additional information, the National Toxicology Program, or NTP, agreed to conduct carcinogenicity and reproductive toxicity studies based on oral exposure. Those studies are ongoing.

In animals, vanadyl sulfate has shown to be absorbed in the gastrointestinal tract. Vanadyl sulfate is, in general, absorbed to a greater extent than other vanadium salts, and this is one of the reasons that vanadyl sulfate continues to be used to provide systemic exposure to vanadium. However, vanadyl sulfate's absolute oral bioavailability in rats is still relatively low at 16 percent.

Following oral or intraperitoneal doses in rats, uptake of vanadium occurs in bones, liver, and kidneys. This distribution of vanadium contributes to the safety issues that have been associated with vanadium compounds that have been studied over the last hundred years.

Additional toxicology data show that

vanadium can cross the placental barrier. It can also accumulate in lungs after being inhaled in rats or humans.

In a clinical study of vanadate as an impurity of albumin solutions, vanadium showed a three-phase elimination. The initial two phases had half-lives of 1.2 and 26 hours, respectively. These were followed by a long terminal half-life of 10 days, which accounted for 80 percent of the AUC. Half of a dose was recovered in the urine after 12 days, but small amounts were measurable in the blood a month after dosing.

Nonclinical safety data show that higher vanadium valences are associated with greater toxicity. The level of toxicity is also related to the route of administration, being highest in association with intravenous administration.

All nonclinical toxicology data that we were able to identify, specifically for vanadyl sulfate, were from studies of oral administration rather than the nominated injectable route.

Single-dose administration of various

vanadium compounds in animals has been associated with serious toxicities, including mortality, neurotoxicity, cardiotoxicity, respiratory toxicity, and hematological findings.

In a 4-week study of rats with and without STZ-induced diabetes, oral vanadyl sulfate was shown to accumulate in kidneys, bones, and other organs. In addition, blood glucose and lipid levels were reduced.

In a 1-year oral study of vanadyl sulfate, kidney injury and other significant abnormalities were observed. Accumulation of vanadium was seen in kidneys, bones, and other organs 16 weeks after the last doses were administered.

Vanadyl sulfate has been studied with in vitro and in vivo genotoxicity assays and found to cause cytogenetic damage and have clastogenic potential. In rodents, vanadyl sulfate affects male fertility and causes embryofetal and developmental toxicity.

Carcinogenicity studies in mice show that oral administration of vanadyl sulfate in drinking

water did not increase the overall number of tumors detected compared to the controls. However, the incidence of malignant tumors was greater among treated mice. In another carcinogenicity study, a significant increase in tumor incidence was seen among female mice but not male mice.

NTP was petitioned to help clarify these equivocal findings and provide a basis for human safety determinations with additional oral carcinogenicity and reproductive toxicity studies. These studies of tetravalent and pentavalent vanadium are ongoing.

A search of the voluntary adverse events reports in the FAERS system identified one case of a patient with Crohn's disease who experienced gastrointestinal events that required hospitalization following the use of vanadyl sulfate for an unspecified period of time.

There were over 1300 reports concerning users of vanadyl sulfate in the CAERS system. However, the relationship of vanadyl sulfate to the events cannot be evaluated due, in each case, to

the concomitant use of multiple other substances.

There were no safety data identified in the literature associated with intravenous or injectable administration of vanadium-containing compounds.

In studies of vanadyl sulfate at doses between 50 and 300 milligrams per day in diabetic patients, the most common adverse events were gastrointestinal.

The literature reports that a drug development program that had progressed to early phase 2 studies in humans for a tetravalent vanadium compound, referred to as BEOV, was halted due to renal toxicity findings in the concurrent nonclinical program.

In conclusion, we lack nonclinical and clinical safety data regarding the use of vanadyl sulfate via the nominated injectable route. Intravenous pharmacokinetic data in humans and oral repeat-dose toxicity in animal show that vanadium accumulates in kidneys, bones, and other organs.

From oral studies in animals, we know that

vanadyl sulfate is associated with renal toxicity, is genotoxic, and is a reproductive toxicant. Gastrointestinal adverse events are common in oral studies of both animals and humans.

Looking at the effects of vanadyl sulfate for the nominated use of diabetes, we found five studies of the oral use of vanadyl sulfate in type 2 diabetic patients. These studies were conducted between 1995 and 2001 and have been reviewed a number of times in the literature.

Each review that we found considered these studies to be individually suggestive of a potential treatment effect, but individually and collectively, they failed to substantially demonstrate efficacy. We concur with the assessment of these reviews.

These studies each included a small number of patients, were of limited duration, and failed to provide an analysis between active and placebo-treatment groups.

We found one study of vanadyl sulfate in type 1 diabetics, and although there was a decrease

in fasting blood sugar and insulin use was reported in the active treatment group, there was a decrease in fasting blood sugar in insulin use in the active treatment group. No analyses between active and placebo-treatment groups were conducted.

A study of patients with impaired insulin sensitivity showed no change in insulin sensitivity after 30 days of treatment.

Looking at hyperlipidemia, we identified five trials in which the lipid parameters were assessed in association with vanadyl sulfate treatment.

In two studies of type 2 diabetes, which are among the five studies discussed on the provide slide, either no change in lipid status was observed or the change could not be attributed to vanadyl sulfate due to limitations in the analyses.

In the study of type 1 diabetics previously discussed, a decrease in total mean cholesterol was observed, but triglycerides were not described as having significantly changed.

In a study with impaired glucose tolerance

patients, triglycerides were increased in vanadyl sulfate-treated patients compared to placebo after 30 days of treatment. However, total cholesterol, HDL, and LDL were not different between the treatment groups.

Finally, one study in weight-training athletes showed no change in HDL, triglycerides, or total cholesterol after 12 weeks of treatment with vanadyl sulfate.

Overall, the studies that assessed lipid parameters did not show consistent results among trials. While several may be suggestive of treatment effects, which would be consistent with vanadium's known insulin mimetic activities, they are insufficient to establish efficacy of vanadyl sulfate in the treatment of hyperlipidemia.

No clinical studies of the use of vanadyl sulfate in the treatment of heart disease or prevention of cancer were found.

Overall, we conclude that in patients with type 1 diabetes, type 2 diabetes, or impaired insulin sensitivity, vanadyl sulfate may have a

potential treatment effect, but it has not been adequately studied in the clinical setting.

Similarly, changes in lipid status observed in studies of diabetics and other patients suggest a potential effect but are inadequate to demonstrate effectiveness of vanadyl sulfate in the treatment of hyperlipidemia. No studies for heart disease or prevention of cancer were found.

Vanadium compounds have been studied in use in treatments of various diseases for at least a century. Vanadyl sulfate has been used for years in pharmacy compound as a capsule and at least one U.S. pharmacy advertises the use of vanadium as a component in an injectable product.

The extent of use of vanadyl sulfate cannot be determined, although it's marketed as a dietary ingredient in dietary supplement products.

In summary, vanadyl sulfate is well-characterized and likely to be stable in an injectable formulation. Regarding safety, we have insufficient clinical and nonclinical data for the nominated injectable route of delivery.

Intravenous pharmacokinetic data in animals and humans show accumulation of vanadyl sulfate in kidneys, bones, and other tissue. Oral in nonclinical studies have shown that vanadyl sulfate produces renal toxicity, neurotoxicity, cardiotoxicity, and other safety issues, and there are ongoing studies at NTP to determine the safety of regular vanadium intake in drinking water.

Clinical studies of oral administration have shown gastrointestinal effects but are inadequate to assess the safety of injectable delivery.

Studies in type 1, and type 2 diabetes, and impaired insulin sensitivity are suggestive of a treatment effect for glycemic control and hyperlipidemia, however, no studies provide substantial evidence of efficacy.

No studies of vanadyl sulfate were found in the treatment of heart disease or prevention of cancer.

Vanadyl sulfate has been used for years in pharmacy compounding as an oral product and may also be being used an injectable. We find that a

balancing of the four evaluation criteria weigh against vanadyl sulfate being added to the list of bulk drug substances that can be used in compounding under Section 503A. Happy to take questions.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Johnson.

Dr. DiGiovanna?

DR. DiGIOVANNA: Can you tell us about the National Toxicology Program? Who are they? What determines whether or not they evaluate a particular drug like this and what the results are of their evaluation?

DR. JOHNSON: I'm going to ask Dr. Harrouk to step up and fill in. But I'll give you the generalities.

In general, a group nominates a substance and provides the rationale for why a substance needs to be studied more completely. In general, they are long-term trials; they're expensive trials, carcinogenicity, reproductive toxicity, that industry just doesn't have incentive to work

on.

In this case, it was a problem from EPA not being able to fill in all of the gaps that they have and answer the questions that they had with regard to vanadium in drinking water and dietary supplement use as well. And because they didn't have enough data to answer their questions, they approached NTP to do these studies.

NTP is actually conducting the studies, and it is a multi-year process. There is an interim assessment and reporting out as they go along.

Wafa, you might want to say more about how we would know when conclusions are going to be formed and that sort of thing.

DR. HARROUK: Yes. My name is Wafa Harrouk. I'm a toxicologist in ODE IV.

For NTP, it has a board of scientists who have different expertise in mostly nonclinical studies. A lot of times, the studies that they conduct are chosen based on the lack of data in the public arena, so they respond to agencies for data gaps.

There's a nomination process. It's a very thorough procedure, and as Dr. Johnson mentioned, it's a multi-year program. So it's well-studied, well-thought out, and the conclusions are all public. So you can go on their website and find all kind of reports with statistical analysis of their data and everything else that Dr. Johnson mentioned about it.

DR. VENITZ: Thank you. Dr. Smith?

DR. SMITH: I have a question. And I know we've touched on this before, but I'd like to look at it a little more thoroughly or ask a little more thoroughly, which is that for vanadyl sulfate, there is evidence of genotoxicity. There is some evidence of increased malignant tumors in mice.

The question is that if this were approved, and one might anticipate then that there might be increased use perhaps that would be in a sense promoted by that, what are the tools that the FDA really has to assure that it doesn't reach vulnerable patients?

Again, I'm particularly referring to

patients who might be pregnant, or patients of childbearing age who might not be adequately protected against pregnancy, or perhaps other individuals who have increased risks, for example, of malignancy.

What are the tools that the FDA has, and what would be used for protection?

DR. JOHNSON: The one thing that I'm going to emphasize is that there is no labeling as there is with an approved NDA product, or BLA product, or ANDA product. So there isn't a fundamental pre-market evaluation of the information that practitioners should have, and there isn't a standard document, standardized document, that goes to all patients or practitioners.

Beyond that, I'm going to let Dr. Dohm talk about the legal aspects of what FDA has control over.

DR. DOHM: Once the substance is added to the 503A Bulks List, it can be used for compounding and prescribed however the physician largely deems fit, unless we put some sort of limitation on the

substance.

There are very few types of limitations we can place on it. One example might be a route of administration, for example. But generally speaking, there is nothing that FDA would do with respect to the bulk drug substances list to limit how the physician prescribes it.

DR. VENITZ: Dr. Johnson, I had a question on slide number 22 because I'm curious on one of the items, one of the bulleted items, that a U.S. pharmacy advertises the use of vanadium as a component of an injectable product.

As an active component or just an ingredient that may not serve any biological function?

DR. JOHNSON: Do you want to go ahead and answer that question? Sure.

DR. MAREK: Hi. Elizabeth Marek. I was a historical use reviewer. It was a component among 13 other components. It didn't say active versus inactive.

DR. VENITZ: Okay. So one out of many but no --

DR. MAREK: Yes, one of 13 other components.

DR. VENITZ: Okay. Thank you.

Any other clarifying questions for Dr. Johnson?

(No response.)

DR. VENITZ: Okay. Thank you, Dr. Johnson. Appreciate it.

DR. JOHNSON: Thank you.

DR. VENITZ: We do not have any nominator presentation, so we're going to move swiftly into the open hearing. I would ask our open hearing speaker to please step forward to the podium and give his presentation.

COL JOHNSON: Jeff Johnson again, representing Medisca. After further reflection, we are graciously going to remove and recuse ourselves from open public hearing. We're done.

DR. VENITZ: Okay. Any questions?

(No response.)

Committee Discussion and Vote

DR. VENITZ: Thank you. We appreciate your open hearing, regardless.

Our discussion is our next agenda item. Any discussion items that anybody wants to raise before with go forward with the vote?

(No response.)

DR. VENITZ: No further discussion. Okay. Then let me do the preliminaries so we can --

DR. SMITH: I'd have some -- I'd like to just make a little discussion.

DR. VENITZ: Okay. Go ahead.

DR. SMITH: Yes. There's a few points I'd like to make, and I'm saying this because we're a panel. If people disagree, it would be helpful for me to hear that.

I have difficulty understanding the clinical context in which one would use intravenous vanadyl sulfate. I mean, I've read the materials, and I didn't ask the FDA because -- speak if you have an answer to this.

I have difficulty understanding that. I'm very familiar with vanadyl sulfate, and I'm very familiar with -- I've used it innumerable times in cell culture experiments and some animal

experiments. And I'm very familiar with the human studies that explore the use of oral vanadyl compounds in diabetes, and I have difficulty understanding what the IV use would be.

I'm saying that not just to talk but because not knowing that, I cannot -- I find it that I can't really consider whether I'm evaluating an acute injection one-time, short-period use, which I have difficulty envisioning what that would be for or this little circumstances, but also whether what I'm looking at is some sort of long-term use but yet intravenous.

I just wanted to state that. I have difficulty understanding what that context might be. If anybody knows something about it, I'd be interested to hear about it.

DR. VENITZ: The only thing I know is what's on the nomination document. Let me just read it.

"Vanadium is used for diabetes, hyperglycemia, hyperlipidemia, heart disease, edema, improving athletic performance in weight-training, preventing malignant cell

development. It is also used for treating tuberculosis, diabetes, syphilis, and a form of microcytic anemia, chlorosis. It's also used as a source of trace mineral supplementation in vanadium-deficient cases." And you probably can clean your house with it too.

(Laughter.)

DR. SMITH: Can I make some more comment? Further comment, just again, to give my perspective is that I'm personally very concerned about potential toxic effects of vanadyl sulfate. There's a host of reasons for that.

It clearly, at adequate dosage, is very toxic in, for example, animal studies. It has a very broad set of mechanisms of altering biological processes. It functions, at least in part, as a phosphate analog. It plugs into ATPases and phosphatases, and often inhibits them, although that need not universally be the case.

For example, in terms of phosphatases, it can affect tyrosine phosphorylation processes throughout the body, but not one tyrosine

phosphorylation process, but potentially many or all.

One of those is the insulin receptor, one of those tyrosine kinases, which might have effects on glucose metabolism, but another is the insulin growth factor receptor, which might promote cell growth and might promote malignancy.

So I have a lot of concerns about its toxic effects. We know that when given orally, in the vanadyl sulfate diabetes studies, it produced some GI side effects that weren't terrible, but they were there repeatedly. So we might say what we were seeing is an effect of the elevated dose at the site of administration on the available cells, the gut lining cells, with an oral dose.

If we're looking at an intravenous dose, then I think we have to ask what might that mean for vascular cells or what that might mean for the myocardium? And we have no data.

So I have grave concerns about the potential toxicity for which I don't see data that alleviates those concerns for me.

DR. VENITZ: Does anybody want to respond? Yes, Dr. Carome?

DR. CAROME: I think the toxicity concerns are great. As a nephrologist, the fact that it accumulates in the kidneys and causes clearly in animals nephrotoxicity, as do many metals, both heavy and not heavy, it's not surprising. I share your concerns that the toxicity signal here and the safety signal here is very, very strong and very worrisome.

DR. VENITZ: It also accumulates in the bones and has a half-life of 10 days.

Any further discussion comments before we move to our final vote today?

(No response.)

DR. VENITZ: Okay. Let me do my usual spiel. If there's no further discussion, we will now begin the voting process. Please press the button firmly on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you've made your selection, the light will continue to flash. If

you're unsure of your vote, please press the corresponding button again.

(Vote taken.)

DR. HONG: For vanadyl sulfate, we have zero yes, 9 nos, and zero abstain.

DR. VENITZ: Okay. As our usual case, we're going to start this time with Dr. Carome. Indicate your name, your vote, and the reason why you voted the way you did.

DR. CAROME: Mike Carome. I voted no for some of the reasons just stated. There is serious safety signal here. The drug causes multiple organ toxicities in preclinical studies, likely to cause significant human toxicity, and there's little evidence that shows it's effective for any of the proposed uses.

DR. HOAG: Steve Hoag. I voted not to include it because of toxicity concerns, and there's already good products on the market for the treatment of diabetes.

DR. WALL: Donna Wall. I voted no for the reasons that my colleagues just stated.

DR. PHAM: Kathy Pham. I voted no for the same safety concerns, and particularly since the nominated form is intravenous, that would be large systemic exposure as well.

DR. DiGIOVANNA: John DiGiovanna. I voted no for the reasons that have been mentioned, particularly the broad array of safety concerns and the lack of any demonstrated efficacy.

MS. DAVIDSON: Gigi Davidson. I voted no. I do regret not hearing the public comments on potential uses for this. I find those to be compelling when I hear what uses might be taking place in patients, however, that didn't happen.

I voted no because it's a known contact irritant. I had serious concerns about administration intravenously, some of the reasons Dr. Smith alluded to. NIOSH recommends pulmonary function tests for anyone who handles vanadium. I had concerns for compounding pharmacy colleagues who might be handling it, and I was concerned about the BEOV product that was in development that halted due to nephrotoxicity.

DR. VENITZ: This is Jurgen Venitz. I voted no, reasons stated before. The one thing that I would like to note is that this is one of those few examples where we had lots of evidence, unfortunately, to the disadvantage of the nominated bulk substance.

DR. GULUR: Padma Gulur. I voted no for reasons that have been clearly articulated by my colleagues.

DR. SMITH: I'm Robert Smith. I voted no because of concerns about toxicity, which are substantial because of the lack of convincing efficacy data for any of the stated potential applications.

Adjournment

DR. VENITZ: Okay. Thank you very much. That concludes the proceedings of our first day. We will adjourn, and I'll see most, maybe even all of you, tomorrow morning at 8:30 when we start our second day. Enjoy the rest of the evening.

(Whereupon, at 3:33 p.m., the afternoon session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Tuesday, May 9, 2017

7:59 a.m. to 11:37 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Hong, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Michael A. Carome, MD, FASHP

(Participation in May 8th session and artemisinin discussion)

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director, Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

John J. DiGiovanna, MD

Senior Research Physician

Laboratory of Cancer Biology and Genetics

Dermatology Branch

Center for Cancer Research

National Cancer Institute

National Institutes of Health

Bethesda, Maryland

William A. Humphrey, BSPharm, MBA, MS

(Participation in May 9th session via phone)

Director, Pharmacy Operations

St. Jude Children's Research Hospital

Memphis, Tennessee

Katherine Pham, PharmD, BCPS

Senior Officer

Drug Safety Project

The Pew Charitable Trusts

Washington, District of Columbia

Jurgen Venitz, MD, PhD

(Chairperson)

Professor and Vice Chairman

Virginia Commonwealth University

School of Pharmacy, Department of Pharmaceutics

Richmond, Virginia

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

TEMPORARY MEMBERS (Voting)

Peter Weina, MD, PhD, FACP, FIDSA

(Participation in May 9th artemisinin session)

Colonel, Medical Corps, USA

Chief, Department of Research Programs

Division of Education, Training, and Research

Walter Reed National Military Medical Center

Division of Education, Training and Research

Bethesda, Maryland

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

(7:59 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 contact for this open session meeting, Ms. Lyndsay Meyer. If you're present, please stand.

Good morning again. 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 to order. We will now ask those at the table, including the FDA staff and committee members, to introduce themselves, starting with the FDA to my far left, and moving along to the right side, ending with one of the industry representatives, Dr. Ned Braunstein. Go ahead.

DR. GANLEY: Hi. I'm Charlie Ganley. I'm

the director of Office of Drug Evaluation IV.

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

MS. BORMEL: Gail Bormel from CDER Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. GHOBRIAL: Michael Ghobrial, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. LAWSON: Rosilend Lawson, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. HARROUK: Wafa Harrouk. I'm a pharmacologist/toxicologist in ODE IV.

DR. NIKHAR: Bindi Nikhar, associate clinical director, and I was on detail to ODE IV and helped with the review.

DR. HONG: Cindy Hong, designated federal officer for the Pharmacy Compounding Advisory Committee.

DR. VENITZ: Jurgen Venitz, clinical pharmacologist and professor at Virginia

Commonwealth University.

MS. DAVIDSON: Gigi Davidson, chair of the USP Compounding Expert Committee and representative for the United States Pharmacopeial Convention.

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

DR. PHAM: Katherine Pham, the Drug Safety Project at the Pew Charitable Trust and public health advocacy expert.

DR. WALL: Donna Wall, clinical pharmacist, and I represent NABP.

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

DR. WEINA: Peter Weina. I'm an infectious disease physician and director of research at the Walter Reed National Military Medical Center.

DR. BRAUNSTEIN: Ned Braunstein. I'm senior vice president at Regeneron Pharmaceuticals for Regulatory Affairs and Pharmacovigilance, and I'm the industry representative on the committee.

DR. VENITZ: And we have one call-in member.

William, do you want to introduce yourself?

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

DR. VENITZ: Okay. Thank you, and welcome again. Let me review the procedures for the upcoming meeting.

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 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 breaks or lunch.

This morning, we will cover one bulk substance nominated for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act, artemisinin.

The April 17, 2017 Federal Register Notice identified the uses FDA reviewed for each of the six bulk substances being discussed at this meeting. As were the five substances we discussed yesterday, the uses reviewed by FDA reflect those for which adequate support was provided in the nomination.

In addition, the nomination and the FDA's review for artemisinin, which is included in the

briefing document posted on FDA's website, identifies the proposed and reviewed uses, dosage forms, and routes of administration. The nominators have been invited to make a short presentation supporting their nomination.

To the extent that the nominators' presentations include information about additional uses, dosage forms, and routes of administration, I'll remind the committee that these additional uses, dosage forms, and routes of administration are not part of the agency's review because the nominators either did not nominate those uses, dosage forms, and routes of administration, or they were not adequately supported.

We will also discuss all solid modified release drug products that employ coated systems, which were nominated to the Difficult to Compound List.

For each topic, we will hear presentations from FDA, ask clarifying questions, hear nominators' presentations, ask clarifying questions, hold an open public hearing, and have a

committee discussion and voting.

Let us begin. We will now have Dr. Cindy Hong, to my left, 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 the 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, or 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; teaching/speaking/writing; patents and royalties; and primary employment.

During the morning session, the committee will discuss artemisinin, a bulk drug substance nominated for inclusion on the list of bulk drug substances for use in compounding under Sections 503A of the federal Food, Drug, and Cosmetic Act, and the uses FDA reviewed: for use in the treatment of malaria, protozoal -- particularly toxoplasmosis -- infections, helminthic infections, stomach ulcers, and cancer. The nominator of this substance will be invited to make a short presentation supporting the nomination. This a particular matter meeting during which a specific matter related to artemisinin will be discussed.

In addition, the committee will discuss oral solid modified release drug products that employ coated systems, which were nominated for the Difficult to Compound List. The nominators will be invited to make a short presentation supporting the

nomination. This is a particular matter meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note that Dr. Michael Carome has been recused from participating in the discussion of voting for the difficult to compound topic.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

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

Section 102 of the Drug Quality and Security Act amended the Federal Food, Drug, and Cosmetic

Act with respect to the advisory committee on compounding to include representatives from NABP and the 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 under particular matters at issue. Instead, they serve as the voice of the NABP and USP, entities with a financial or other stake in the particular matters before the advisory committee.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ned Braunstein is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions

involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topics that could be affected by committee's discussions. Thank you.

DR. VENITZ: Thank you. We will now proceed with the FDA presentation on artemisinin from Dr. Harrouk and Dr. Nikhar, please.

FDA Presentation - Wafa Harrouk

DR. HARROUK: Good morning. Welcome back. My name is Wafa Harrouk. I'm a pharmacologist/toxicologist in ODE IV, and along with Dr. Bindi Nikhar, we will be discussing the nomination of artemisinin this morning. We are grateful to the large team who worked on this review, in particular members of the Division of Anti-Infective Products.

Artemisinin has been nominated for inclusion

on the list of bulk drug substances for use in compounding under Section 503A of the federal Food, Drug, and Cosmetic Act, for use in the treatment of malaria, helminthic infections, protozoal infections, stomach ulcers, and cancer. The nominated routes of administration are oral and injection. We have reviewed available data on physical chemical characteristics, safety, effectiveness, and historical use in compounding for this substance. The presentation will follow this order of criteria.

To start with, artemisinin is a botanical compound isolated from the leaves of the plant Artemisia annua and has been used in traditional Chinese medicine. It has many names, but the most common ones are Chinese wormwood or sweet wormwood.

The chemical structure of artemisinin is well characterized and is shown on this slide. Artemisinin is not soluble in water but is usually extracted with organic solvents. It is very labile in acidic and basic environments. A very characteristic aspect to the structure is the

presence of a reactive peroxide group. It's shown here with the arrow on the structure. This particular bridge is a very reactive one and has been found to be stable under neutral pH conditions and ordinary source conditions.

Although it is feasible for scientists to synthesize artemisinin, the majority of artemisinin supply comes from the extraction of the plant Artemesia annua. Potential impurities of the plant extraction include residual solvents from the extraction process and purification procedure, as well as trace amounts of degradation products of artemisinin.

Though artemisinin has [indiscernible] its short half life limited solubility, especially for parenteral formulations, for bioavailability and reliance on plant cultivation conditions, [indiscernible] for semisynthetic and fully synthetic alternatives.

Artemisinin and its derivatives are a family of sesquiterpene trioxane lactone agents containing a peroxide bridge, which have been investigated

largely for their effectiveness as antimalarial agents. The potential mechanism of action of artemisinin in various disease models will be discussed later on in this talk. While this review focuses on the nomination of artemisinin, some information was also included for some of the derivatives because of their similar mode of action.

Shown on this slide is the structure of artemisinin and some of its derivatives. Commonly available derivatives include artemether, arteether, artesunate, and the active metabolite dihydroartemisinin. A common theme among all these structures, as you can see, is the presence of the endoperoxide bridge, which is believed to confer the antimalarial activity of this compound. As a result, the efficacy and safety data associated with the derivatives may be relevant to the consideration of efficacy and safety for the parent drug artemisinin.

In terms of mechanism of action, although it's not completely understood, the antimalarial

activity of the artemisinin class is believed to be a result of the highly reactive peroxide bridge. What happens is that this bridge generates reactive oxygen species, which can bind and modify the function of proteins and DNA molecules.

Turning now to nonclinical pharmacokinetics, we did find some studies on PK in animals. In a rat study, artemisinin was found to be rapidly absorbed with peak concentrations reached within an hour after oral administration of radiolabeled artemisinin. Direct concentrations were highest in the liver followed by the brain, plasma, and lung. Low detectable levels were also seen in the kidneys, muscle, heart, and spleen.

Artemisinin tissue levels decreased drastically by 24 hours post-treatment, and the excretion was mainly seen in the urine. Primary metabolism of artemisinin and its derivatives involved hepatic bioreduction by the cytochrome P450 system, mainly CYP2B6 and 2A6. These result in the production of the dihydro form of artemisinin, as I mentioned earlier,

dihydroartemisinin, as well as various inactive metabolites.

The toxicokinetics profile of artemisinin was obtained following administration of a single dose, oral that is, or repeated daily dose of artemisinin for 5 consecutive days in male rats. Artemisinin was rapidly absorbed with a short plasma half-life following a single dose or repeated dosing. Systemic exposure of artemisinin decreased significantly with repeated dosing, which was likely due to auto-induction caused by the first pass metabolism.

In terms of toxicity studies, we found some single-dose studies and some repeated-dose studies. I'll start with the single-dose studies. A single dose of artemisinin resulted in a lethal dose among 50 percent of dosed animal at a concentration of 3,840 milligram per kilogram, and this was in mice. The LD50 in rats following intramuscular injection was 2,571 milligram per kilogram.

Clinical signs preceding death included behavioral changes, respiratory difficulties, and

cardiac arrest. Dose related transient CNS, central nervous system, effects were observed following a single dose of artemisinin given intramuscularly to dogs. Other effects included significant decreases in the reticulocyte count.

In terms of repeat-dose toxicities, we were able to find a number of short-term studies, including 5, 7, and 14 days toxicity in the dog and rat. These studies did not report any toxicological effects. In a 14-day study in monkeys, there were several toxicity signs. One of them is death at the highest dose. The non-lethal dose findings included a bunch of behavioral effects, decreased heart rate, and changes in hematopoietic inhibition in bone marrow.

I should mention that there were no chronic toxicities conducted for artemisinin or its derivatives.

One of the major toxicities that have been identified for artemisinin is neurotoxicity, and this was found in studies conducted with artemisinin as well as its derivatives. It is

recognized as a class effect for artemisinin.

This effect seems to be related to dose levels, dose duration, administration route, physicochemical properties of the derivatives, formulations, species, and it's a very visible sign in many studies.

Major neurotoxicological effects were seen in mice, rats, dogs, and monkeys, and again, behavioral changes were seen, abnormalities in balance and coordination, changes in auditory discrimination task tests, and loss of spinal reflex, pain-response reflex, and loss of brain stem and eye reflexes.

Histological examinations of treated animals reveal extensive damage to the brain stem, the eye of the reticular formation, the vestibular system, and the auditory system. Artemisinin was negative in genotoxicity testing, and this was done in the Ames in vitro bacterial reverse mutation assay and in vivo micronucleus test.

I'm showing here an example of one of the derivatives, artesunate, which was found to be

positive in several gene-tox tests. This is important to note because sometimes the findings in those derivatives could really differ from the parent drug, so it should be kept in line.

Other toxicity aspects that have been studied include the developmental and reproductivity toxicity testing. This particular testing has been explored for artemisinin and for its derivatives and included -- it mostly focused on embryo-fetal stages of development, and the toxicities that have been reported range from total embryonic loss, ranging all the way down to various structural malformations in the cardiac, visceral, and skeletal system among surviving pups.

In animals, these seem to be sensitive. The sensitive stage of development appeared to be in the mid to late stage of development, embryonic development that is. Also, there were studies conducted to assess the effects on sperm, and there were findings in terms of spermatogenesis, and these include reduced epididymal sperm counts and abnormal shapes of sperm.

Lastly, in terms of toxicity, there were no carcinogenicity testing conducted for either artemisinin or its derivatives. As I mentioned earlier, this is important for long-term chronic diseases such as the gastric ulcer and cancer.

To summarize the nonclinical aspects of artemisinin, we have found in the literature significant artemisinin related toxicities and include mortality, neurotoxicity, hematotoxicity, and teratogenicity in various animal species. The finding appears to be a class effect for artemisinin and some of its derivatives.

In general, the toxicities are reported to be dose, treatment frequency, and duration related. In addition, toxicities were related to administration routes, the physicochemical properties of the chemical administered, and the formulation used.

Orally administered artemisinin is rapidly absorbed and cleared from the plasma, which is distributed primarily to the liver, and to a lesser extent, to the brain and lungs. Artemisinin

metabolites are mainly excreted in the urine. Toxicity studies that have been reported show that the cardiovascular and neurological systems are the primary target organs for toxicities in monkeys and dogs. Artemisinin was not found to be mutagenic. We did not find any chronic toxicity or carcinogenicity studies for artemisinin.

Orally dosed artemisinin and its derivatives can cause lethality and developmental toxicity in pregnant mice at doses relevant to human therapeutic doses, particularly in mid and late stages of development in various species. So that was found in the rat, rabbit, and monkey suggesting a potential risk for teratogenicity in people exposed to these products.

The next section discussed is the human pharmacokinetics data for artemisinin. Just like I have mentioned in the animal studies, artemisinin and derivatives are rapidly absorbed with a short elimination half life following a single dose or repeated dosing.

As you can see on this table, systemic

exposure to artemisinin, so the AUC Cmax, decreased significantly with repeated dosing. This might be likely due to auto-induction of drug metabolism. Repeat-dose toxicity studies and other longer-term studies should be interpreted with caution because this exposure might not be constant over time. It decreases in terms of concentration as you dose.

The bioavailability of the oral suspension of artemisinin seemed to be much greater than the aqueous formulation when administered by the intramuscular route. The IM route showed greater intrasubject variability compared to the oral route, making the intramuscular route of administration reliable for dosing purposes.

This slide shows a graph where the pharmacology of artemisinin and its derivatives are shown. What you can see is in terms of artemisinin metabolism in humans, it seems to be extensively metabolized by the liver mainly by CYP2B6 to turn into inactive metabolites. None of the metabolites seem to have the endoperoxide bridge, and these were shown to be inactive against malaria.

Artemisinin induces cytochrome CYP3A, 2B6, and CYP2C19. Because of its effect on multiple cytochromes, artemisinin is likely to have significant drug-drug interactions with drugs metabolized through the CYP pathways. Artesunate, arteether, and artemether seemed to be metabolized by various cytochromes to hydro-artemisinin, which is the active metabolite of this family.

With that, I'm going to turn the talk to Bindi to discuss the clinical findings. I can take questions now or at the end, up to you.

DR. VENITZ: The end.

DR. HARROUK: At the end? Thank you.

FDA Presentation - Bindi Nikhar

DR. NIKHAR: Thank you, Dr. Harrouk.

I'm Bindi Nikhar, and I'll continue with the rest of the artemisinin presentation. We'll focus on safety-related issues first, followed by effectiveness, and then we'll just tie everything up together.

The safety for artemisinin was derived from an assessment of the FAERS and CAERS databases,

which I'll come to in a minute, as well as literature and available labeling. As such, the safety for artemisinin included artemisinin as well as its common derivatives given that they're thought to have a common mechanism of action.

Moving on to FAERS data, FAERS stands for FDA Adverse Event Reporting System, and an assessment of this database showed 11 cases of which 2 cases I included here because they describe hepatic dysfunction that may have been associated with the use of artemisinin.

The first patient was a 69-year-old patient who took artemisinin for malaria prophylaxis. Now, bear in mind that artemisinin or its derivatives are not indicated for malaria prophylaxis. He also took echinacea concomitantly. Jaundice was reported 5 days after the last dose of artemisinin. While the dose and duration of artemisinin is not known, a liver biopsy showed drug-induced hepatitis.

The second patient was a 69-year-old patient with breast cancer who was treated with

anastrozole, artemisinin, and radiation. She had massively elevated ALTs and AST. The ALT was 13 times the upper limit of normal, and the AST, 10 times the upper limit of normal. The anastrozole and artemisinin were discontinued, and the liver function tests returned to normal. The anastrozole was restarted, and about 8 weeks later, the liver function tests remained normal.

While there is missing data in both cases, this is largely in keeping with voluntary adverse event reporting, and the cases are confounded by concomitant medications and therapies. The causality in both cases is suggestive of artemisinin-induced hepatic dysfunction.

Now moving on to CAERS data, CAERS stands for CFSAN Adverse Event Reporting System. An assessment of this database for adverse events associated with artemisinin supplement use showed 14 cases of which 8 cases are included here. The majority of these cases were associated with liver dysfunction, but neurological adverse events were also described.

The cases of liver dysfunction showed potential artemisinin-induced hepatotoxicity and likely drug-induced liver injury, and in 6 cases who had massive elevations of ALT, AST, and bilirubin.

Going on to discuss these cases -- and I will discuss them in a bit more detail in the next slide -- in 3 cases, only artemisinin was ingested, which made the causality more compelling. And while there was missing data, overall they appeared to have no other risk factors.

Two patients had a liver biopsy showing drug-induced hepatitis. The artemisinin doses were unclear, but they appeared to be between 2 to 8 milligrams per kilo for about 2 weeks or longer, and the causality in these cases was suggestive of drug-induced liver injury.

In two other cases, tricycline was ingested. Tricycline contains artemisinin, berberine, grapefruit citrus seed extract, and black walnut hulls. In still one more case, artemisinin was ingested for Babesiosis. The causality in these

three cases was suggestive of the potential for drug-induced liver injury but not entirely clear given the confounders.

Notwithstanding the limitations of voluntary adverse event reporting, including missing data and confounding events, the temporal relationship between the ingestion of artemisinin and the massive elevations of liver enzymes and bilirubin, as well as the positive dechallenge noted in some cases, the lack of risk factors, and liver biopsy findings in some of these cases, suggests the potential for artemisinin associated liver toxicity.

This toxicity appears to be associated with larger doses and longer durations than the typical malaria treatment doses, which are usually about 4 to 6 milligrams per kilo per day for about 3 days.

Here's a breakdown of the CAERS data. The three cases in italics are those cases where only artemisinin was ingested. The first patient was a patient with breast cancer who received multiple alternative therapy treatments, including

artemisinin. She went to a clinic in Mexico where she apparently received chemotherapy in addition to an alternative therapy. This patient eventually died. The causality is unclear in this case. It is possible that her cancer metastasized and led to her death.

The second patient was a patient with prostate cancer who also went on to receive multiple alternative therapies, including artemisinin. The dose was unknown, but he had normal liver function tests at baseline, and after about 4 weeks, he developed massive elevations of ALT, AST, and bilirubin, and modest elevations of alkaline phosphatase.

At the peak, his ALT was 5 times the upper limit of normal, AST 8 times the upper limit of normal, and bilirubin 25 times the upper limit of normal. He had deep icterus, including scleral icterus, and intense pruritus. His hepatitis serology was negative. He was taken off artemisinin and sent to Duke for consultation, where at that time his liver function tests was

starting to improve, and the liver biopsy was not thought to be necessary. Eventually, he did have a positive dechallenge with the liver function tests resolving.

The third patient took artemisinin for an unknown indication and had a past history of Lyme disease. In about the third day, after starting artemisinin, she developed vertigo, dysarthria, and paresthesia. She came off the artemisinin, and her symptoms resolved after about 5 to 6 weeks. Her symptoms may have been related to artemisinin.

The fourth patient took artemisinin for malaria prophylaxis at about 100 milligrams per day and after 2 weeks developed hepatotoxicity. The weight was unknown, but assuming an average 50 kg patient, the dose would have worked out to be about 2 milligrams per kilo per day. His hepatitis and Epstein-Barr virus serology was negative, an MRI showed no obstructive processes, and a liver biopsy showed drug-induced hepatitis.

The fifth patient took artemisinin for Babesiosis. The dose was unknown, but after about

90 days, he developed hepatotoxicity. Babesiosis has also been associated with jaundice and hepatomegaly.

The sixth patient took tricycline for an unknown indication and had a past history of Lyme disease. After about 1 month, this patient developed hepatotoxicity with ALT being 2 times the upper limit of normal and bilirubin 13 times being the upper limit of normal. Berberine is known to cause scleral icterus in newborns, but in our search, we were not able to find that it is associated with drug-induced liver injury, and berberine is contained is tricycline.

The seventh patient took tricycline for parasite cleansing purposes, and about 2 weeks later, she also developed hepatotoxicity with massive elevations of liver enzymes. And the ALT was 11 times the upper limit of normal, the AST, 10 times the upper limit of normal, and bilirubin, 4 times the upper limit of normal.

The eighth and the last patient, again, took artemisinin for malaria prophylaxis at about

200 milligrams twice a day, and after 2 weeks, he developed hepatotoxicity. His weight was also unknown, but again, assuming an average 50 kg patient, the dose would have worked out to be about 8 milligram per kilo per day. An MRI showed no obstruction, and a liver biopsy showed drug-induced hepatitis.

These are the adverse events associated with artemisinin and its derivatives in general. Neurotoxicity, dizziness, tinnitus, vertigo, nystagmus, ataxia, dysarthria, and paresthesia. As you'll note, these are largely in keeping with the animal toxicity events that Dr. Harrouk just discussed: GI toxicity; hematotoxicity, transient reticulocytopenia, neutropenia, and post-treatment hemolysis; hypersensitivity; and hepatotoxicity.

Further, there are two additional case reports of potential artemisinin-induced hepatotoxicity in patients with no obvious risk factors. And by that, I mean there were no concomitant medications, had no viral infections, no autoantibodies, and no obstructive processes.

The first case is a 43-year-old female who had normal liver function tests prior to presentation. She took 125 milligrams of artemisinin 2 to 3 times a day for just general health maintenance purposes. Her weight was unknown, but again, assuming the average 50 kg patient, it would have worked out to be about 5 to 7.5 milligrams per kilo per day.

She was seen 6 weeks after starting artemisinin at which point she had developed hepatitis, but it probably started earlier. Her ALT was 12 times the upper limit of normal, the AST, 4 times the upper limit of normal, and the total bilirubin 13 times the upper limit of normal.

The liver biopsy but a week later showed cholestatic hepatitis with portal and lobular inflammation. But now bear in mind that this picture was about 6 to 7 weeks after starting artemisinin, so we don't know what the picture looked like earlier. She had a nice, positive dechallenge with the elevated liver function tests resolving after discontinuing the artemisinin.

The second case is a 52-year-old male, and this is a CDC report. And by the way, this report is also on the NIH liver tox website. This patient also had normal liver function tests 5 months prior to presentation. He took 100 milligrams of artemisinin, 2 capsules 3 times a day for identified protozoal infection. His weight was unknown, but the dose described it as being 7.5 milligrams per kilo per day.

After about a week, he developed hepatitis, and his artemisinin tablet samples were sent to a lab for analysis and were found to contain no contaminants. His ALT was 16 times the upper limit of normal, the AST 7 times the upper limit of normal, and the bilirubin 3 times the upper limit of normal. He also had a positive dechallenge within about 2 weeks of discontinuation of artemisinin.

In both cases, the temporal relationship between artemisinin and ingestion and the massive elevations of ALT, AST, and bilirubin, as well as the positive dechallenge with resolution of those

elevated liver function tests on discontinuation of artemisinin and no obvious risk favors, if you take all these factors into consideration, there's suggestion of a causal relationship between artemisinin and ingestion and the potential for drug-induced liver injury.

To conclude the safety discussion, the majority of safety assessments for artemisinin come from use in the malaria setting where artemisinin is generally considered safe and well-tolerated as antimalarial therapy for short-term treatment. The severe toxicities in animal studies, such as the neurotoxicity, the embryotoxicity, and the hematological toxicity are not generally observed in short-term human studies. But based on the case reports and the FAERS and CAERS data that we just discussed, higher doses and longer durations of treatment appear to cause drug-induced liver injury.

This hepatotoxicity may be dose related, it may be idiosyncratic, or it may be both, and importantly, the safety of artemisinin for

long-term and chronic use has not been evaluated.

Now, moving on to general pharmacology across the various indications, for malaria, artemisinin is thought to be active against the asexual erythrocytic forms of Plasmodium falciparum and vivax, but it is inactive against the extra-erythrocytic forms.

For helminthic infections, artemisinin and its derivatives appear to have an inhibitory effect via the endoperoxide bridge when used at high doses in rodent models against Schistosoma mansoni, haematobium, and japonicum, as well as against the other non-schistosomiasis helminthic infections, as indicated below.

Moving on to protozoal infections, this review focused on Toxoplasma gondii, where the nonclinical in vitro and in vivo studies suggest that artemisinin and its derivatives may affect different steps of Toxoplasma gondii's life cycle by affecting calcium homeostasis and inhibiting replication, growth, and attachment to host cells.

For gastric ulcers, artemisinin and

derivatives appear to increase prostaglandin levels in the gastric mucosa and exhibit bactericidal activity against Helicobacter pylori in rodent studies. And for cancer, artemisinin and its derivatives are proposed to decrease cell growth, proliferation, and metastasis perhaps via the endoperoxide bridge, causing the creation of reactive oxygen species, by the formation of alkylating agents inducing apoptosis, and by down-regulation of vascular endothelial growth factor, inhibiting angiogenesis.

Now moving on to effectiveness in the malaria setting, historically, artemisinin has been used in the treatment of malaria. But over the years, the low bioavailability of artemisinin led to the development of the semisynthetic derivatives that are now used as part of WHO recommended artemisinin-based combination therapy.

As such, artemisinin and its derivatives have a rapid onset of action with a short half-life. So per WHO guidelines, artemisinin derivatives are used in combination with

longer-acting drugs that have a slower onset of activity. This combination therapy is believed to offer rapid and complete eradication of the parasite and prevent drug resistance.

In the U.S. we have Coartem, which is a fixed-dose combination of artemether and lumefantrine, and this is the only artemisinin derivative-containing antimalarial drug approved by FDA to treat uncomplicated P. falciparum infections. Intravenous artesunate is not marketed, but it is available from CDC, and this is typically used for early stages of severe falciparum malaria infections. But the prophylaxis of malaria by artemisinin and derivatives is not recommended.

Moving on to schistosomiasis, this is a waterborne helminthic infection affecting about 200 million people worldwide, but it's really uncommon in the U.S. The common types include Schistosoma mansoni, haematobium, and japonicum. The endemic areas for these infections are southeast Asia, China, areas of the Middle East, and some countries

in Africa.

Based on the mechanisms of action, it has been hypothesized that artemisinin and derivatives -- by targeting the eggs in juvenile worms in combination with praziquantel targeting mainly adult worms -- may have complementary modes of action and perhaps affect the entire life cycle of the worm, but there were no clinical trials on artemisinin in the treatment of schistosomiasis.

Based on clinical trials for artemisinin and derivatives, it appears that artemisinin and derivatives, generally in combination with praziquantel, may have a prophylactic and treatment effect against the three common types of schistosomiasis. But as monotherapy, they appear to be ineffective for prophylaxis and treatment. It should be pointed out here that there is worldwide concern regarding the use of artemisinin in areas that are endemic to both malaria and schistosomiasis to prevent resistance of malaria parasites towards artemisinin.

Regarding other helminthic infections, there

were few studies that assessed the use of artemisinin and derivatives in certain trematodal and nematodal infections. These infections of such are also uncommon in the U.S. In the studies discussed below, artemisinin and derivatives did not appear to be effective compared to praziquantel. And overall, there was no evidence that artemisinin and its derivatives are efficacious in treating non-schistosomiasis helminthic infections.

Now going on to toxoplasmosis, this is a protozoal infection caused by an intracellular parasite Toxoplasma gondii. The infection occurs through ingestion of undercooked meat from infected animals, by contact with feces from infected cats, or congenitally via placental transfer.

We were not able to find any clinical studies that assessed artemisinin or its derivatives in treating T. gondii. And likewise, no clinical studies were found that assessed the efficacy of artemisinin or its derivatives in the treatment of gastric ulcers. And for cancer, there

were no clinical studies that assessed the efficacy of artemisinin per se in the treatment of cancer, but there were some pilot clinical studies and case reports that assessed artemisinin derivatives and artemisinin annua for cancer treatment.

Those reports contain insufficient information to support the usefulness of artemisinin and derivatives in cancer treatment, and there is concern that synergistic toxicity and drug-drug interactions would be expected to occur if artemisinin and derivatives were added to current treatment regimens.

Now moving on to approved therapies for the diseases we just discussed, for malaria, there are multiple FDA-approved drug products for treatment and prophylaxis of malaria, and this is in addition to the artemisinin and derivative-containing product, artemether-lumefantrine.

For helminthic infections, praziquantel is the FDA-approved drug for all forms of schistosomiasis as well as Clonorchis sinensis and Opisthorchis vierrini. For protozoal infections,

pyrimethamine and sulfadiazine are FDA approved for treatment of toxoplasmosis. And of course, for gastric ulcers and cancer, there are multiple FDA-approved products in various drug classes.

To summarize effectiveness across the various indications, starting with malaria, artemisinin has been used for the treatment of malaria but is not currently recommended as part of WHO-recommended combination therapy to treat malaria. Artemisinin and derivatives are used in the treatment of malaria as part of WHO-recommended artemisinin and combination-based therapies with other antimalarial drugs.

Because of their short half-life and the potential for drug resistance, artemisinin and its derivatives should not be used as monotherapy. Lastly, artemisinin and its derivatives are not recommended for prophylaxis of malaria because of concerns regarding resistance.

For helminthic infections, there is some evidence that suggests that artemisinin and derivatives, in combination with other therapies,

may improve clinical response in the treatment of schistosomiasis, and there is limited data that does not support use for the other helminthic infections.

For protozoal infections, again, there were no studies in the use of artemisinin or its derivatives in the treatment of T. gondii in humans. For gastric ulcer, the same thing, no studies in the use of artemisinin or its derivatives were found. For cancer, the limited reports regarding use of artemisinin and derivatives lacks sufficient information to support use.

Now moving on to historical use in compounding, there's insufficient information available to determine whether and/or how long artemisinin has been used in pharmacy compounding in the U.S. Based on internet searches, artemisinin does not appear to be available as a compounded product in the U.S.

Artemisinin is listed in the Chinese Pharmacopoeia and is available in combination with

piperaquine or naphthoquine through Chinese manufacturers, and it is available as a dietary ingredient in dietary supplement products.

Here are some important considerations to bear in mind. Artemisinin is physically and chemically well characterized and stable under ordinary storage conditions. Artemisinin is metabolized via the cytochrome P450 enzyme system, which raises implications for drug interactions when used daily. There have been elevations of transaminases and bilirubin in patients taking artemisinin for longer than the typical 4 to 6-day regimen to treat malaria.

Artemisinin and derivatives are an effective therapy for the treatment of malaria when used in combination with other therapies, but it should not be used for prophylaxis because of concerns regarding resistance. Artemisinin has not been shown to be an effective therapy for non-schistosomiasis helminthic infections, gastric ulcer diseases, and cancer. There is insufficient information to determine how long artemisinin has

been used in pharmacy compounding.

Finally, a balancing of the full evaluation criteria weighs against artemisinin being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act. That's it. Thank you.

Clarifying Questions

DR. VENITZ: Thank you, Dr. Nikhar, and thank you, Dr. Harrouk. We now have time for clarifying questions.

Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. Thanks for that nice, broad overview. I have a number of questions.

There have been a number of reported instances of toxicity, which seemed to occur more commonly after repeated doses. And you showed in slide 17 some human pharmacokinetics, but the longest time was only after 5 days, after which there was a substantial drop in the levels of the drug. And you also in slide 12 showed repeated-dose study toxicity in dogs where there

was apparently no adverse effect.

So it raises a number of questions. Is there additional data on human pharmacokinetics and metabolism after -- longer than 5 days, and are there absorption problems or other reasons for other species, like the dogs, not having toxicities?

DR. HARROUK: I can take that. In terms of the human PK exposure, the data presented here were the only data that we were able to find. Now, in terms of the toxicities, or lack of, in some of these studies, as I mentioned, the toxicities are very much formulation-dependent. So if you have the intramuscular you can get one dose via [indiscernible] formulation, but it's not really consistent because it's not dissolved very well in some of these formulations.

There could be other actives that we're not aware of that might be inducing the toxicities besides the ones that were measured. But in general, everything that we were able to find in the literature was included in the review and the

talk. So we don't really have a lot of information to shed light on this issue that you're raising, but these are good points.

DR. DiGIOVANNA: So of the cases that were reported of all of the hepatotoxicity, are all of those reported from the U.S., or would some of those have been from other countries and would there be perhaps many different formulations or extractions of the drug that might account for some of the toxicities that were seen, hepatotoxicity?

DR. HARROUK: Well, I think if you start with the FAERS data, I believe those were U.S. cases. The CAERS data, mind you, refer to artemisinin and supplement use. Those are based in the U.S. And then the two case reports were also U.S. cases, yes.

I think to answer your question, yes, there may be autoinduction that takes place over a course of time. But we don't know what accumulates and what metabolites accumulate. And frankly, the etiology of the drug-induced liver injury, the potential for drug-induced liver injury, is frankly

unknown. It appears to be dose related, but may well be idiosyncratic. We just don't know.

DR. BRAUNSTEIN: Hi. This is Ned Braunstein. I'd like to probe your thinking about the weighing, if you will, all of the data to come to your conclusion because that's a very broad statement. So I'd like to understand what actually you are weighing in making that assessment.

Is there a legitimate use for this product? Is there a need for this product? Would not putting this on the list create a shortage for this product? That's on one side. Then what are you weighing on the other side? Is it life-saving on the one hand? I haven't seen really any -- I saw the liver cases. Obviously, we do understand that. But were there deaths attributed to the use of this product, on the other hand?

So how are you actually doing that weighing? Because I think we have to shine some light on that to really have a good understanding of what the FDA's thinking is when you make broad statements, when a federal agency makes broad statements that

says, well, overall, we weigh something, and we come to a conclusion.

DR. DOHM: I think I'll start, and then you can jump in if you have additional information to add.

As you know, there are four criteria that the agency considers when it is evaluating whether or not to recommend putting something on the 503A Bulks List. And you know those four criteria are systematically discussed in all of the presentations, so safety, efficacy, physicochemical characteristics, and the historical use in compounding.

Now, I think what you're asking is about the weight that you might give to any given factor given the facts of the case and the circumstances arising from it. And I think the balancing is obviously a totality of the circumstances, but I think that the doctor will be in a much better position to talk about the weight or the concerns with respect to each of those factors.

But I think you identified a number of

factors that don't squarely fall within any of those criteria, such as whether or not putting it on the list would cause a drug shortage, was one example. Obviously, if those things were relevant to any of the factors, they would have come up in the presentation, but I don't recall hearing that factor in particular.

DR. NIKHAR: Thank you, Dr. Dohm.

So let me just weigh in a little bit there, and let's just start with effectiveness.

As I pointed out, artemisinin has been used historically in the treatment of malaria, but it is not recommended. It is not the current recommended drug to use for malaria because it's the artemisinin and derivatives that should be used as part of WHO-recommended combination therapy. Then again, we also have other drugs for prophylaxis and treatment of malaria.

Regarding the other protozoal infections and helminthic infections, we have other drugs that can treat them, and likewise for gastric ulcers and cancer.

From a safety perspective, as I pointed out, a large part of the safety is obtained from using an antimalarial setting.

For schistosomiasis, focusing on that at present, the studies that we came across were all conducted previously. We don't have much information, and they were largely used in combination with praziquantel. And when used one to one, compared one to the other, praziquantel, which is a currently an approved drug, came out on top.

The other concern is also they were usually single-regime studies, and these infections are difficult to treat. I'm talking about schistosomiasis, and it's likely that you'd require multiple doses of longer periods in a couple of different treatment regimes. So we don't know the toxicities in that setting. The same applies for toxoplasmosis, and then again, for gastric ulcers, and cancer.

Now, cancer seems to be an active area where artemisinin and derivatives are being studied, but

again there are concerns about add-on toxicities, cumulative and synergistic toxicities, and the drug-drug interactions. So that's kind of where we are.

DR. GANLEY: Charlie Ganley. I just wanted to follow up on the earlier question about whether we had pharmacokinetic data. There is a study that was done to look at the effects on some drugs, and the latest that I found was 10 days of treatment, and you still had the induction.

Just for an example, the data very much mimics what you saw in the 5-day study where the area under the curve for the pre-induced state was 1696, and in the induced state was 285. The clearance was 304, and the pre-induced state, 1755 after 10 days.

Again, this drug was initially developed for malaria, and generally the duration of treatment was just several days, 5 or less days. So I don't suspect we would find a lot of data where the pharmacokinetics is studied after a month of treatment. I think that's one of the issues we

have also.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. CDC makes available an IV derivative of artemisinin. I assume that's done under an IND. Do you know for what uses they will release that drug for use under the IND?

DR. NIKHAR: Right, as I pointed out. But typically for severe falciparum infections in the earlier stages because afterwards, you would then revert back to the oral artemisinin.

DR. CAROME: So there's also the FDA-approved combination drug with artemether and lumefantrine, which is approved for malaria.

DR. NIKHAR: Right.

DR. CAROME: Are you aware of any evidence for someone who might need artemisinin or one of its derivatives where either the CDC available drug or artemisinin itself, or the FDA-approved combination drug, would have advantages over artemisinin, either from a toxicity standpoint or efficacy standpoint?

DR. NIKHAR: Well, as part of the WHO recommendations, it has to be combination therapy to prevent resistance and recrudescence. So from that point of view, that's the combination -- there are other drugs as well that are approved for prophylaxis and malaria treatment, but talking of artemisinin, we only have that one combination.

DR. CAROME: And just lastly, the FDA-approved labeling for the combination drug artemether and lumefantrine has in the warning section, precautions section -- it mentions or discusses prolonged QT interval. Do you know if that relates to -- why it has that labeling, why the combination product has that labeling?

DR. NIKHAR: Right. And that's been studied extensively. As I understand, that relates largely to lumefantrine.

DR. VENITZ: Dr. Weina?

DR. WEINA: Pete Weina. I just want to try and clarify the nomination itself and kind of tease out what we have here. Artemisinin itself, we're using that as this drug that's available on the

internet in capsules virtually everywhere, including Amazon. You can have it delivered the next day to your front door in 100-milligram and 200-milligram capsules.

The majority of the data that's out there, though, has been done with the derivatives, particularly, artesunate, which is used for severe malaria, and artemether, which is used for uncomplicated malaria, but also there is some data on some of the other derivatives as well.

The question that I had about the nomination itself, they talked about the routes of administration being both oral and injection. We struggled with this for 20 years with trying to get a drug that was injectable, and the only one that we could get that was really well formulated was artesunate because it was soluble in aqueous solutions.

What would be the way that they would formulate artemisinin itself, the parent if you will, into an injection up to 240 milligrams? I'm not aware of how they would do that. Would that be

done for intravenous use, for intramuscular use? Would that be done in peanut oil, or how would that be formulated?

I think it's a very relevant question, especially if it's going to be used in things like the helminthic infections or in cancer, because that's probably the way it would be used rather than in an oral formulation.

DR. VENITZ: Maybe we should ask a follow-up question, then, to our two presenters. Did you find any information on intravenous, either use, PK, safety in humans?

DR. HARROUK: The information that was mostly available to us was oral. In terms of the IV, we didn't have much data in humans or animals to be able to answer your questions. As far as Dr. Weina's question about the nomination, we don't know what exactly the nominator wanted to use it for. This is all the information they provided. It would have been nice to know, but we don't have more information on that.

DR. WEINA: I was just going to say, if

we're going to vote on it -- when they put in there injection, but not knowing how it's going to be formulated or put together, given what I know of the difficulties of getting this stuff into an injection and the stability of the product when it's actually in an injection is very relevant to the discussion.

DR. DiGIOVANNA: Yes. One of the concerns that Dr. Braunstein mentioned was that we don't seem to be considering the landscape of what is available in the compounding arena, particularly where it might want to have a useful niche for patients that don't have availability or efficacy from other products.

Your slide 36 looked at the effectiveness of approved therapies, and it appears there are limited drugs for helminthic and protozoal infections. So my question is, are there scenarios you're aware of where those available limited drugs do not work, or where there are organisms that are resistant to those limited therapies where there might be a utility for this particular preparation?

DR. NIKHAR: Well, for helminthic infections, we did a broad search as we were trying to find if there were any studies looking at artemisinin and its derivatives, and for most studies, praziquantel was given prior to introducing any of the artemisinin and derivatives. Frankly, there were no studies for artemisinin per se, and I'm talking about artemisinin and derivatives. Typically, praziquantel was given before because the presumption is to use them together, then it affects the entire life cycle of worm.

So in most of those studies, even in those studies, artemisinin did not seem to do well. And then there were a few studies where they compared one against the other. And there, too -- it's described well in the review, I believe. We have all the studies there, including a tabular format, where again it didn't seem to show much effectiveness. And praziquantel still skims to the top in terms of being effective against the various forms of schistosomiasis.

Likewise, for the non-schistosomiasis helminthic infections, all the other approved therapies at present, they appear to do better than the artemisinin and derivatives. There are very few studies for non-schistosomiasis helminthic infections, the other nematodal and the other infections, too.

DR. DiGIOVANNA: I guess my question is the opposite of that. Are there organisms that are resistant to the standard therapies where there might be a novel utility for this?

DR. VENITZ: Dr. Braunstein first.

DR. BRAUNSTEIN: I'm sorry?

DR. VENITZ: You wanted --

DR. BRAUNSTEIN: No, no. I'm sorry. I'm going to pass. The question was answered.

DR. VENITZ: Dr. Davidson and Dr. Weina.

MS. DAVIDSON: I wanted clarification on the active metabolites. I believe you said that artemisinin is not metabolized to active metabolites, whereas the derivatives are. And my question is, does that contribute to the activity

of the available products. Then I have a follow-up question, which might be better for the discussion. But it's about the proposed monograph for artemether as a substance, and we can talk about whether that could be use to compound with later.

DR. NIKHAR: Well, that's a good question. And as was pointed out earlier, it is well understood that the three semi-synthetic derivatives do get converted to dihydroartemisinin. With artemisinin, there's some ambiguity, but it's largely believed that it does not get converted to dihydroartemisinin. And if it does get converted to DHA, it's a small amount.

The other issue is, in terms of treating infections like schistosomiasis and toxoplasmosis, the short half-life -- it just makes me wonder, the short half-life of these drugs precludes use in those infections. And frankly, if you look at the literature, you have even second and third-generation artemisinins now coming forth. And who knows what utility you will find from those artemisinins in the future, whether it's for these

infections, for cancer, for gastric ulcer treatment. That remains to be seen.

MS. DAVIDSON: To follow up on Dr. DiGiovanna's question, I wonder if there was treatment failure to artemether or artesunate, would you expect the artemisinin to be effective. I would not from what I heard today.

DR. VENITZ: Dr. Weina?

DR. WEINA: Actually, I was going to provide a follow-on for you. Absolutely correct that artemisinin itself in the formulation that we're talking about doesn't go to the active component DHA, but the derivatives do -- or some of the derivatives do. Actually, artelinic acid itself doesn't, or the artesunic [ph] acid or artesunate does convert to DHA.

The only work that's actually been done in other types of infections has been principally with artesunate, and there has been shown to be some efficacy for ganciclovir resistant CMV for transplant patients. And there's fairly good data on that, and there's ongoing clinical trials for

that, and also some efficacy and some rather limited clinical trials having to do with non-small cell lung cancer, and some efficacy for artesunate for that. But it's principally with the derivatives and not with this parent compound that doesn't go into DHA.

DR. VENITZ: Any further questions for Dr. Harrouk or Dr. Nikhar? Dr. Wall?

DR. WALL: The CAERS data that you put in here with the 8 cases, could you determine from these cases, is this a drug that people are buying off the internet, or do we actually have prescribers who are digging into this and prescribing it for these patients?

DR. NIKHAR: It's both actually. And if you look, for example, at that second patient, the one with prostate cancer, that patient actually had gone to some kind of holistic retreat or treatment place in Colorado, and that's where he actually received artemisinin under the guidance of, I believe, physicians at that knee-jerk sort of result. So it's both. People, I believe, are able

to buy that off the internet and they can get prescribed. That's my understanding.

DR. VENITZ: Any further clarifying questions? Yes, go ahead.

DR. DiGIOVANNA: So it's my understanding, then, that since artemether is available in an FDA-approved formulation, that it could be compounded.

DR. DOHM: Yes, components of FDA-approved products can be used for compounding under Section 503A.

Committee Discussion and Vote

DR. VENITZ: Okay. Thank you for your presentation.

We now move to the nominator presentation, but there isn't one because we don't have a nominator. So we're moving to the open public hearing, and there won't be one because we don't have an open public hearing speaker either.

So our next order of business is to start the discussion in order to get ready for the vote. So any discussion items? Dr. Davidson?

MS. DAVIDSON: I wanted to go back to the concept of applicable monographs. If a monograph for a substance -- in this case artemether -- is in revision and therefore not currently official, is that acceptable to be compounded with since it's a subject of an approved finished product?

MS. BORMEL: So independent of the monograph, components of FDA-approved products may be used for compounding. So there's kind of three ways in which you can be a substance use for compounding: a component of an FDA-approved product subject to a USP monograph -- and as you know, we say applicable monograph means drug monograph -- so not a dietary supplement monograph or the like; and then the last way would be that if you make it on to the positive list, so the 503A Bulks List.

MS. DAVIDSON: So if someone wanted to compound monotherapy with -- I'm going to try to say this right -- artesunate, they could use the USP monograph -- I'm sorry, artemether -- substance even though it's not official yet.

DR. DOHM: Artemether is a component of an FDA-approved product, so even though there might be additional components, that doesn't matter for purposes of whether or not it could be used as a bulk for compounding. So the mere fact that it's a component of an approved product will enable it to be used.

MS. DAVIDSON: Okay. So it doesn't have to be an official monograph as long as it's part of a product monograph.

DR. DOHM: That's correct.

MS. DAVIDSON: Got it. Thank you.

DR. VENITZ: Further discussion?

(No response.)

DR. VENITZ: It looks to me like the committee is ready to proceed for the vote. Okay. Let me go through the preliminaries.

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. After everyone has voted, the

vote will be complete. Voting will be on the drug product just presented.

Go ahead, please.

(Vote taken.)

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

DR. VENITZ: Okay. As is customary, I'd like to go around the table and each member please indicate your name, your vote, and the reason that you voted the way you did, starting with Dr. Weina.

DR. WEINA: Pete Weina, Walter Reed. I voted no. The DHA is really the active component of the artemisinins in which we have actual data that shows that it's got any kind of efficacy against any kind of disease process. And since artemisinin itself in at least the nominated formulation doesn't go to DHA, I believe that there's very limited data to actually show that it has any kind of efficacy against anything. And it's the derivatives that are really the principle efficacious components.

The other aspect is that the safety of the

artemisinin by itself, there's actually truly limited data on how well -- or how safe this product is, and it's the derivatives that we've got most of the data. And the animal data itself actually isn't reflected in the human experience that's been used with the vast majority of the derivatives that have been used for antimalarials. And a lot of the toxicity that's been seen in the animal models with the artemisinins as a class hasn't been borne out in human use.

So for that reason, I just don't think that this ought to be made available for formulation.

DR. CAROME: Mike Carome. I voted no for similar reasons. It has a complex safety profile that's still not well characterized, and there are available alternative derivative drugs that can be used either through the FDA-approved version, through compounding of the component of the FDA-approved drug, or through the IND for the product that CDC holds.

DR. WALL: Donna Wall. I voted no for the reasons that my colleagues mentioned. And that

safety profile really concerns me, especially the fact that these people are buying it off the internet, and then we're seeing the kind of side effect profile that we are seeing. I think it's a danger to our citizens.

DR. PHAM: Kathy Pham. I voted no for the serious safety concern, particularly the potential neuro- and hepatotoxicity, as well as the potential for drug interactions. These things should be rigorously tested and be under approved labeling through an FDA-approved product, as well as the concern for potentiating drug resistance that can affect the efficacy of the alternatives, particularly the FDA-approved combination product, as well as the product available through the CDC.

DR. DiGIOVANNA: John DiGiovanna. I voted no for the reasons that have been mentioned, particularly strong safety concerns and the lack of efficacy and the concerns for promoting resistant organisms.

MS. DAVIDSON: Gigi Davidson. I voted no for all the reasons stated. And I generally worry

very much about limiting access to patients for a substance when I make a vote, but it seems like if a provider did want to prescribe artemisinin, then they could through a dietary supplement. But for all the reasons stated for the safety signal and the efficacy of the derivatives as opposed to this substance, I voted no.

DR. VENITZ: I voted no for the same reason. The only thing I'd like to add is I enjoyed reading the careful review that FDA put together, especially all the appendices. That really helped me understand the issues involved, so thank you for that.

Okay. With that in mind, we've --

DR. HUMPHREY: This is William Humphrey. I voted no for many of the same reasons, including its unclear scientific evidence for use and its safety profile, and the fact that there's several effective alternatives available.

Adjournment

DR. VENITZ: Thank you for your vote. That concludes our first order of business. I'm going

to take the prerogative of the chair and move up our breaks since our break is not really scheduled until 10:30. So we'll take our break right now and reconvene at 10:10.

(Whereupon, at 9:56 a.m., a recess was taken.)

DR. VENITZ: Welcome back to our second and last topic for today. We are now going to start discussing the Demonstrably Difficult to Compound List and what might be drugs that should be put on there. And the FDA's going to give us the introduction to that. Dr. Ashraf is going to talk about oral solid modified release drug products that employ coated systems and how that might relate to the Difficult to Compound List.

FDA Presentation - Muhammad Ashraf

DR. ASHRAF: Hello. I'm Dr. Muhammad Ashraf, laboratory chief in the Office of Testing and Research in OPQ CDER. I'm going to talk today on oral solid modified release drug products that employ coated systems.

This is the outline of my presentation,

which essentially includes three components. First I'm going to describe some background, what is considered MRC and what is not considered MRC. Then I'm going to explain with examples the evaluation criteria the agency has employed to define what are included as oral solid modified release drug products that employ coated systems, which are complex formulation; complex drug delivery mechanisms; complex dosage forms; complex characterization and control of bioavailability; complex compounding processes; and complex physicochemical and analytical testing. And at the end, I'm going to present the agency's recommendation for this purpose.

Coming to MRC background, what are MRCs? This slide represents an example of a diffusion-based MRC example, which employs coated beads. According to USP, what is modified release, a dosage form with a drug substance release pattern that has been deliberately changed from that observed for immediate-release dosage form of the same drug substance.

For the purpose of today's presentation, FDA defines MRC as oral solid modified release drug products that consist of an active ingredient-containing core enclosed within a polymeric coating membrane. These systems are designed to release drug substance of the active ingredient at a specified rate, at a specified onset and pattern in the gastrointestinal tract. So these systems can be for local action as well as for systemic actions.

MRCs are of three types, which are included in today's discussion. These systems are based on diffusion, on enteric coating system, and on osmotic pumps.

This schematic shows two of the systems based on diffusion as well as based on enteric coating. On the left-hand side is an active-containing a core tablet, which is coated with a polymeric membrane, which controls the release of the drug at a specified rate and onset and pattern. On the right-hand side, this blue circle, is a coated pellet.

So this system can be either containing one core tablet or it can have multiparticulate systems, active-containing cores coated with a polymer. These coated polymers, the multiparticulate systems, can be then filled into the capsules or they can be compressed into the tablet. These membranes, which are applied on the compressed tablets or on the particles, they control the release at a predetermined rate and pattern.

In osmotic systems, it may consist of a core tablet, which may be a matrix type containing the active ingredient as well as the osmogen, or it may be a bi-layer in which osmogen and the active ingredient are in two separate layers of the compressed tablet. These tablets are coated with semipermeable membrane of the polymer, and they have a hole drilled into it, which controls the release rate of the drug -- of the active ingredient from the system throughout the duration when it is transiting through the gastrointestinal tract.

Most importantly, what is not considered MRC for today's discussion are the simple matrix systems. These matrix systems are simple mixtures of active ingredients with release-controlling polymers, which are filled into -- these mixtures are filled into either capsules or compressed into tablets. They do not have a polymeric coating applied to it, which controls the release. There is a matrix system which is controlling the release.

For the purpose of our review and this presentation, FDA does not consider matrix systems that are not coated to be MRC and has not yet evaluated them. These systems essentially are different from MRC because they do not have a polymeric coating, so that is a key difference.

These MRCs are very complex to design and produce. The complexity resides in very, very special raw materials, selection and control and a very sophisticated and complex design of the dosage form itself, very specialized distinctive manufacturing processes, and unique in-process and

final control measures. All these things together, when put in the right fashion, they control the release of the active ingredient from the dosage form at a specified rate onset and pattern that ensures the safety and efficacy of the final dose of the MRC.

As I mentioned earlier, we have six evaluation criteria for determining where there's some modified release dosage form difficult to compound. The first criteria is the complexity of the formulation.

Complexity of the formulation resides in the very special characteristics of the active ingredients as well as of the excipients. These factors make it difficult to maintain intended performance of MRC throughout its residence in the GI tract and may affect its safety profile.

Active ingredients have certain properties such as polymorphism, such as their solubility, such as their compatibility with the other tablet ingredients and polymers and purity profiles, which may vary from vendor to vendor, from supplier to

supplier, and from batch to batch. These properties are very critical to be controlled because if a slight variation occurs, they can change the dissolution.

For example, polymorphism can change the dissolution profile. And if the dissolution profile is changed, the release rate from the dosage form will be altered, which eventually will affect its bioavailability and its pharmacokinetic profile, thus affecting its therapeutic efficacy and its safety. Similarly, compatibility with the other excipients, if not done right, then this can change the dissolution rate of the active ingredient from the dosage form and affect its bio performance throughout its transit in the GI tract, et cetera.

So these properties of the active ingredient are to be very, very tightly controlled, which needs very sophisticated R&D setup to perform, and it's not easy. Companies spend a lot of sophisticated R&D resources to do all these things.

There are a number of diverse excipients in

any dosage form, but these MRCs contain some special ingredients, which are polymers and are used to coat the particulate system or the core tablets, which eventually controls the release. These polymers can be hydrophilic, hydrophobic [?], et cetera. They appear in many grades. They are available from various sources, manufacturer, et cetera.

There are a lot of variabilities. The name may be the same, HPMC, but when it is manufactured by 10 different manufacturers from different countries, et cetera, they have different properties. And those properties are important because they affect the drug release from the dosage form.

Similarly, they are osmotic agents, there are cushioning agents, et cetera. So all these have to be very tightly controlled in designing the right dosage form with the right performance, which is suitable, which has been demonstrated to be effective for treating certain disease conditions, et cetera.

Similarly, these osmotic agents, the release-limiting polymer coating and release modifier can heavily impact the performance of MRC. So these properties include, for example, molecular weight distribution, is the same polymer, but its molecular weight may differ from batch to batch and from supplier to supplier. Similarly, its viscosity grade may change. Its impurities may change and the percent of cross-linking in that polymer. And the cross-linkers may change from manufacturer to manufacturer. These cannot be easily controlled.

So the name of the polymer will be exactly the same, but it will have different behaviors in terms of controlling the release of the dosage form.

When the dosage form is designed, these properties are very tightly controlled. First, they are characterized and determined how they are going to affect the performance of the given drug for treating a particular disease, and once those are determined, then they are tightly controlled.

These excipients individually and collectively influence the release mechanism and the overall product performance. Similarly, the MRCs, which are based on osmotic systems, contain osmogens. These osmogens are electrolytes like sodium chloride, like potassium chloride. They can be carbohydrates such as mannitol, et cetera. When the dissolving medium from the gastrointestinal fluid enters into the system through the semipermeable membrane, they dissolve. And they dissolve and they create an osmotic pressure.

So the purity profile of these materials, the wicking action of these materials -- the impurities in them, et cetera, they can alter the osmotic pressures and [indiscernible]. Just like all the ions in the body, in the cells, they are controlling the diffusion through the cell membranes, in the same fashion, these are controlling those things, the movement of the liquid, et cetera, which determines and governs the osmotic pressure, which eventually controls the release rate from the dosage form itself.

So a slight alteration even in the purity of these materials, in the particle size of these materials, can make a big difference in the drug-release rate from the dosage form. Each osmogen has to be characterized and its raw material characteristics has to be determined such as particle size, wicking pressure, solubility, et cetera.

So it consistently, each time when it is used and each batch when it is manufactured, delivers the same release rate and same therapeutic efficacy.

In conclusion, MRC formulations are very complex, and that's why they are difficult to formulate. The complexity of these formulations is due to the characteristics of the active ingredients and due to the characteristics of the excipients in active ingredients to develop these products, and the way they are controlled, et cetera. If they are not properly controlled, it may lead to dose-dumping, et cetera, and may lead to toxic effects, side effects, as very often we

see sometimes in the failure of these dosage forms.

I'll jump this and go to the next slide first. The second criteria for evaluating the difficulty to compound MRCs are the complex delivery mechanisms, which for MRCs, for today's discussion, are based on three systems: enteric systems, diffusion-based systems, and osmotic-based systems.

In the enteric system, the polymeric coat, as I showed in the schematics, which is a coating outside the particle or around the tablet, dissolves. It consists of a polymer, which is sensitive to the pH. And when it reaches the right pH, or the desired pH in the intestine, in the gastrointestinal tract, it dissolves and releases the active ingredient to that location where the drug can be absorbed, or it can be used for local action over there, for local therapeutic action.

For example, all the proton pump inhibitors, they are enteric coated. They are used for systemic action. But they are enteric coated because if they are not enteric coated at a highly

acidic medium, they degrade, and they do not perform. So they have to be protected. They have to be released down in the intestine around pH 5.5 so they can dissolve over there.

The other category is the MRCs, which are based on diffusion. In the diffusion-based system, the polymeric coat is retained throughout the transit in the GI tract, and it absorbs moisture and dissolves the drug. The dissolved drug then diffuses out. So the characteristics of the polymeric membrane in this system controls the release rate of the active ingredient from the dosage form. Similarly, in osmotic pumps, the release rate is controlled by the geometry of the aperture in the polymeric membrane, which is semipermeable in this case.

These mechanisms of releasing the drug are controlled by a very complex physical design of the dosage form itself. For example, in diffusion-based systems or for enteric systems, the thickness of the compressed tablet and its surface area and the thickness of the polymeric membrane

around it, and the pore-forming agents in it, et cetera, it is a very, very tightly control the release. If these characteristics of these polymeric membranes are not controlled, then the release rate will vary, and it may not be useful for the therapeutic reason it has been given.

Similarly, in osmotic systems, the distribution of the osmogen in the core tablet may influence the release rate; or the aperture in the membrane through which the drug has to be released, if it's not controlled and it is not very precise and accurate, it may change the release rate and affect the therapeutic effectiveness and the safety of the active ingredient.

In conclusion, the complexity of the mechanism of drug release from the MRC and its design and control throughout the GI tract is very complex. And it is very difficult to compound without a sophisticated R&D effort.

The third criteria, which we have applied to determine the difficulty to compound MRC, are the complex dosage forms. As I have explained, the

selection of the raw materials, et cetera, and of the excipients, and of their characteristics, and designing the mechanism and the dosage form are very complex, which leads very complex processes, to design all those properties.

These are very complex dosage forms. They are not easy to design because of the characterization and the special selection and precise control of the raw material requirement, and also controlling the manufacturing process, which a slight variation of the process -- which I'll show later in my presentation how it can affect the performance of these dosage forms in terms of drug-release rate, et cetera.

The fourth criteria is the most complex in my opinion, is the bioavailability of the MRC, which is very difficult to characterize and control. A modified release dosage form is designed to obtain a predetermined release rate, and that release rate is determined based on its clinical performance.

In industrial setups, these complex studies

are done, clinical studies are done, and pharmacokinetic studies are done to determine what kind of release profile and what kind of plasma profile in the patient is effective in treating a condition, and when it is safe and when it is not safe.

Once those parameters are determined, then they are correlated to the dissolution, how the drug is going to release from the dosage form, at what rate, at what time the onset starts, and how long it goes.

For example, if you look at modified release dosage forms for sleep disorders, the drug has to release immediately and at a concentration which is effective to induce sleep. If it takes time, then there's no use of it. Then it should not stop abruptly. It should continue for the duration a patient has to sleep.

So if there are slight alterations in dose-release rates, in the onset, in the pattern, then the dosage form will not be effective. This is even more critical in case of ADHD examples.

Those patients, those children, they need a dose which is immediately effective before the child goes to the school. And it has to remain effective during the whole period until he reaches home and his mother gives him another tablet.

So slight alterations in release rate can affect the performance of these dosage forms and the plasma levels. The pharmacokinetic behaviors will change, then the effectiveness and/or the safety of these products will be compromised.

These bioavailability behaviors and the pharmacokinetics are very, very difficult to characterize. For systemically-acting MRC products, characterizing the pharmacokinetic behavior of such MRC formulation is very critical. And for locally-acting drugs, which are designed to release a drug in some region of the intestine, pharmacokinetics and bioavailability, they might have almost no absorption, or small absorption, but it may be not effective or useful in explaining the clinical need.

In those cases, in addition to in vitro

dissolution tests, evaluation by clinical endpoints and pharmacodynamic studies are done with the dosage form to determine with what characteristic a dosage form will be effective.

The pharmacokinetic characterization is further complicated by the physiological factors in the GI tract such as food, fasted condition, pH, bile, et cetera, et cetera. In the industrial setup, those sponsors do multiple pharmacokinetic studies and bioavailability studies to characterize the pharmacokinetic profile, which can deliver safely an effective therapeutic dose to the period it is designed for. Without those characterization and pharmacokinetic studies, it's very difficult to design a modified release oral dosage form with a coating, which can be safe and effective.

In conclusion, subtle changes to MRC components, composition, and the manufacturing process, et cetera, can significantly affect the release rate and the pharmacokinetic behavior, and therefore make it very difficult to compound, and in vitro assessments like dissolution tests,

et cetera, are not adequate without correlating them to the bio studies, et cetera. That makes these MRC systems very complex to compound in a compounding setup.

The fifth most important criteria, which makes the MRCs difficult to compound, is the compounding process itself. MRCs require complex and specialized production processes, including the use of specialized equipment to yield predictable delivery of drug products within and across the batches.

These processes, although they are applied by the manufacturers, et cetera, to make other dosage forms as well, like mixing of the ingredients, like coating and layering of the ingredient, in this case -- as I will explain later -- these operations become very, very critical because they influence -- they affect the release rate from the dosage form, like filling and compressing the tablet, et cetera.

Mixing is an operation which requires sophisticated equipment, and it needs control of

the material properties to achieve an homogeneous mixture. This specialized equipment is very critical because it's not easy to mix two different materials. If you mix two liquid materials like water and oil, you cannot mix it unless you use very sophisticated forces.

Liquids are easier to mix, but these are powders, which do not easily lend themselves to mixing. So the micromagnetic properties, the properties of these materials such as particle size, such as particle shape, such as density of those materials, and for dynamic and kinetic conditions, et cetera, they are very critical, and they have to be controlled. And to control them, you need sophisticated testing, which I will show later.

Blend uniformity is dependent also on the mixing parameters of the increments and of the process like impeller speed in the mixer and like how long you have to mix it. Mixing doesn't mean that you put in a mixer like in a kitchen blender in a home, and you turn the button on, and after

some time, you say it's mixed. It's not the same.

These powders are very difficult to mix and very sophisticated. RLDs determine how to mix it because once you mix it, there's an endpoint, and if you continue the process, it will start the de-mixing also. So one has to determine that endpoint exactly, which needs very sophisticated testing as well.

Similarly, in a multiparticle diffusion system, the ratio of the blend for filling into capsule or compression into tablets, et cetera, is in turn dependent on the ratio of the coated subunits of the active ingredient and of the extragranular excipient mixture. So incomplete mixing or undermixing -- overmixing is also undermixing because if you start overmixing, it will start the mixing at the same time, so it will not be a homogenous blend.

That's what makes it complex. The most important unit operation in manufacturing and compounding MRCs is the coating layer itself. This is the most difficult unit operation in even a

normal manufacturing plant, which is equipped to do all these operations because it involves very sophisticated equipment, which have very sophisticated and complex controls. And the parameters to design a particular layer around the dosage form, like tablet around the particles, is very complex.

These coating processes involve methods of successive layering and drying according to the specific design to achieve the desired release rate and pattern. When coating, one equipment is a fluid bed. In this, the powder bed, the tablets are fluidized. They are suspended in the air, and then from the spray gun, which is in the bottom -- or it could be from the side as well -- they are coated.

While they are suspended in the air, one has to determine has the system or the process applied the right amount of the coat, which has the right thickness, because the thickness is going to control the release rate, and a slight variation can affect its therapeutic performance.

So determining the thickness of the core while the process is ongoing is a very complex phenomenon. So it's not easy to determine those characteristics while the process is going on. It needs a lot of complex in-process testing to control. So a slight variation in the thickness or in the weight gain of the residual solvent left in the system, et cetera, can directly impact the active ingredient content and release characteristics.

So the drying process during fluid bed process is a critical step in controlling residual solvents and volatile polymeric impurities, et cetera.

Another manufacturing step is compaction of the tablet. Compaction of the tablet is done on automated tablet machines or the multiparticulate systems are filled into the capsules using capsule-filling machines. These machines apply compression forces and ejection forces.

Now, these automatic machines, they have controls to control the compression force out of

the ejection force. Sophisticated RLD effort is needed to determine how much to compress so the tablet is not fragile after it is manufactured. But at the same time not to compress too much because if it is compressed too much, it can -- for example, in osmotic systems, if its porosity is below a certain level, then the wicking action and the ultimate osmotic pressure generated will be not right. So that has to be titrated out with a compression force.

Similarly, if one is compressing the multiparticulate system, which each particle has a polymeric coating to control the release, now you are compressing those particles. You're applying force on them. You can rupture the coating. So that can lead to dose-dumping. If all the dose is suddenly dumped into the system, it can lead to serious consequences to the patient if it is not done right. There are a lot of deaths that have been reported in many cases because the dose was released -- I have read reports in schizophrenia that -- for some drugs, I've heard the names, when

they're released, that they caused toxic symptoms in those patients.

So compaction forces above certain predefined limits can lead to fracture and dose-dumping. Compression forces below predefined limits can lead to fragile and friable and non-consistent tablets.

For osmotic system, appropriate compaction is critical for maintaining a consistent wicking action of osmotic agent, which is crucial for product performance, effectiveness, and safety. And similarly, the capsule filling and capsulation applies also the compression force and the ejection force, and they have similar consequences.

For the osmotic system, once the tablets are compressed and they are coated, then the last step is to drill a hole, a delivery orifice in the membrane, which will control the release rate. So the size that I mention of this aperture, of the orifice and its depth, et cetera, along with the osmotic pressure generated inside the tablet, controls the release rate.

If the aperture is bigger, than even the osmogen can go out, and there will be no osmotic pressure inside the system to release the drug, or if it is too small, then the release rate will be slower. The osmotic pressure will keep increasing inside, may rupture the system, and lead to dose-dumping. So just making a small hole in the tablet can lead to serious consequences.

These holes for laser-drilled orifices, the size, the depth of the orifice, are controlled by laser beam parameters such as laser power, firing pulse, and duration of the laser applied. Drilling parameters are individually selected based on the specific osmotic system.

So it's not one size will fit all osmotic systems. For each drug, for each dosage form, for each strength, it has to be individually determined to find out what size of the orifice will give the desired release profile and release rate. The size of the delivery orifice must be optimized in order to control the predetermined release rate and pattern of the release.

In conclusion, the complex compounding process is very complex, and that makes the compounding of MRCs difficult in a compounding setup because of specialized equipment, and appropriate in-process controls are critical for production. And improper selection or control of any of these production steps will likely affect MRC performance, effectiveness, and safety.

The sixth evaluation criteria, now I will discuss briefly, is the testing. As we have been talking in the previous slides, we have to select the raw materials based on their properties. We have to develop the tests and specifications to accomplish that goal, then we have to control the manufacturing process.

So we have to develop in-process tests, and for those in-process tests, you have to develop analytical methods, et cetera, to control the production, so that each time you produce the dosage form, it is consistent with what you want to produce, and there is no variability from batch to batch or from time to time.

Extensive characterization and developmental studies on the specific formulation, functional properties, and production processes are a necessity to develop these specifications and in-process controls that should be used to ensure that the product will perform at predetermined specifications.

A large number of complex tests are needed to ensure satisfactory and consistent performance of MRC, such as, I explained, the raw material testing, in-process controls, and in-process tests. Then once the dosage form is manufactured, then we need to test the quality, whether it has been manufactured right or not. Then at the end, you have to do the stability testing, that once you dispense it, or once you manufacture it, it stays stable throughout its shelf life and throughout its use.

These tests for raw materials, et cetera, first it needs characterization of the raw materials, especially the polymer, the rate-controlling polymer, the osmogens, et cetera.

Very critical, the polymer and their properties have to be very, very tightly controlled. Once it is determined what we need for a particular therapy, for a particular drug to develop a modified release dosage form, then those properties have to be very tightly controlled from batch to batch.

Those need testing. And a lot of complex tests have to be developed such as one has to continuously test viscosity, which needs very sophisticated equipment to test the viscosity of these materials, the swelling ratio, the dissolution, the impurity contents, et cetera, which all can affect the release performance. So they all need the test methods and the specifications.

Commercially available raw materials could vary from manufacturer to manufacturer. Each lot of material once arrived has to be tested very thoroughly to ensure that it conforms to the specifications, which have been determined to deliver a particular release rate from the dosage

form.

Then once you have developed the dosage form, when you have manufactured the dosage form, it has to meet quality criteria. USP describes tests such as identification, assay, and impurities for the oral dosage forms. Specifically, these tests, they are tests for volatile content, for disintegration, for friability, breaking force, uniformity, et cetera. They all need sophisticated instruments and equipment and analytical instruments to perform all these tests.

Also, USP does not give, for many of these tests, very precise, step-to-step detail of the methods. So many of these tests are not really articulate, rather only general methods for testing the dissolution rate and pattern are described. Important active ingredient release tests for MRC include in vitro dissolution, assay, content uniformity, disintegration, friability, impurity, and residual solvent.

All of these tests, as I said, need sophisticated and specialized equipment and

instruments to perform these tests to ascertain the quality of the dosage form manufactured.

When manufacturing these dosage forms, at certain stages, certain in-process tests have to be developed and conducted to determine the manufacturing process is proceeding and producing the desired results in the dosage form.

For example, precise control of production process is a necessity to ensure proper performance of MRC; loss on drying, percent weight gain, thickness of the coating membrane, et cetera. For these, generally dissolution tests are performed in situ while this manufacturing is going on to determine that the right membrane that has been coated on the particles are on the tablet or not.

These dissolution methods, they have certain nuances such as apparatus design, the volume and the composition of the dissolution medium, et cetera, the stirring rate, the temperature, and the sampling schedule, et cetera.

Now, these things will become [indiscernible] effect if they are not correlated

with the pharmacokinetic behavior of the dosage form. So these methods are not described how they should be systematically done for the dosage form specifically for many drugs. Variation in any of these parameters can significantly impact the meaningfulness of the results.

Lastly, is the stability testing. Once the dosage form is manufactured, then it has to demonstrate -- it has to exhibit stability throughout its shelf life and through the period of use. These product quality stability testing is critical to ensure there is stability throughout the dosage form shelf life and in used period after dispensing to the patient.

The selection of conditions for stability testing, for example, storage time, container, closure, whether it's open, not sealed, presence or absence of desiccant, fill volume, et cetera, they are critical because under certain conditions, a drug may change its polymers. If it changes its polymer, one has to determine whether during the shelf life after manufacture, it has maintained its

properties or not.

For example, to test polymorphism, you need sophisticated equipment such as x-ray diffraction, which can detect these kinds of changes. So most of the tests used for stability testing are not ordinary tests; they are specially developed to indicate the stability. So these are called stability-indicating tests. So it's necessary to develop stability-indicating tests, et cetera, to test the stability of the product, which ultimately is very critical for right performance.

In conclusion, MRC requires complex testing and procedures to ensure accurate characterization of raw material, product quality, performance, and stability. The appropriate tests are difficult to develop, validate, and perform routinely. Proper testing involves highly specialized equipment and analysts that have received considerable training.

Based on these six evaluation criteria, these were used to determine the difficulty to compound, and based on these criteria, MRCs are difficult to compound drug dosage forms. The risk

and benefit to patients, FDA-approved MRCs are currently used for the management of severe pain, hypertension, diabetes, attention deficit syndrome, hyperactivity -- attention deficit, hyperactivity disorder, Parkinsonism, epilepsy, and schizophrenia.

These products are monitored by FDA to identify drug safety concerns and recommend actions to improve product safety and to protect the public health. There is currently an adequate supply of approved MRC on the market, and thus there is limited, if any, benefit to expand the market to include compounded MRC.

As discussed, MRC design and the relationship between excipient and active ingredient directly impacts the release rate and pattern, product performance, effectiveness, and safety. Substituting or removing the excipient is likely to aversely impact the product performance. Precise and consistent quality control of raw materials, manufacturing processes, and the final product is essential for predictable and

reproducible active ingredient release, drug product performance, and its safety.

Based on these evaluation criteria and the risk and benefit to the patient, FDA believes that MRC presents demonstrable difficulties for compounding that reasonably demonstrate and is reasonably likely to lead to an adverse effect on the safety or effectiveness of this category of drug products. Taking into account the risk and benefit to patients, FDA believes MRC should be included in the Difficult to Compound List under Section 503A and 503B of the FD&C Act.

Now, I can take any questions.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Ashraf.

Any clarifying questions? Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. Thank you for the nice, broad, detailed review. There are apparently a number of MRC products, branded products, that have been approved. I wonder if there are any generic products that are available based upon those MRC products. And if so, how does

the FDA evaluate whether they are prepared properly in their stability?

DR. ASHRAF: Yes. To my knowledge, Pristiq was an antidepressant manufactured by Wyeth, and now its generics are available. One generic was from Teva, which was approved a couple of years ago. And when those generic products are approved, those applicants, they have to submit all the development data. They have to demonstrate their bioequivalency to demonstrate they are equivalent to RLD, to the brand product, so they submit pharmacokinetic data.

So that data is used to determine the equivalency of those products in terms of performance, in addition to so many other things.

DR. DiGIOVANNA: So they actually do pharmacokinetic data on their product?

DR. ASHRAF: Oh, yes. Generic companies have to do. Without that -- and it's just not one pharmacokinetic study; it's multiple studies. For modified release dosage form, a multiple number of studies are done under fed condition, fasted

condition, in patients, in healthy volunteers, and then they determine how it's going to behave.

DR. VENITZ: Dr. Humphrey?

DR. HUMPHREY: Yes. This is William Humphrey. Is there any evidence that compounds in pharmacies are offering MRC dosage forms?

DR. GHOBRIAL: The agency is not aware of any.

DR. VENITZ: Dr. Pham?

DR. PHAM: Just some further clarification on what's not considered MRC because I think this would help in our continued discussion of what types of products are included in this potential addition to the list.

If there is -- if I'm reading it right, for these systems, the finished dosage form is prepared by mixing the active ingredient with the polymer, followed by either filling into a capsule or compressing into a tablet.

So if you have perhaps like an empty capsule shell that's coated, are we then talking about the bulk substance powder also needing to have some

sort of complicated matrix or -- like kind of trying to figure out what is an example of what's not an MRC that still employs coating.

DR. ASHRAF: As I've explained, what we are not including in MRC definition are those modified systems which do not employ a coating process. And this coating is controlling the drug-release rate as desired for its therapeutic performance.

Concerning those capsules which are available, we have not yet evaluated, and we are not including them at this stage. We have not evaluated them.

DR. VENITZ: You are not distinguishing between local delivery and systemic delivery. Can you elaborate on that?

DR. ASHRAF: Yes. Actually, we have -- these enteric systems, the majority of the time, they are for local actions. They can be of systemic action as well. Like I gave the example of proton pump inhibitors. They are enteric-coated systems, but they are designed to deliver the drug further down in the GI tract because if they are

released earlier, in the stomach for example, they will be degraded, and they won't have any useful effect.

But there are systems, enteric systems, which are designed. For example, many drugs I have designed myself when I was in industry to deliver in the distant part of the GI tract for irritable bowel syndrome; for example, IBS, et cetera. So they are for local actions, and we are including those systems.

DR. VENITZ: The examples that you mentioned, I noted that they were all systemically-active drugs. So is that just by coincidence because that's where the majority of the MRCs are being used for?

DR. ASHRAF: Yes, you are right. I have given these MRCs -- example, like PPI for systemic effect, but there are examples which are for local effects. But the mechanism is the same for releasing the drug. Whether it's for systemic or for local effect, it's protecting the drug release -- it's preventing the drug release in

certain parts of the regions. And these polymers are sensitive, and they are designed to deliver to the particular location where there is a very specific pH.

So when the dosage form reaches that pH, it immediately dissolves that membrane and releases the drug, whether it's for local effect or whether it's for systemic effect.

DR. VENITZ: No, I understand. But you're proposing that both of them are considered to be difficult to compound.

DR. ASHRAF: Yes.

DR. VENITZ: Okay. Dr. Davidson?

MS. DAVIDSON: I wanted to follow up on Dr. Pham's question just to make sure I understood what you said.

There are commercially available pre-enteric coated capsules specifically for the purpose of compounding. It's a gelatin capsule that compounders already use to compound with, but it's coated with a polymer coating in a lock, a locking system, that if they fill the substance into the

capsule, it's designed to release above pH 5.5 for distal delivery in the gut.

Are those pre-purchasable capsules considered as MRCs for this vote?

DR. ASHRAF: We have not evaluated them. That's the first point. Secondly, when those capsules -- these gelatin capsules, whether they're coated with whatever polymer, they come in two pieces. So once you fill the drug inside, they have to be banded. And the band has also to be enteric coated, otherwise when it is slipped on, the fluid will go inside, and the coating will not work. This is my personal experience in the industry, but we have not evaluated them yet.

The third point I would like to say, that for every drug -- it's not one size fits all. For every drug, these systems have to be evaluated very carefully to decide whether they're suitable or not.

DR. VENITZ: Thank you. Any further questions for Dr. Ashraf?

(No response.)

Open Public Hearing

DR. VENITZ: Thank you for your presentation.

We do not obviously have a nominator to present, but we do have an open public hearing session. And before we proceed with that, let me go through the stuff that I have to read on the record.

We will now proceed to hear open public hearing speakers. I will read the following OPH statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you

may have with the products and, if known, its direct competitors.

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

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing

to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation, and I'm calling our one and only OPH speaker.

COL JOHNSON: Good morning. Again, sir, thank you for the opportunity, to the panel, to the FDA, colleagues. I am Colonel United States Air Force Retired Jeffrey A. Johnson. I am a pharmacist. I am a naturopath, and I'm also a PharmD.

As I stated yesterday -- I'll just review real quickly -- I graduated from Purdue University with my B.S. in pharmacy in 1978, finished my naturopathic degree in 1999, and earned my PharmD from the University of Kansas in 2003. I am also -- as far as my financial concerns, I'm the medical liaison for Medisca, Incorporated, which is a compounding pharmacy supply firm.

This is an interesting topic for me, and I just first off wanted to make a quote from Dr.

Joseph L. Goldstein, who was an American biochemist in 1985, won the Nobel Peace Prize in Medicine. And he stated, "Creation through invention, revelation through discovery, are two different routes of advancement in the biomedical sciences."

The reason I bring that up is that speaks to the point of innovation. And one of the things as a pharmacist now for almost 40 years, I have found it very interesting -- because I have to tell you this is the first time I've sat in on a government working group. I find it interesting and fascinating to see the PCAC, the FDA, and the compounding industry working together to try to make sure we're doing the best for compounding. However, I must admit, I'm somewhat discouraged because of what I saw yesterday and I'm seeing again. It seems like tool after tool is being pulled out of the compounding pharmacist's hands for whatever reason.

The perception is that compounding pharmacy has little to offer or no place in pharmaceutical care. That's very disconcerting for me because we

go back all the way to Hippocrates, which most of us have heard of before, and he was a compounder. That's all he had to work with. So I think we have to remember that compounding remains an important skill set for us as medical providers.

My past experience itself, having practiced in austere conditions in deployed locations, being able to have the ability to compound a tailored medication for a troop ensured their combat readiness. And not to have had that would have lacked the opportunity for me to make sure I could get that troop back into battle in an effective manner.

I wanted to address a couple things Ms. Pham and Ms. Davidson had brought up about the concern with regards to the capsules. And that was one of the things I kind of looked into last night because I want to make sure as well that if this proposal is approved, that those products are not included in that. I went through; I found seven online that talked about it. I just want to talk about two of them real quickly.

One is by a company called CapsCanada. The other one is by a company called Capsugel. I have no interest in either of those companies. I do not represent them. But it was interesting to find that both of those, the CapsCanada, their product is called K-Caps. It's a hypromellose capsule. It has a low moisture protective barrier. It helps protect APIs or moisture-sensitive, hygroscopic, also liquid forms.

It's a non-animal content, so therefore it could be used by vegans, by non-GMOs, by vegetarians, by Halal, and it's also considered kosher, and it's stable over a wide range of temperatures and humidity.

Interestingly enough, it is approved by the FDA as a GRAS status. It's also found in USP and EP as being compliant with their dissolution rates. It's also in the FDA drug master file, and it's included on the FDA's inactive ingredient database.

So it would be a product that a compounding pharmacist could use. And I'm not saying in any way, shape, or form -- because I agree with

Dr. Ashraf that the MRC is a very complex product, and it would be very difficult for a compounding pharmacy to do those right now. But with the K-Cap -- and I'm not saying they're equal, but it does give us an opportunity to use something similar to an MRC.

The other one would be called -- and there are seven different ones, but I'm only going to cover two of them -- DRcaps by Capsugel. And Mr. Wynn yesterday kind of mentioned this one. Again, it's a vegetarian capsule. It's a vegetable-based capsule. It's acid resistant. I've only got 21 seconds left, so I'm going to have to hurry. There is no need to add chemicals, solvents, other coating materials, low-moisture capsule, protects the API, sensitive to water and acid, and it goes through those things.

So in conclusion, I would again say I agree with Dr. Ashraf that for us as compounding pharmacists, to try to do a MRC, osmotic or whatever you want to say, it would be very difficult because the current technology does not

exist for a compounding pharmacist to do that.

However, what I would say, I think that if you improve this -- so I do recommend the committee reject it -- it would inhibit our future innovation, and it would hamper us and take away from us the opportunity if a delivery system of this type would be what we need to do for our patients and for our providers. And it doesn't just affect the 503A, but also the 503Bs.

I would add in as well, as the FDA and all of us know, if there is a medication shortage, a 503B has the opportunity to try to supply that product. Would that be in an MRC, then the 503B because of this would not have the opportunity to do that.

Then lastly -- and this is just probably kind of silly, but I'll throw it out there anyway -- I think it creates an unfair barrier within free enterprise, and that's what America's based on.

So that's all I have, sir. I'm open to questions.

Clarifying Questions by the Committee

DR. VENITZ: Thank you, Dr. Johnson.

Any clarifying questions by the committee? Go ahead.

MS. DAVIDSON: Dr. Johnson, thank you for that clarification. I have been looking at those capsules myself quite a bit. And it's good to know that you have found status for them in FDA materials and files.

Are you aware -- can you share with us -- incidence of needs for pharmacists to compound using these sort of capsules? In my world, I would use something like that for non-human patients, but that's off the table for discussion here. So I would be interested in hearing about humans.

COL JOHNSON: Ma'am, I'd have to say from my own experience, I have not. But I can see instances where that could happen when you have -- like with some of the products we talked with yesterday, when we know something is either acid sensitive or moisture sensitive, those would

be opportunities where we could use something like the K-Cap or the Capsugel to do that.

Now, again, I have not had the opportunity to compound any of those at all.

A.J., any -- I'm just going to ask -- any thought? Okay.

So to answer your question, no, ma'am, I'm not aware of any specific instances. I can think of possibilities where that would be a potential we would want to use.

DR. VENITZ: Any other questions? Yes? Dr. Wall?

DR. WALL: Being a compounding pharmacist, if you were presented with one of these devices, basically, for drug delivery, how do you go back and assure that it is meeting what it needs to do for your patient? How are you going to go back and check that dissolution? How are you going to go back and look at things; not trust, but make your own patient-specific review and identification that this thing is working like it is supposed to work for this patient?

COL JOHNSON: And ma'am, that's an excellent question, and I appreciate you asking that. I think Dr. Ashraf brought up several opportunities of talking about how as compounding pharmacists, we need to make sure we are doing exactly that.

As a compounding pharmacist, one of the things that I have in my practice -- and I'm currently not practicing at this point. But in my past practice, what we would do, as we do one prescription, we would set aside a certain set of those to make sure and go back through and test those.

So for example, with dissolution, one of the things we would have to do would be simply to drop those into a simulated, in vitro model, and then take those and analyze them and assay them to see if that's correct [indiscernible]. Now, can I do that in my own pharmacy? No, ma'am. I'm going to have to send that out to a lab and have them check that.

So before I would ever dispense that first batch to a patient, I'm going to make sure that

that formulation and that product is doing what it said it would do. So if you're the provider giving me that prescription, I'm going to be very straightforward and transparent with you and tell you, I'm going to have to make sure that this works before I can put my name on it and my pharmacy's label, and hand it out to the patient.

So you're going to take some time for that. So if we know one of those is coming at us, it's not going to be something I tell the patient, guess what, 15 minutes, I'll have it ready to go. No, ma'am. It's not. It's going to take a lot of time to make sure that works. But that would be the kind of process I would go through if I had one of those come to me.

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

COL JOHNSON: Sure.

Committee Discussion and Vote

DR. VENITZ: Appreciate it.

This concludes the open public hearing portion of this meeting, and we won't be taking any more comments. It also means we are now moving

into the panel discussion stage. Any items the committee wishes to discuss?

May I maybe go first and ask our FDA colleagues, MRC -- it doesn't work without the C, right? I want to make sure that I fully understand what we are ultimately going to vote on. That unless there's a coating, it wouldn't apply; what we are proposing would not apply.

MS. GORMEL: That's correct. You heard already from Dr. Ghobrial and from Dr. Ashraf that the question specifically was about capsules that were coated -- they were manufactured and pre-coated. That's not the topic of the discussion today.

In addition, we heard discussion at the OPH about these K-Caps that are comprised, as far as we can tell, of a HPMC material. The actual capsule is comprised with that. Those are also not considered MRC.

DR. VENITZ: And erosion-control polymers would not apply because they involve any coating.

DR. GHOBRIAL: I'm sorry?

DR. VENITZ: Erosion-control polymers, where you have a polymer that dissolves, and then the process releases API.

DR. ZIDAN: So for erosion-control polymers, as long as it's forming a matrix with the active ingredient, so it's not covered under MRC.

DR. VENITZ: Right. That's what I'm saying. So the coating has to apply, otherwise -- we're not talking about modified release products. There has to be active coating involved with the intent to affect the release rates.

DR. ZIDAN: Yes.

DR. GHOBRIAL: So to be clear, regarding MRC -- just to clarify a few points and bring to light some of the examples that were discussed not only today at Dr. Ashraf's meeting, but yesterday during our discussion on NADH -- there are two key elements to MRC, modified release coating, or coating principles, being applied to the dosage form or a subunit of the dosage form.

Examples of oral solid modified release systems that are not coated, and therefore not

considered MRC, are drug products that are compounded by physically mixing active ingredient and release-modifying polymer, such as HPMC, in a mortar and pestle, and with that trituration, filling it into a capsule. That is not considered MRC because that does not employ any coating principles.

Secondly, drug products that are compounded by filling active ingredient into an empty capsule composed of a release-modifying polymer matrix are not considered MRC, again, no coating.

So regarding the capsules that Dr. Johnson mentioned, it appears from a brief look at the website that these are HPMC capsules. These are hydroxypropyl methylcellulose composed capsules. There are some with matrix, in a matrix with gelatin or other excipients. Some are entirely composed of HPMC. There are many different forms. Because there's no coating principle, these are not considered MRC.

DR. VENITZ: Thank you. That helps.

DR. DiGIOVANNA: John DiGiovanna. So the

coating principle doesn't necessarily require for it to be an MRC that the compounder actually prepare or make the coating? In other words, if someone purchases a capsule that is considered coated capsule, might that be included as an MRC?

DR. GHOBRIAL: So regarding the examples that we use that were brought up earlier, in those instances, those capsules were not coated. They were some sort of matrix with HPMC or HPMC entirely. In instances where the compounder coats the final dosage form, that would be considered MRC.

As far as in the scenario where a compound purchases a coated empty capsule, we haven't discussed that -- we haven't contemplated that in our materials, which we are presenting here today.

DR. DiGIOVANNA: So once we vote on this, then products that may be developed that may be different from the ones that either were seen today or available today, it would appear to me, could create confusion with respect to the way this is worded.

So what's been presented to us, very eloquently by Dr. Ashraf, has been a large series of very complicated processes that together would make it extremely difficult, if possible at all, to easily replicate. But any one of those individual processes, like the word "coating," which might be easily created, would be prohibited if they're included in the wording.

I don't know if I'm clear in what I'm saying. But if someone manufactures and sells a coated fillable capsule, then the word "coated" may preclude that from being compounded, even though it doesn't necessarily involve any of those very complicated steps, complicated polymers, or stabilization, and other things that have been described.

So I think there's a little bit of confusion in my mind with the wording, and that's not separated out by the actual working of the compounder to do a process, which may be obscure because the branded manufacturer has developed that, compared to something which may be purchased

and be able to deliver what's ever necessary, but then can no longer be used in compounding because of the way this information is worded.

So I'm a little bit unclear in what we're voting on.

DR. DOHM: I think I can answer that. Our intent was not to capture these pre-fillable capsules. And obviously it came up yesterday and we internally discussed. And we can be explicit in the DTC list that we are excluding these pre-fillable capsules for purposes of this entry.

DR. VENITZ: Further comments for discussion. Dr. Pham?

DR. PHAM: I appreciate the FDA's thoughtful consideration of those products, because as we've seen, things that involve the chemical and physical stability and characterization of bulk substance can obviously make it volatile, and there are certain techniques that are currently being employed by the compounding pharmacies.

But the other thing that I just need to make the comment to the group in general is that this is

all still based on -- I still have concerns that we don't know what we don't know. So when it comes down to would this be a product that should employ an MRC versus a filled capsule, you still don't know that much about the bulk drug substances, as we've seen from nomination after nomination, after nomination.

There's not enough pharmacokinetic and pharmacodynamic data of the actual drug substance itself to know whether there should be a certain technology employed for a certain release time or site of action. Sometimes maybe the nonclinical data might infer that, but, again, how that translates to human in vivo data, it's all still what we don't know.

So the caveat being that although I think it's appropriate to be having conversation about adding the MRCs to the list, we still should keep in mind that these bulk substances, we have not been given all the data to even know whether or not they're sensitive to release modifications in the body.

So yes, we can still use the empty capsules, however they're coated, or matrices -- I'm going to make up a word -- but we still don't actually know what the bulk drug substance needs sometimes as we approve these things. But because of concerns for our patient access, I do appreciate FDA's considerations.

DR. WALL: Question for FDA. We vote on this, but let's say somebody comes up with something. Can they bring it to you at any time and you have a discussion, or does it shut off the discussion? So that as we go forward and things move along, and technology develops, and somebody comes up with something that really works.

DR. DOHM: To put entries onto the DTC list, it has to be subject to notice and comment rulemaking. So in a hypothetical where we promulgate a final rule that includes an entry for MRC that is overly broad, for example, or inadvertently captures technology that develops in the future, there will be a process. It's something called the citizen petition process that

one could use to ask the agency to remove that overbreadth or that scope of the rule that would capture the technology. And we could go through that process to consider it.

MS. BORMEL: And I just wanted to add that before we get to the final rule, there will be a proposed rule. And so there will be a lot of opportunity to comment even in that stage.

DR. WALL: But we still have the flexibility, then, based on all of this, that if new technology comes forward, we'll still have the opportunity to look at it, talk about it, and be able to change and implement if appropriate.

DR. DOHM: Yes. The process would look slightly differently if there was a final rule in place. But if it's prior to the promulgation of the final rule, then we can certainly use this process as it is to discuss the scope of that. And when we put the propose rule out, there will be an opportunity to comment.

So I think it all depends on the timing of this new technology you're talking about and its

impact, but there will be processes in place in order to consider whether or not the rule should be amended in some way to exclude a new technology that we think could be appropriately utilized by the compounders.

DR. WALL: I just think about when I'm writing rules for my board, and you have to write rules for 10 years down the road. But in 10 years, things can change a lot. And how will be able to use things that could be new technologies or things appropriate for patients, and be able to use them quickly and effectively if it deems that this is something that's good?

DR. DOHM: No, understood. And I think that a lot of the complexities that were described today and that would be captured as entry are ones that perhaps might be problematic to be done without the proper testing even in the future.

DR. VENITZ: Okay. Thank you.

Any further discussion? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. I think the point that Dr. Wall is making about envisioning, making

rules, but envisioning what technology might present us with in 10 years, is important from this perspective; at least it's important in my mind. I never thought that we would have the availability of self-driving cars, but that appears to be on the forefront.

I would have felt more comfortable with that if the way this was written incorporated the difference between utilizing a commercial product that may have been tested and approved and marketed to be able to do some of these complicated processes that are difficult for the compounder to do, and separated that, and put the onus on the process that the compounder actually themselves needs to do as individual operators, whereby that might be very complicated for any of these steps to be done by an individual without the experience, and the knowledge, and the technical facilities to do that.

Just that there is an available, pre-marketable capsule, there may be other marketed components that can achieve, or simplify, or

standardize many of these complications that we don't envision now but will be very difficult, or will require revising the rules to be able to use.

I kind of would have felt it a little more complicated if that would have been explored, the separating out, utilizing an approvable device that can actually do this, from making a difficult to compound incorporate some of the expertise required, or the facilities required by the individual compounder. I don't know that there's a way to actually do that at this point.

DR. DOHM: As I said before, it was not our intent to capture these kind of pre-fill -- these fillable capsules that you can purchase. So when we go through this rulemaking process, when we come out with a proposed rule with a Federal Register notice, we'll be clear on this point and make it explicit in the entry.

DR. VENITZ: Any other comments?

(No response.)

DR. VENITZ: Okay. Then let's proceed with the vote. I think Cindy's going to pull them up.

We have one question. So this is the one and only question to vote, so let me read the preliminaries.

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. After everyone has voted, the vote will be complete.

Please proceed.

(Vote taken.)

DR. HONG: We have 6 yes, zero nos, and zero abstain.

DR. VENITZ: Okay. So let's go around the [indiscernible] again. Everybody please introduce yourselves by name, indicate your vote, and the reason why. Let's start with Dr. Humphrey.

DR. HUMPHREY: William Humphrey, and I voted yes. I agree with the FDA's assessment.

DR. VENITZ: This Jurgen Venitz. I voted yes. I agree overall, but you can tell we want to make sure we don't exclude something that really shouldn't apply.

MS. DAVIDSON: Gigi Davidson. I voted yes for the reasons stated. And I would also request that in addition to including the clarification on the pre-coated tablets, that you also make it clear that this does not apply to the Methocel and active ingredient inside a capsule in this ruling.

DR. DiGIOVANNA: John DiGiovanna. I voted yes, but it was a bit problematic for me. I think that having to exclude what we know, which are those pre-fillable capsules, limits the arena in that there are probably other advances that may allow for safe construction of these products.

So I would have felt a little better if the coated product wording would have included something on the order of "to be constructed by, manufactured by, applied by," or somehow involved the individual doing it so that technological advances that might occur within the next few years wouldn't automatically be barred because of the labeling.

DR. PHAM: Kathy Pham. I voted yes. Although I appreciate the considerations of

advancement of technology for compounding practice, I do feel that when it comes to nominations for the Difficult to Compound List, we should be capturing what we feel currently, in present time, is something that involves enough complexity to be overseen in the GMP of conventional drug manufacturing processes.

So although I do encourage the compounding facilities not only to continue their own quality assurance processes, which we've heard about a little bit today, but also to maybe still contribute to that body of knowledge of what we do and don't know about these bulk drug substances and how they behave in the body.

But that said, I do think that the MRCs as presented today do present the complexities that I would expect drug manufacturers to be producing under that level of GMP, specifically with the sensitivity of release and getting to a specific site of action when that is known, that this warrants being included on a difficult to compound list.

DR. WALL: Donna Wall. I agree with my esteemed colleagues. I think that they brought up a lot of the things that we are looking at, and I would encourage the FDA as they're working in this to think about ways that we could -- when there is new technology, we can think about how to fast-track some of that to be able to get to our patients and make their lives a little bit better taking these medicines.

Adjournment

DR. VENITZ: Thank you for your contribution. This concludes our meeting, and I'll adjourn it.

(Whereupon, at 11:37 a.m., the meeting was adjourned.)