FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Wednesday, September 12, 2018

8:18 a.m. to 12:40 p.m.

Morning Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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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

(8:18 a.m.)

Call to Order

Introduction of Committee

DR. VAIDA: Good morning. Sorry for the late start here. We'll try to make up a little time here during the day. I'd first like to remind everyone to please silence your cell phones and any other devices if you have not already done so. And I would also like to identify the FDA press contact for this open session meeting, Mr. Jeremy Kahn. If you're present please stand.

Good morning. My name is Dr. Allen Vaida. I'm the acting chairperson for today's meeting of the Pharmacy Compounding Advisory Committee, otherwise referred to 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.

Hello. My name is Julie Dohm, and I'm the

agency lead on compounding, also known as the senior science advisor for compounding within the Center for Drug Evaluation and Research.

MR. JU: Good morning. My name is Ray Ju. I'm the senior advisor for compound in CDER.

DR. BORMEL: My name is Gail Bormel. I'm in the Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs.

DR. ROTHMAN: Good morning. I'm Sara Rothman. I'm senior policy advisor in the Office of Unapproved Drugs and Labeling Compliance in CDER's Office of Compliance.

DR. LAWSON: Good morning. I'm Rosilend Lawson. I'm also in the Office of Unapproved Drugs and Labeling Compliance in CDER.

DR. GANLEY: I'm Charley Ganley. I'm an office director in the Office of New Drugs in CDER.

DR. BRAVE: I'm Michael Brave. I'm a clinical reviewer.

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

DR. HUMPHREY: William Humphrey, director of

pharmacy operations at St. Jude Children's Research Hospital.

DR. PATEL: Kuldip Patel, associate chief pharmacy officer at Duke University Hospital representing hospitals and health system pharmacy.

DR. FAJICULAY: Jay Fajiculay, acting designated federal officer for the Pharmacy Compounding Advisory Committee, FDA.

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

DR. BOGNER: Robin Bogner, professor, University of Connecticut.

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

DR. WALL: I'm Donna Wall. I'm a clinical pharmacist, but I represent an NABP on this committee.

DR. JUNGMAN: Elizabeth Jungman. I direct public health programs at The Pew Charitable Trusts.

DR. DESAI: Seemal Desai. I'm a dermatologist and clinical faculty at the University of Texas Southwestern in Dallas.

DR. SUN: I'm Jeanne Sun, manager at United States Pharmacopeia.

DR. IKONOMIDOU: Good morning. I'm Chris Ikonomidou. I'm a professor of child neurology at the University of Wisconsin in Madison.

MS. KHURANA: Sandeep Khurana, medical director of liver transplant, Geisinger Health Care System.

DR. CHELIMSKY: Tom Chelimsky, a neurologist, Medical College of Wisconsin. It looks like we have a Wisconsin unanimity for neurology.

DR. GHANY: Good morning. I'm Marc Ghany. I'm a hepatologist in the liver diseases branch, NIDDK, National Institutes of Health.

MR. SMALLEY: Hello. I'm Chris Smalley, pharmacist and industry representative.

MR. MIXON: Bill Mixon, former owner of the compounding pharmacy in Hickory, North Carolina,

nonvoting industry member.

DR. VAIDA: Thank you. I'll now call the meeting to order and read the opening statement.

For topics such as those 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 they're 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 asked that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media may be anxious to speak with 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.

Today, we will receive updates on certain issues to follow up on discussions from previous meetings, including balancing criteria for the 503A bulk substance evaluation, dietary supplements, and recently issued FDA guidances. We will also cover 5 bulk drug substances nominated to compounded drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act: alpha lipoic acid; coenzyme Q10; creatine monohydrate; pyridoxal 5 phosphate; and quercetin dihydrate.

For each of these 5 substances, we will hear presentations from FDA; ask clarifying questions; hear nominators' presentations; again ask clarifying questions; hold an open public hearing; and have committee discussion and voting. As described in the July 24, 2018 Federal Register Notice, the committee will be discussing 6 bulk substances, but one drug substance product, chlorine chloride, has since been removed from this

list and will not be discussed today.

The Federal Register Notice identified the uses FDA reviewed for each of the 5 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 FDA reviews of the bulk substances, which are included in the briefing document posted on FDA's website identify 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 nominators; presentations include information about additional uses, dosage forms, and routes of administration, I 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 begin now, and I'll turn this over to Dr. Jay Fajiculay to read the Conflict of Interest Statement.

DR. FAJICULAY: Before I read the Conflict of Interest Statement, we have two participants on the phone. Can you please introduce yourselves?

DR. VENITZ: This is Jurgen Venitz, clinical pharmacologist and professor at Virginia Commonwealth University.

DR. FAJICULAY: Dr. Gulur?

(No response.)

Conflict of Interest Statement

DR. FAJICULAY: Okay. I'll proceed with the Conflict of Interest Statement.

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 U.S. 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 federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflicts of interests or when the interests of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may

expect from the employee.

Related to the discussion at today's meetings, 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 and minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

During this meeting, the committee will receive information on the following two issues to follow up on discussions from previous PCAC meetings: balancing the criteria for a 503A bulk drug substance evaluation and compounding as it relates to dietary supplements.

In addition, the committee will discuss 5 bulk drug substances nominated for inclusion in the Section 503A bulks list. FDA will discuss the following nominated bulk drug substances and the

uses FDA reviewed: alpha lipoic acid for diabetic neuropathy and associated pain, acute liver toxicity from Amanita species mushroom poisoning, and other toxins, hepatitis C, cancer, cirrhosis, fibromyalgia, and muscle pain; coenzyme Q10 for mitochondrial disorders; creatine monohydrate for mitochondrial disorders; pyridoxal 5 phosphate for epilepsy and seizure disorders; and quercetin dihydrate for asthma, allergy, cancer prevention and treatment, and hypertension.

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 5 bulk drug substances will be discussed.

Based on the agenda for today's meeting and all financial interests reported by committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 USC Section 208(b)(3) to Dr. Stephen Hoag. Dr. Hoag's waiver involves his stock holdings in three competing firms. The aggregate value of his

stock holdings is between $100,001 and $300,000.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which are posted at FDA's website at www.fda.gov/advisorycommittees/committeemeeting materials/drugs/default.htm. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, in Rockville, Maryland, 20857, or a request may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the bulk drug substances. We'd also like to note that Dr. Donna Wall is a representative member from the National Association of Boards of Pharmacy and that Jeanne Sun is a representative member from the United States Pharmacopeia.

Section 102 of the Drug Quality and Security

Act amended the Federal Food, Drug, and Cosmetic Act, with respect to the Advisory Committee on Compounding, to include representatives from the NABP and USP. Their role is to provide the committee with the points of view of the NABP and USP. Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment -- [break in audio] -- matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Mr. Christopher Smalley and Mr. William Mixon are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Mr. Smalley is employed by ValSource, Incorporated and Mr. Mixon is employed by the Compounding Pharmacy.

We would like to remind members and temporary voting members that if the discussions

involve any other bulk drug substances not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the topic at issue that could be affected by the committee's discussions. Thank you.

DR. VAIDA: Thank you. I'd 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. We will now proceed with FDA introductory remarks from Dr. Julie Dohm.

FDA Introductory Remarks - Julie Dohm

DR. DOHM: Thank you, Dr. Vaida. And again, good morning to everyone. I am Julie Dohm, the agency lead on compounding, and I'd like to

welcome you to the ninth meeting of the Pharmacy Compounding Advisory Committee.

Today, as you heard, we will discuss 5 bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A. They are alpha lipoic acid; coenzyme Q10; creatine monohydrate; pyridoxal 5 phosphate; and quercetin dihydrate.

Please note, we will not discuss choline chloride at this meeting, even though it was included in the Federal Register notice published in July. We intend to discuss choline chloride at a later meeting.

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 use this opportunity to provide you with an update on our policy development since the committee last met in November.

In January, FDA published a final guidance concerning compounded drug products that are essentially copies of a commercially available or

approved drug products under Section 503A and 503B of the Federal Food, Drug, and Cosmetic Act. FDA also published a final guidance concerning mixing, diluting, or repackaging biological products licensed under Section 351 of the Public Health Service Act.

In March, FDA published the draft guidance concerning the evaluation of bulk drug substances nominated for use in compounding under Section 503B. This guidance addresses FDA's policies for developing the list of bulk drug substances that may be used in compounding by outsourcing facilities under Section 503B, including the agency's interpretation of the phrase "bulk drug substance for which there is a clinical need." You will hear more about this draft guidance shortly.

In May, FDA published a final guidance concerning the definition of facility under Section 503B. This guidance provides the agency's current thinking on issues such as whether multiple suites used for compounding human drugs at a single street address constitute one or multiple facilities, or

whether a single location where human drugs are compounded can be subdivided into separate operations compounding under different standards.

In August, FDA published a Federal Register notice concerning the list of bulk drug substances for which there is a clinical need under Section 503B. Drug products that outsourcing facilities compound using bulk drug substances on the 503B bulks list can qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act.

This notice identifies 3 bulk drug substances that FDA has considered and is proposing not to include on that list: bumetanide, nicardipine hydrochloride, and vasopressin. You will also hear more about this Federal Register notice this morning.

Finally, last week, FDA issued a revised draft memorandum of understanding, or MOU, between the FDA and the states. Section 503A directs the FDA to develop an MOU with the states, addressing distribution of inordinate amounts of compounded drugs interstate by compounders operating under

503A. The MOU also cover states' investigations of complaints associated with compounded drugs distributed out of state.

FDA's policy documents, including the five guidances and Federal Register notice 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 our work together. Thank you.

DR. VAIDA: Thank you.

We'll now proceed with an FDA presentation on compounding updates and review from Ms. Sara Rothman.

FDA Presentation - Sara Rothman

MS. ROTHMAN: Good morning, everyone. Again, my name is Sara Rothman. I'm going to go over about three different topics that are related subtly, but different categories of topics. The first is going to be policy updates.

As Julie mentioned, we've issued a number of

policy documents since our last meeting, and we could spend the entire meeting just talking about those. I thought the documents that would be of particular interest to the committee would be those pertaining to bulk drug substances under Section 503B. So I'll talk a little bit about our draft guidance on that topic, as well as a Federal Register notice that we recently issued.

At the last committee meeting, there was a request that we review how to balance the criteria that we've set forth for determining whether to include a bulk drug substance from the 503A bulks list. I think this will be a review to many of the veteran members, but perhaps new to some of the newer members.

Finally, dietary ingredients used in compounding. This has come up in multiple committees, again, a likely review for many of you, but may be of particular interest to some of the new members because this issue does arise in multiple contexts.

So beginning with a recent policy

development on 503B bulks, I think it will be helpful to start out with the statutory framework. The framework for bulk drug substances that can be used in compounding under Section 503B is very different from Section 503A. And in fact, all of the conditions of Section 503B, or most of them, are quite different and may not be familiar to everyone.

To back up even further, when the DQSA, the Drug Quality and Security Act, was enacted in 2013, Congress amended Section 503A, which is the subject of most of our discussions during these committee meetings, and created a new section, 503B, that created a new type of compounder, called an outsourcing facility.

Outsourcing facilities are subject to a number of conditions, but primarily, if an outsourcing facility meets all of those conditions, then the drugs that are compounded are exempt from certain requirements of the Act.

Like Section 503A compounders, the drugs can be exempt from Section 505 concerning new drug

approval requirements. Similarly, labeling with adequate directions for use under Section 502(f)(1) and also supply chain security requirements under Section 582, and that's different. And what's particularly noteworthy here is that outsourcing facilities are subject to CGMP, current good manufacturing practice requirements, while 503A's are not.

Another key difference that I think is important to point out is that your 503A facility, which are state-licensed pharmacies, federal facilities, physicians, have to compound drugs pursuant to patient-specific prescriptions, and that's in the law. Outsourcing facilities are not bound by that requirement.

So there are a number of differences between the two entities. Congress, I think because of those differences, decided to impose different conditions relating to the use of bulk drug substances.

Under Section 503B, one of the conditions that has to be met for a drug to be eligible for

the exemptions that I just went over is that the outsourcing facility does not compound using bulk drug substances unless one of two criteria are met. The first is the bulk drug substance appears on a list developed by FDA of substances for which there's a clinical need, or two, the bulk drug substances used to compound a drug that appears in FDA's drug shortage list at the time of compounding, distribution, and dispensing.

There are additional conditions pertaining to use of bulk drug substances.

(Pause.)

MS. ROTHMAN: While we're sorting out the technical issues, additional conditions for your background that are important on both bulk drug substances using compounding under 503B are that there doesn't have to be USP, United States Pharmacopeia, or National Formulary monograph.

DR. VAIDA: We're going to take just a 2 or 3-minute break while we have to switch computers.

(Pause.)

MS. ROTHMAN: There are some additional

conditions in Section 503B that apply to bulk drug substances. There doesn't have to be a United States Pharmacopeia or National Formulary Monograph for an outsourcing facility to use a bulk drug substance in compounding. But if there is such a monograph, the outsourcing facility has to comply with that monograph.

The bulk drug substances have to be manufactured in a facility registered with FDA under Section 510 of our Act, which is registration requirements for manufacturers, packagers, and distributors; and the bulk drug substance has to be accompanied by a valid certificate of analysis. These are actually conditions in Section 503A as well.

Moving on to our process for developing the 503B bulks list, similar to but diverges from the process for Section 503A because of the differences and the statutory frameworks, in 2013, we opened up a docket a few days after DQSA was passed, this list of nominations for bulk drug substances for both the 503A bulks list and a separate request for

the 503B bulks list.

We decided that we needed to issue in 2014 another Federal Register notice clarifying the information, that we needed to be able to do even a basic review of these substances. So we opened up a new docket in 2014 and issued a new Federal Register notice requesting nominations.

That docket closed, the comment period closed, and we received feedback from stakeholders that there might be substances that they hadn't previously nominated that might be important for patient care. So in 2015, we opened up another docket to provide stakeholders with additional opportunity to nominate bulk drug substances, and that docket remains open. We did that again for 503A and a separate one for 503B.

At this stage -- or the next stage, I should say, we have a number of nominations. The statutory standard under Section 503B for including a bulk drug substance on the list, clinical need, is different from 503A. So we're reviewing the bulk drug substances to assess whether we

preliminarily think that there's a clinical need to use them in compounding.

I say preliminarily because the process set forth in the statute is a notice and comment process. We issue by Federal Register notice, which is what the statute prescribes; a proposal for prospective substances. The statute says we need to put out those proposals for a public common period of 60 days or more. And then after that, after considering the public comments, we'll publish again in the Federal Register our final determinations regarding the substances.

Once we make those final determinations, the substance will either appear on the list and be eligible for use in compounding under 503B, or not appear on the list and not be eligible for use in compounding unless of course it's to make a drug in shortage.

I should note that the requirements pertaining to consultation with the advisory committee also differ. Under Section 503B, there is no such requirement, but we intend to convene

the committee and review bulk drug substances if during the course of our review or review of the comments, we think that doing so will be helpful to the agency's decision-making or particularly helpful for particular substances.

So with that background, I'll talk a little bit about our draft guidance that we issued.

(Pause.)

DR. FAJICULAY: We apologize for the issues, the technical difficulties. For right now, we're going to have the presenter just continue on. For those of you who do not have the copies of the handouts, they are available outside. We're just going to follow along with the handouts, if that's okay.

MS. ROTHMAN: Do you all have page numbers, slide numbers, numbers on your -- okay, great. So I'll be sure to note the slide number.

Slide 8, we issued a draft guidance in March, evaluation of bulk drug substances nominated for use in compounding under 503B. The purpose of this guidance is to describe the factors that we

intend to consider and the process by which we intend to consider bulk drug substances for inclusion on the 503B bulks list, again, applying the clinical needs standard and the statutes.

Slide 9 -- and again, I'll preface this by saying this is all draft guidance. We received public comments on the draft guidance and are working through them as we work on the guidance. So these are our proposed policies.

We say that we would include, or we would consider including, a bulk drug substance on the 503B bulks list if, 1) there is a clinical need for an outsourcing facility to compound the drug; and 2) a drug must be compounded using the bulk drug substance. And that's our proposed interpretation of the clinical needs standard under Section 503B.

On slide 10, we go through a two-part analysis or we propose to use a two-part analysis to evaluate nominated bulk drug substances. We have part 1 and part 2. Part 1 applies only to bulk drug substances that are components of FDA-approved drug products. Part 2 applies to such

bulk drug substances that proceed through the part 1 analysis, as well as bulk drug substances that are not components of FDA-approved drug products.

Slide 11, a little bit about part 1. We call it a threshold review for components of FDA-approved drugs. And we ask two questions with a couple of sub-questions.

The first question, is there a basis to conclude, for each FDA-approved drug that includes a nominated bulk drug substance, that, 1) an attribute of the FDA-approved drug makes it medically and unsuitable to treat certain patients with the condition identified for review; and, 2) is a drug proposed to be compounded intended to treat that attribute?

So essentially, why do you need a compounded drug? Why can't you just use the approved drug?

Subsection B, is there a basis to conclude that the drug proposed to be compounded must be compounded from a bulk drug substance rather than an FDA-approved drug? So not only do we ask why do you need a compounded drug; we also ask if you need

a compounded drug, why does it need to be compounded using a bulk drug substance? That's part 1.

Under part 2, you'll see that the facts I think will be very familiar to you because they're very similar to the criteria that we use under 503A. We're proposing to look at the physical and chemical characterization of the substance, any safety issues, available evidence concerning efficacy or lack of efficacy if of course such evidence exists, as well as current and historical use.

You'll see the word "current" there that's not in 503A. And we thought that was important to include explicitly, whereas it might be implicit elsewhere, and we'll talk a little bit about that.

Slide 13, we recently entered into collaborative agreements with two universities, University of Maryland and Johns Hopkins University. Both universities house what are called CERSIs, Centers for Excellence and Regulatory Science Innovation. Pursuant to these

agreements, these collaborative agreements, the University of Maryland is going to be doing some work looking into how the bulk drug substances nominated for 503B are being used in clinical practice. And that goes directly to the current use that we're considering.

We received a number of comments on the draft guidance that I discussed suggesting that it's important that we consult with practitioners to understand how these substances are being used. And of course, the standard in Section 503B is clinical need. So we think that this agreement will yield a lot of really great information that will inform our review.

For Johns Hopkins, they're doing a more specific evaluation for us. They're looking at substances nominated or used to treat autism spectrum disorder, and they're going to be looking at information not only about how the substances are used in clinical practice, but also about safety and effectiveness and information out there about that use.

Those are two agreements that are underway that we're very excited about, and we think that they'll really help, as we say on the slide, our regulatory decision-making, as well as providing more information to the public about how these are used.

That's a very high-level overview of the guidance, as well as our CERSI endeavor. Next, I'll talk about the Federal Register notice issued recently to begin to establish the list of bulk drug substances under Section 503B.

Moving on to slide 15, as I mentioned, under the statute, we have to provide our proposals of bulk drug substances that we intend to include on the list through the notice and comment Federal Register process. We decided that it's important to also do so for substances that we're deciding not to put on the list, to go through that process and receive public comment.

We issued a proposal, as Julie mentioned during her opening remarks earlier, concerning bumetanide, nicardipine hydrochloride, and

vasopressin. All three substances are components of FDA-approved drug products, so we evaluated -- under the framework that we proposed, we considered whether there is a basis to conclude that there's something about the approved drug that makes it medically and unsuitable for a patient. And if there is, whether there's a basis to conclude that it must be compounded using the bulk drug substance.

We reviewed the nominations and found that they didn't include any information indicating why the FDA-approved drugs containing substances could not either be used or adapted instead of compounding the drugs using the bulk drug substances -- or why you had to compound using the bulk drug substances rather than using the approved drug or adapting the FDA-approved drug.

There wasn't information saying that that's something that had to be done, so we looked at this with the nominations and the context of, again, the statutory standard of clinical need. And based on that standard, we proposed in the Federal Register

notice that there is no clinical need to compound using these bulk drug substances. Pursuant to the statute, we put out a 60-day public comment period. And I believe that closes on October 29, 2018. So I hope we receive robust comments on that proposal, and we look forward to reviewing those and considering them when the comment period concludes.

I know we're running late, so I'm going to go very quickly through the next couple of slides, slide 17 and slide 18, I won't read them. Julie mentioned some of these, but there have been a number of other policy documents, really important policy documents and our view that we've issued since the last advisory committee meeting.

In January, the commissioner put out his priorities for compounding in 2018, so there are a number of policies on slide 18 that are underway that we expect to complete in 2018 pursuant to that plan that the commissioner issued.

Moving on to slide 19, balancing the criteria. Again, I think this will be very familiar to those of you who are veterans to the

committee because you've all been doing this for the last several years. But I think, hopefully, an overview would be helpful to the newer members.

Slide 20, 503A of the statute actually gives us guidance on this, a little bit of guidance at least. Section 503A says the criteria for determining what's going to appear on the list has to include historical use, reports and peer-reviewed medical literature, or other criteria that the FDA may identify.

In consultation with the advisory committee, we discussed this at the first meeting, and we've proposed, in a proposed regulation, four criteria, and those appear on slide 21: physical and chemical characterization; safety issues; effectiveness information; and historical use of the bulk drug substance in compounding.

Those are the criteria that you all have been applying when you're reviewing these bulk drug substances and deciding what advice to provide to the agency. And these are also the criteria that FDA has been considering when deciding whether to

propose in rulemaking, to include or not to include a bulk drug substance on the 503A list.

Going into a little bit more depth, slide 22, physical and chemical characterization, is the substance well characterized physically and chemically such that it's appropriate for use in compounding?

Obviously, there are consequences if the substance is not well characterized. As we say in slide 22, there can be no assurance that its properties and toxicities, when using compounding, would be the same as the properties and toxicities reported in the literature and considered by FDA. So that's an important consideration.

I'm going to go through this a little bit fast because I know we're running behind. Slide 23, safety, are there any safety issues associated with the substance? Some of our considerations when we're looking at safety appear on this slide. I want to emphasize, where there have been questions in the past, is, well, how do you weigh this and what happens when there is FDA

approval alternatives? How does that factor into your analysis?

What we say is that we consider the availability of approval alternatives in the context of evaluating safety and in the context of weighing this criterion. When we say the risks of using a substance with significant toxicity is likely to outweigh the benefits when the approved alternative therapies are available. So that's one of the ways that we weigh this factor or take into consideration alternatives.

Slide 24, effectiveness, is there information of efficacy? Often there is very minimal information about efficacy because the substances that we're reviewing are components of FDA-approved drugs. I probably should have paused in the transition and emphasized that we're now moving to the 503A discussion, whereas before, I was talking about 503B.

503B, you have some that are components that are approved drugs and some that aren't. 503A, the nature of the statutory framework is such that the

only substance that will be considered by this committee are substances that are not components of FDA-approved drugs because if you are a component of an FDA-approved drug, you can automatically be used in compounding under 503A without going through this process.

Effectiveness, when we look at whether there's information available, we look at, for example, reports and peer-reviewed medical literature and any other information identified in the nominations.

Slide 25 goes to weighing this factor. Of course, if the proposals treat a less serious illness, we may be more concerned about information of safety issues than efficacy issues. But as you can imagine, if it's intended to treat a serious or life-threatening illness, efficacy will be particularly important.

So the weight that we give to safety versus efficacy in this context will necessarily differ, depending on the facts of a particular situation and what we're looking at in the nature of the

diseases that the nominators are proposing to treat, or other diseases that we look at.

Again, the way the alternative therapies play into this analysis, when there are approved alternatives and there's very little effectiveness data, if any, the fact that there are approved alternatives may inform how we weigh the efficacy analysis because if there's information that the substance is not effective and there's no approved drug, you can imagine that would be an important consideration.

Lastly, slide 26, historical use of the substance in compounding, we look at the length of time the substance has been used to treat medical conditions, how widespread it's used, references, and other pharmacopeias or medical literature. And of course if it's enjoyed widespread and used in compounding over a long period of time, this factor might weigh in favor of including the bulk drug substance on the list.

Often, there's very little information to us about how this substance has been used

historically. So with all of these criteria that we review, it's just really important to remember this is not the same as the standard for the FDA approval process.

We don't have the same information available to us. And with historical use, as with the other criteria, we use the information that we can find -- that the nominator or supplier, that we can find ourselves, to inform our proposals to include these on the list or to not include them.

Slide 27, just an important reminder that these criteria are comprised of balancing tests, so no one criterion is dispositive. We consider the criteria in the context of each of them; in the context of the drug that we're reviewing; in the context of the diseases that it's being proposed to treat; and the information available to us. So it really is a balancing test that we apply.

The final topic, slide 28, dietary ingredients nominated for use under Section 503A. Many of you are familiar with why this is an issue that we're discussing today. But just to give some

of the newer members a little bit more context, one of the ways that you can use a bulk drug substance under Section 503A -- without going through the advisory committee process, without the USP consultation process as well, and without appearing on a list of bulk drug [indiscernible] regulation -- is if the bulk drug substance is the subject of an applicable USP or national formulary monograph.

So there have been questions about what the word "applicable" means. And we've said, as I'll discuss in more depth going through the slides, that that means a drug substance monograph because these are drugs that you're producing, and when you use a bulk drug substance to create a drug, it's a drug. So the applicable monographs are for drug monographs.

Some folks have suggested that USP dietary supplement monographs should be considered applicable monographs for purpose of this provision. I'm going to walk through why we've opted to adopt the first approach that I mentioned,

that these are drugs, and the USP drug monograph is the appropriate one.

Beginning with an overview of how dietary supplements are regulated, slide 30, I'll just start with the caveat that I'm not an expert in this piece, so we have someone here from our Office of Dietary Supplements who can answer questions, if they arise, about the regulation of dietary supplements, generally.

To give a very brief overview, slide 30 under Section 201(ff) of the Act, a supplement is one that's intended to supplement the diet, contains at least one dietary ingredient, and is intended for ingestion -- and I'll emphasize that point because it becomes very important that the only way something can be a dietary supplement is that if it's intended for ingestion -- it's not represented as a conventional food or a meal replacement or to replace the entire diet; labeled as a dietary supplement; and also certain articles approved as new drugs or investigation of a new drug application are not permitted to be dietary

supplements.

So, bottom line, there are a number of statutory restrictions on what can be considered a dietary supplement.

Slide 31, as I mentioned, this is very important that dietary supplements are intended for oral ingestion only. If you take, for example, a dietary supplement or an ingredient that's a subject of a USP dietary supplement monograph and not subject to a drug monograph, and you make a compounded drug for intravenous injection, that's a drug.

It doesn't matter that it contains dietary ingredients or substances that are often considered to be dietary supplements. You're creating a drug because of the route of administration and perhaps because of other factors as well. That's something that's really important to keep in mind.

Slide 32, structure function versus disease claims, there are limitations on the types of claims that dietary supplements can make before they cross over into the drug realm. They can

include claims to affect the structure or function of the body, but they can't in general make claims to diagnose, mitigate, cure, or prevent a disease, which is of course part of the drug definition under our act.

There are a couple of exceptions here, which I won't go over. But to give you a few examples of the types of claims: helps the immune system versus relieves crushing chest pain and angina, so some of the types of claims and a few examples the dietary supplements can make versus drugs.

Slide 33, there are certain quality standards that apply to dietary supplements. Something that will be familiar you is the idea of compliance with CGMP or current good manufacturing practice requirements. I think it's really important to know, however, that the CGMP requirements applicable to dietary ingredients, versus dietary supplements, versus bulk drug substances, versus finished drug products differ. The type of GMPs that you have for a dietary supplement or a dietary ingredient are not

comparable to the GMPs that you have for a drug under our act.

A few examples on slide 34. In the interest of time, I'm not going to read these, but, again, route of administration is something that's key. The nature of the claim is also key. Those are two differences to look out for in particular; again, not exhaustive, but just really important for our purposes.

Slide 35, now I'm going to talk about how this is relevant to our discussion under Section 503A. Slide 36 to understand that discussion. It's important to understand the statutory basis for what a drug is. I mentioned disease claims a few minutes ago. Drugs can make disease claims that are intended for diagnosis, cure, mitigation, treatment, or prevention of disease. They can also make structure/function claims to be a drug, and those are two of the parts of the drug definition in our act.

Slide 37, this is what I alluded to at the beginning of my discussion of this topic. A bulk

drug substance can only be used in a 503A, I'm going to reiterate because it's so important, if it's a subject of an applicable USP or NF monograph; component of an FDA-approved drug; or appears on the bulks lists that we're developing. And that's what we're doing together here today, working on the bulks list.

Applicable USP or National Formulary monographs, we've said is a drug substance monograph, as I mentioned earlier. Some of the bulk drug substances that have been nominated for discussion by this committee for consideration for inclusion on the list are the subject of dietary supplement monographs. And again, we say for purposes of the 3-pronged analysis for whether you can use a bulk under Section 503A, those are not applicable monographs.

Again, if you compound a drug, if you're making a drug, all of those substances have been nominated to treat diseases, to make drugs. And Section 503A only applies to compounded drugs. And if you're an ingredient used to make a drug, if

you're a bulk drug substance used to make a drug, you're a drug. You no longer are a dietary supplement.

If you say I'm going to take curcumin, which we've seen, and I'm going to make it into an injection to treat cancer, you're making an injection; you're not ingesting it, and you are treating obviously a disease. So just because curcumin is [indiscernible] to the monograph does not mean that you can automatically use them in compounding under the provision that you can use things that are applicable, USP or NF monographs in compounding.

That does not mean, however, that you will necessarily not be able to use in compounding substances that are the subject of a USP dietary supplement monograph. All it means is that if you want to use it, you nominate it, and we consider it with the advisory committee, with the USP, and decide whether to include on the list through rulemaking.

So it just means that you can't

automatically use it. The first prong of the 503A test or provision, it means that we would have to consider it through this process.

If you look on slide 39, why is it important? When Congress created this provision that you can automatically use things that our components of approved drugs, automatically use substances that are subject to a monograph, there is information known about those substances because the monograph -- because are used to make FDA-approved drugs.

When you're using a substance in compounding that don't fall in either of those two buckets, very little may be known about it; for example, whether it's safe to take something that's typically used orally and make it into an injection, whether it's effective to treat cancer; whether the quality profile is appropriate.

So the standards in the monograph as well, another point is the monograph may not be appropriate for the drug that you're making. If the USP monograph is going to contemplate for

dietary ingredients, something for ingestion, it won't necessarily contemplate the appropriate levels of impurities, for example, if you're making something for injection. In fact, in the general notices, there are differences between impurities, and that's one example.

Slide 40, some of the reasons why it's important for us to review these substances with the advisory committee going through the rulemaking process, again, dietary supplements are for ingestion only. Something might be fine to swallow, but then when you inject it, it might be very problematic and might be ineffective for the disease intended to be treated, not well characterized, not stable, and have safety risks.

Those are some of the reasons why, again, we're not saying you can never use a dietary ingredient to compound a drug under Section 503A. Rather, it's a drug, and it needs to go through the applicable process for drugs.

To conclude on slide 41, drugs and dietary supplements, as I said, are subject to different

regulatory schemes. I went over those very briefly. Obviously, there's much more depth to that, and Bob Dworkin from dietary supplements is here in case you have questions about that. Section 503A applies to compounding drug products. And when you take a substance to make a drug, it's a drug. And the appropriate method for review is how we review drugs; important public health protection, as I went over just a second ago.

I really want to emphasize that we're not saying these substances can ever be used. They can be used if they go through this process and we decide they're appropriate for inclusion on the list. And I'll all end there. Thank you.

Clarifying Questions from the Committee

DR. VAIDA: Thank you. Although we're running a little late, we will accept some clarifying questions from the committee. Just remember to try to keep your questions to the speaker, just clarifying any of the remarks. Dr. Bogner?

DR. BOGNER: Robin Bogner. I have two

questions to clarify. So if in a pharmacy licensed in a state, somebody is mixing dietary supplements or repackaging let's say in a capsule a dietary supplement, but not as a drug, that's outside of drug compounding.

MS. ROTHMAN: That's a great question. You ask an important point. If you are taking a dietary supplement, putting it into a different container -- I think was your hypothetical -- and repackaging it; or even if you mixed two dietary supplements together, if you don't make drug claims and are intended for ingestion; you follow all the requirements that apply to dietary supplements, you're not under 503A. You're operating within the dietary supplement framework.

There are other requirements that might attach to. You might be a dietary supplement manufacturer that has to undergo certain other requirements, but you're not within the realm of Section 503A and compounding.

DR. BOGNER: Thank you. then I think it's a related question. This historical use, it concerns

me because as we get further from when DQSA went into effect, if you're not allowed to use a bulk drug substance until it's on the list, how do you have historical use if you've not been allowed to use it?

Do you understand?

MS. ROTHMAN: I understand and also a great question. Yes. A few things. When we're looking at historical use, say we're not just looking at since DQSA. We're looking at how substances have been used since the '90 even, whatever information we have available to us of how they've been used.

The other point I'd like to make to address that is we do have an interim policy that's out there right now. We recognize that some compounding using some of these substances might be important to patient care in the interim period while we're developing the bulks list. So compounders are using some of these substances currently while we're developing the list pursuant to that interim policy.

So again, very little information is

available to us sometimes, so we gather what we can find about how it's been used historically. But we're looking at recently as well as far back as we can find.

DR. VAIDA: I'd just like to have Dr. Gulur on the phone introduce herself, please.

DR. GULUR: Hello. This is Padma Gulur, Duke University, professor of anesthesiology.

DR. VAIDA: All right. Dr. Wall?

DR. WALL: Donna Wall; clarifying question. If this committee reviews a substance that has been traditionally a dietary substance and determines that it is now or that there is an actual drug part of it, does it eliminate it from the dietary side or are you still going to have that split?

MS. ROTHMAN: So what we're looking at are substances intended to treat medical conditions. To the extent that there's dietary supplements out there that are not making such claims, that are compliant with other requirements for dietary supplements, we wouldn't necessarily say that they can't continue to do that. But if you're going to

use something to treat a disease or to make something with a different route of administration that's not appropriate, or whatever else, that substance is going to have to go through the process because it's a drug.

Just because you're making a drug over here doesn't mean you can't also make a dietary supplement over here, provided that each complies with the appropriate framework.

DR. WALL: Even if they're the same concentration, the same everything; it's just that your intended use is going to differentiate it?

MS. ROTHMAN: Again, there are a number of requirements for drugs versus dietary supplements, and one of them is if you meet the definition of a drug, you're drug. If you are making -- if I'm the substance and I say I'm going to be used to treat cancer, and then I have the same substance, but I say I'm going to improve whatever structure/ function claim, I believe our answer would be that they could both coexist.

But the one that's making the medical claim

that is a drug, it has to be regulated as a drug; whereas if you have a substance being used as a dietary supplement, appropriately meeting all the statutory and regulatory requirements of dietary supplements, that can continue to be sold as a dietary supplement. But the moment you say I'm using this to treat a disease or whatever else, whenever it meets the definition of a drug, it's going to have to be regulated as a drug when it's used for that purpose.

DR. VAIDA: Mr. Mixon?

MR. MIXON: Sara, can we assume that if we take a manufactured dietary substance that's FDA approved off the shelf and convert it to a liquid or maybe some other way, customize it, that's not considered part of this guidance?

MS. ROTHMAN: So a couple things there. It wouldn't be FDA approved as a dietary supplement. But the question I know has come up -- the question is raised about whether you can take a dietary supplement sort of finished off the shelf, and if you use that in compounding, what is it?

I can tell you that we're working through that question. I know it's come up. It's an important issue, and we're looking at that. So I can't give you an answer right now, but I will say as a general matter that if you take a dietary supplement and you intend to use it as a drug, it's a drug.

Now, what the implications are for purposes of compounding, what framework is going to apply, whether both provisions apply, that I can't answer right now.

MR. MIXON: Yes. As I see it, it would still be a dietary supplement if it's administered orally and you're simply taking, say, a capsule of curcumin and converting it to an oral solution or suspension of curcumin to be administered orally. From my view, that it would still be a dietary supplement.

MS. ROTHMAN: Yes. I would just clarify my answer, too. So in your hypothetical, you're not making any drug claims, right? You're just changing the route of administration or the dosage

form, I should say, and not making drug claims. Is that --

MR. MIXON: Correct

MS. ROTHMAN: Okay. Then, yes. Let me revise my answer. I understood your question to be a little bit different. If you're just manipulating a dietary supplement, you make a dietary supplement, you label in accordance with the dietary supplement requirements, you can apply a dietary supplement with GMPs, and whatever else you have to do, you're in the dietary supplement framework and you're not in the 503A compounding framework if you're not intending it to be a drug and labeling it, and whatever else and such.

DR. VAIDA: Dr. Jungman? Desai, first?

DR. DESAI: Seemal Desai. Thank you, Sara, for that great presentation and overview. Just a logistical question. If a dietary supplement then does make drug claims and has to then be on the 503A list, would it have to go through this committee just like any other nominated substance?

MS. ROTHMAN: If it's -- yes. I want to be

careful here because we're not addressing at this point a finished dietary supplement; you go to the store and buying crushed [indiscernible]. But if you have a dietary ingredient, a USP dietary supplement monograph or whatever else, and you want to use it to make a drug, it has to go through this process.

DR. VAIDA: I'll take two more questions; one from Dr. Venitz on the phone.

DR. VENITZ: Yes. My question is a dietary supplement that is compounded as a drug product, how is that labeled?

MS. ROTHMAN: Good question. The question is if you take a dietary supplement and compound a drug product, how is it labeled? In that scenario, within the construct of Section 503A, Section 503A doesn't impose specific labeling requirements on any compounded drug, so you would be in the same sort of scenario, any compounded drug and whatever labeling requirements that apply to compounded drugs generally, they would apply to you.

But again, in our experience, many

pharmacies don't include much labeling on compounding drugs. And Section 503A doesn't have specific provisions concerning labeling. There might be other labeling requirements in different parts of the Federal Food, Drug, and Cosmetic Act that apply generally, but nothing additional or specific in Section 503A.

DR. VENITZ: Thank you.

DR. VAIDA: Dr. Carome?

DR. CAROME: Mike Carome. In one of the nominators' statements for a drug being considered today, they express concern that the FDA was not allowing nominated substances to be considered for use solely for the effects on structure or function of the body and not intended to treat, cure, or prevent a disease. And that first part about structure and function of the body is part of the drug definition. So I wonder whether FDA has a response to that comment.

DR. GANLEY: Yes. As you've heard, the structure/function claims for dietary supplements are very different from drugs. But when you look

at drugs and a structure/ function claim -- I'm just going to give you an example -- it doesn't have to be treating a disease. You can treat a condition.

One example would be pregnancy where you have drugs that help prevent pregnancy. Pregnancy is not a disease. The caveat there is, though, there are certain standards you have to meet under the drug regulations with regard to what's the treatment effect? Is it going to be beneficial? Can I deliver the drug to the site of action? Are there drug interactions? So it brings on a completely different set of standards than are necessary in the dietary supplement realm.

Does that answer your question? But again, a drug should have a clinical utility that's definable or a clinical benefit that's definable. It doesn't have to be a disease. It could be a condition.

Another example in the over-the-counter realm are sunscreens. Sunscreens are drugs in the United States. They affect the structure of the

skin by preventing sunburn. We set up standards as to what requirements need to be met to become a sunscreen in terms of testing and things like that. So that's really the best way I can explain it.

DR. VAIDA: Name, for the committee?

DR. GANLEY: Charley Ganley, Office of New Drugs.

DR. VAIDA: Dr. Chelimsky, and this will be the last question.

DR. CHELIMSKY: Thank you for the very helpful presentation. I'm new to this. I just wondered if you could say more about the definition of clinical need. It seemed like a lot of emphasis was being placed on that. Is that just the balancing act that you talked about, or is there more to clinical need?

MS. ROTHMAN: Sure. So the statute says clinical need. So of course when we're deciding whether something meets that standard, we necessarily have to give some interpretation to clinical need in the statute. And the interpretation that we propose in our draft

guidance is that there's a clinical need for an outsourcing facility to compound the drug, and the drug must be compounded using a bulk drug substance.

This is a provision of Section 503B concerning outsourcing facilities. So we're looking at whether an outsourcing facility compounds the drug, clinical need for an outsourcing facility to do it. Our thinking, as I went over, and the tests that we're proposing is if you can use the approved drug or if you can use the approved drug to compound, it may not be a clinical need to compound it from bulk.

To answer your question about whether it's a balancing test, the factors that we set forth to arrive at our interpretation of clinical need or our proposed interpretation of clinical need has a two-part analysis. And the first part is really looking at whether you need to use a bulk drug substance at all, whether you need a compounded drug at all. And if you answer no to those questions, we're saying, our proposal to say,

there's no clinical need

Now, if you answer yes to those questions, we think that in addition to looking at whether you need to make it from bulk, whether you need a compounded drug, it's important to look at are there safety concerns, are their efficacy concerns. I think part 2, looking at those four factors, is more of a balancing test. Part 1 is more looking at do you need to do it from bulk at all? That's sort of less of a balancing test. So I hope that helps.

DR. CHELIMSKY: Thank you.

DR. VAIDA: We'll take one more question. Dr. Ghany?

DR. GHANY: Marc Ghany. My question is along the same lines. If you have a compound A that you want to use for indication B, but where effective therapy does exist, then does that come under clinical need still?

MS. ROTHMAN: If the bulk drug substance that you're proposing to use is a component of approved drug B, we would look at it under the

first threshold factors that we described about whether you need to use a compound drug at all. And if you do, you need to compound it from bulk drug substances, or if you can just make the approved drugs.

If it's not under part 1 because it's not like a component of the approved drug, it would go under part 2. Just as in the context of the factors that I described, the purpose of the 503A, we consider the availability of approved alternatives when weighing safety and effectiveness and would similarly do that when we evaluate the 503B bulk drug substances.

So the availability of approved drugs that have been proven safe and effective will come into play in two ways. The first way is under part 1, if the bulk drug substance is a component of such drug, we would consider whether you can just use that drug; and if you can't, whether you need to do it from bulk.

So for example, let's say there's a safe and effective treatment that's approved at a higher

strength that what the patient needs. We might look at the patient perhaps couldn't use the approved drug because strength is too high. But then can you just dilute the approved drug? Why do you have to make it from bulk?

So that's where that all comes to play. And if we decide it makes it through part 1, or if we say it's not a component of an approved drug, will consider the availability of approved alternatives when weighing the safety and effectiveness and other factors.

DR. VAIDA: Dr. Bormel?

DR. BORMEL: Gail Bormel from FDA. I just wanted to expand on what Sara's saying and make it clear that the clinical need that we're talking about relates to the evaluation of bulks nominated for the 503B list. That's not what we're going to be talking about today. She's clarifying a lot of our new guidances and FRNs that have come out.

For purposes of today's discussion, we're talking about bulk substances that were nominated for the 503A list. And Sara had gone through the

criteria that we discussed in context of evaluation of the 503A list and the balancing of those. The criteria, again, are the physical and chemical characterization of the substances, any safety issues, available evidence of effectiveness, and the historical use of the substances.

MS. ROTHMAN: Thank you, Gail. And 503A doesn't use the term "clinical need." That's 503B only.

DR. VAIDA: Thank you for that clarification.

We'll now proceed with the FDA presentation on alpha lipoic acid from Dr. Michael Brave.

FDA Presentation - Michael Brave

DR. BRAVE: Good morning. I'm Michael Brave, and I reviewed the nomination for alpha lipoic acid on behalf of the FDA. I'd like to acknowledge my colleagues listed on this slide who participated in this review.

Alpha lipoic acid, or ALA, has been nominated for inclusion on the list of bulk substances that can be used in compounding under

Section 503A of the Federal Food, Drug, and Cosmetic ct. The uses for which ALA has been proposed are listed on slide 3. The proposed routes of administration are oral, intravenous, and topical, and the references provided in the nomination included both nonclinical and clinical information.

ALA is an 8-carbon dithiol that is part of a redox pair, the other member of the pair being dihydrolipoic acid or DHLA. ALA has one chiral carbon, and thus exists as R or S isomers. The R isomer is present in all prokaryotic and eukaryotic cells and is the naturally occurring form. Most commercial formulations contain a racemic mixture.

When exposed to light, ALA undergoes photolysis to form DHLA. ALA is also sensitive to temperature. At 25 degrees centigrade and 100 percent relative humidity, 20 percent of ALA decomposes after 48 hours.

ALA can be synthesized easily, efficiently, and inexpensively. In the synthetic route shown here, DHLA and ALA are produced from cyclohexanone

and vinyl ethyl ether. Likely impurities in the finished product include trace amounts of residual solvents like cyclohexanone and vinyl ethyl, DHLA generated from photolysis of ALA, or as a residue from the last step in ALA synthesis, and oligomers from the polymerization of DHLA. None of these likely impurities are thought to be very toxic.

In humans, ALA is part of several acid dehydrogenases involved in energy production. ALA binds acyl groups and transfers them from one part of the enzyme to another. The illustration here shows ALA reduced to DHLA and then reoxidized by lipoamide dehydrogenase in the presence of NADH.

ALA is absorbed quickly following oral administration in rats and dogs and exposure is dose proportional. Following absorption, ALA undergoes rapid biphasic elimination. It's main metabolite, DHLA, is predominantly excreted through the urine. Studies in the rat showed that topically applied ALA was absorbed systemically.

The liver and kidney were targets of toxicity in short-term studies in rats and cats.

No toxicity was seen following long-term exposure in dogs. No data are available for reproductive developmental toxicity. ALA was not mutagenic in the Ames assay and micronucleus genotoxicity assays. And finally, rats fed a high ALA diet for 24 months did not have a higher incidence of tumor formation compared to control rats.

The main sources of clinical safety information, which the FDA identified for ALA, were several randomized controlled trials assessing the efficacy of ALA in patients with diabetic neuropathy and several case series reporting the outcome of patients with amatoxin mushroom poisoning who received ALA.

No randomized trial reported an excess of toxicity in the ALA group, although most randomized trials that we reviewed did not appear rigorously designed to collect adverse event data. Likewise, no case series of patients treated with ALA reported any serious toxicity. The only toxicities reported were nausea, vomiting, and the vertigo in up to 10 percent of patients at doses of 1800

milligrams daily.

A search of the FDA Center for Food Safety and Nutrition's Adverse Event Reporting System, or CAERS, and the FDA Adverse Event Reporting system, FAERS, contained a combined 119 individual case reports mentioning ALA.

From the information provided in these reports, it was not possible to directly establish a causal relationship between ALA in any of the reported adverse events, as little detail was available concerning the adverse events such as time to onset relative to ALA exposure, the action taken with the event, or the outcome. Common adverse events and the CAERS and FAERS database included palpitations and metabolic events such as hyperglycemia.

The clinical setting in which ALA has been most extensively studied is in the treatment of pain due to diabetic sensory motor polyneuropathy. The FDA identified 10 randomized controlled trials evaluating ALA for this indication. ALA was administered orally, intravenously, or both, at

doses ranging from 100 to 1800 milligrams per day.

Most of these trials were limited to patients with type 2 diabetes. Intravenous ALA was given for up to 3 weeks, and the duration of oral administration varied between 3 weeks and 4 years. Although 5 of these randomized controlled trials were conducted by the same group of German investigators, there was no indication of patient overlap between reports.

The primary outcome measure in 6 of these randomized clinical trials was the Total Symptom Score. This questionnaire asked patients to assess the intensity and frequency of 4 symptoms, pain, burning, paresthesia, and numbness, resulting in a total score in which zero means no symptoms and 14.64 means that all 4 symptoms are severe and continually present.

A clinically relevant improvement in neuropathic symptoms was typically defined as a 30 to 50 percent change or a decrease in 3 points in total score. It is not clear how this definition was arrived at.

Seven of 10 randomized trials that we identified evaluating ALA in peripheral diabetic neuropathy concluded that ALA led to modest short-term improvements in neuropathic symptoms. Caveats are that few trials included patients with type 1 diabetes, no trial showed ALA to improve diabetic autonomic neuropathy, and no trial demonstrated an effect on the long-term natural history of diabetic neuropathy.

Moving on to amatoxin mushroom poisoning, the FDA identified 6 non-randomized case series involving a total of 410 patients with amatoxin poisoning during the period from 1971 to 2003. Most patients in these trials were treated before 1980. Of these 410 patients, 352, or 86 percent, survived.

The FDA also identified 5 additional reports not shown here of a total of 7 patients with amatoxin poisoning, all of whom survived following treatment with a comprehensive protocol that included ALA.

There are limitations to interpreting these

case series. For example, it is not possible to isolate the treatment effect of ALA because patients with amatoxin are typically treated in an intensive care setting with comprehensive protocols that include other drugs to protect the liver, such as benzyl penicillin, procedures to accelerate the elimination of amatoxin such as activated charcoal lavage, and supportive care measures such as vitamin K, and ultimately a liver transplantation if necessary.

A second limitation so the interpretation of these reports is the use of historical controls for comparison, the patient's hospitalized and supported aggressively immediately after ingestion of amatoxin-containing mushrooms reported mortality rates as low as 10 percent, whereas patients presenting 60 or more hours after ingestion of poisonous mushrooms have up to a 90 percent mortality rate. Additional variables are that some mushrooms contain other compounds other than amatoxin and are therefore less toxic.

Other authors reported less satisfactory

results with ALA. For example, a multiple regression analysis performed by Floersheim in 1982, using the data from some of the trials on the previous slide, found that patients with amatoxin poisoning who received ALA had lower survival than patients who did not receive ALA.

ALA has not been recommended by most poison control centers for amatoxin poisoning for approximately 2 decades, long enough to be represented as fact in tertiary textbooks. The FDA searched the American Association of Poison Control Centers' national database and found 1217 cases of amatoxin poisoning between 2005 and 2017. Of these 1217 cases, 70 percent received therapy and none received ALA. We also note that the mechanism of action of ALA and amatoxin poisoning has not been established.

Last, the FDA identified no convincing reports that ALA has clinical activity or benefit in pancreatic cancer, liver disease, or muscle pain associated with fibromyalgia.

To summarize clinical information on ALA, 7

of 10 randomized controlled trials concluded that ALA led to modest short-term improvements in neuropathic symptoms of peripheral diabetic neuropathy with the caveats previously mentioned. Published case series in aggregate suggests that the addition of ALA to comprehensive treatment protocols may increase the odds of survival with full recovery.

Nonetheless, ALA is no longer recommended or used for this indication. This discrepancy could be explained in part by reporting bias, the process whereby the dissemination of research findings is influenced by the nature and direction of the results. The FDA found no convincing reports that ALA has clinical activity in pancreatic cancer, liver disease, or fibromyalgia.

Compounding pharmacy journals suggests that ALA has been compounded for at least 19 years. Internet advertising suggests that ALA has been compounded as an injection, suppository, topical, and troche formulations, as well as intravenous formulations for administration to treat diabetes

and diabetic neuropathy. Insufficient data are available to determine the extent of ALA use in compounded products.

In summary, ALA is adequately characterized chemically. ALA is stable in solid but not in liquid formulations. Clinical reports to date have revealed no serious safety concerns. Clinical data suggests a therapeutic potential for patients with diabetic neuropathy.

Clinical data on the use of ALA for amatoxin poisoning are difficult to interpret, and we found no credible evidence of meaningful clinical effectiveness in pancreatic cancer, liver disease, or fibromyalgia. ALA appears to be compounded as an injection suppository, topical product, and troche formulations.

Based on a balancing of the 4 evaluation criteria, we find solid oral formulations of ALA to be suitable for substances to be compounded under Section 503A of the Federal Food, Drug, and Cosmetic Act. In recent weeks, FDA has established that we wish to consider as part of the subsequent

public notice and comment rulemaking process whether liquid formulations, including intravenous and aqueous oral formulations, should be added to the list as well. Thank you.

Clarifying Questions from the Committee

DR. VAIDA: Thank you. We will now entertain some clarifying questions from the committee. Remember again, just clarifications of the presentation. Dr. Wall?

DR. WALL: Question. We're talking about the metabolite is DHLA. Is this an active metabolite? And if so, which it's mostly eliminated in the urine, have there been, as you evaluated these studies, any use in renal failure or in patients with renal insufficiency, and any problems?

DR. BRAVE: DHLA and ALA interconvert from one to the other. I don't know whether that technically is considered part of the definition of an active metabolite, but you can't have one without the other.

I'm sorry. What was the second question?

DR. WALL: Your slide says that it is eliminated in the urine, so I wanted to know if you've looked at any renal failure or renal insufficiency patients that you pulled out of looking at these studies and if there were any problems with it.

DR. BRAVE: That's a good question. I'll refer that to Dr. Harrouk, our toxicologist on this application.

DR. HARROUK: Hi. My name is Wafa Harrouk. I'm the toxicologist who reviewed this application, and I looked at the nonclinical aspects of this substance. Basically, we had one study where the investigator, Fuke et al., 1972, studied ALA IP intraperitoneally, and they did show some kidney findings. However, when you look, there were some changes. But we had another study, which was the 2-year carcinogenicity study. In that study, the report did not include any kidney complications.

So it was seen in one report, and the 6-month -- the 2-year carci [ph] study did not show any kidney toxicity. I hope this answers the

question.

DR. WALL: What kind of kidney complications did they see? do you remember?

DR. HARROUK: The relative weight of the kidneys were increased in the high dose in all treated males and 2 of the highest doses in the females. The changes were increased in kidney weights; no histopathology. There were none that we found in the literature, so just increased kidney weight.

DR. WALL: And to clarify, these were in subjects who had compromised kidneys to begin with or was this just the effect that they saw on normal subjects and their effects on the kidneys? I'm looking more in particular of -- the diabetic population has a huge problem with the kidneys. So has there been anything that anyone has seen with this product and its active metabolite, negative on not being eliminated very quickly?

DR. HARROUK: So just to clarify, the studies that I'm referring to are in the rat. These are nonclinical animal models. The animals

were normal. They weren't with any kidney diseases. So I can answer what happens if you have a compromised kidney function.

DR. WALL: Thank you.

DR. VAIDA: Dr. Desai?

DR. DESAI: Seemal Desai. Thank you for the presentation, Dr. Brave. I don't use alpha lipoic acid in my clinical practice to treat diabetes. As a dermatologist, I don't really manage diabetes on a day-to-day basis. However, I was interested that when studying this nomination and looking at the science, I do recommend alpha lipoic acid, particularly in its oral vitamin formulations that are available as antioxidants over the counter.

I use those, in particular, in patients with autoimmune skin diseases, in particular, vitiligo, where it's shown a remarkable benefit when combined with phototherapy and repigmentation combined with vitamin C, vitamin E, and oral alpha lipoic acid, which is typically found in an over-the-counter formulation. And I know in your research, you reference several studies that talked about the

antioxidant benefits.

My question is, did you happen to see any data on some of the available formulations that are over the counter currently for alpha lipoic acid?

DR. BRAVE: I didn't encounter any of that data. Vitiligo and dermatologic conditions were not part of the nomination.

DR. VAIDA: Thank you.

DR. JUNGMAN: Hi. Elizabeth Jungman from Pew. I was hoping just to clarify the question that we're being asked here. I think typically when we're asked to consider, or when FDA is recommending that a particular dosage form be placed on the list, we're being asked to put that on the list and kind of explicitly not put other dosage forms on the list.

It sounds like here, we're talking about a different circumstance where if we follow the agency's recommendation, you would place the oral formulation on the list and then other formulations would still be outstanding. And I want to kind of understand -- my assumption there is that means

that under FDA's interim policies, that compounders would continue to be able to use the other formulations even once enforcement has begun in earnest.

Can you just help me understand kind of what's actually the precise question here?

DR. BRAVE: I will defer that to our legal colleagues.

DR. DOHM: Yes, a couple of things. One, you're right, that the specific question here is going to be whether or not the committee wants to put solid oral dosage forms of ALA onto the 503A list.

As to your second question of what that means for this interim period and whether or aqueous or liquid formulations of ALA can be used, so long as ALA remains in category 1, which is described in our interim policy, that means that it would be eligible for the policies set forth in that guidance.

So absent some action by the agency to move ALA, specifically the aqueous formulations, into

category 2 or category 3, that would still remain to be true.

DR. JUNGMAN: Thank you.

DR. VAIDA: Dr. Sun?

MS. SUN: Hi. This is Jeanne. I had a couple of questions on the dosage forms. It looks like at least in the clinical studies, that the IV formulation was used at least in some of the diabetic neuropathy, and IV formulation was exclusively used for treating the toxicity. And I think one of the reasons for excluding the IV formulation was the stability concern. Can you comment a little bit about this stability concerns?

Also, in one of the nominations, a nominator had talked about topical formulation, and I didn't notice any of that in the
the review.

DR. BRAVE: We found no reports of clinical safety or efficacy with topical formulations. Regarding the stability issue, Dr. Sood is our chemist on this nomination.

DR. SOOD: I'm Ramesh Sood. I'm from the

Office of New Drug Products. Regarding the stability issues with ALA, ALA salt has been found to be unstable, and their instability could come from the moisture. So we didn't find any published literature on the stability of the liquid formulation of ALA. That's one thing.

But because the salts are not stable under the humid conditions, as Dr. Brave talked about, the 20 percent was degraded sodium salt and 100 percent relative humidity in 48 hours. The second issue is that ALA itself was not that unstable under these humid conditions, but ALA salts were. Now, ALA to dissolve in liquid forms, ALA would not dissolve, but ALA salts would. But the nominated product is ALA.

DR. SUN: Just a follow-on to that, I think one of the comments that came in also noted that there was a commercially available injectable solution in Germany. Can you comment on the stability of that?

DR. SOOD: We looked at that product also, and that's a different salt of ALA. It's

not -- like it's a [indiscernible] salt of ALA.

DR. VAIDA: Dr. Venitz on the phone, and then Dr. Ghany.

DR. VENITZ: My question has already been asked and answered. Thank you.

DR. VAIDA: Dr. Ghany?

DR. GHANY: Yes. I wonder if the -- I'm sorry I ask this question again, but I just would like some clarification. Can the FDA advise the committee on whether we're asked to also consider effectiveness of these compounds for other clinical indications to which they're being requested to be used? Because data was presented on effectiveness but I don't know if we're asked to consider that data in making our assessments.

DR. BORMEL: This is Gail Bormel from FDA. Effectiveness is one of the criteria that you have to balance when making your recommendation.

DR. VAIDA: Last question, Dr. Carome?

DR. CAROME: I just wanted to follow up on the question Elizabeth asked and the response from FDA. Suppose FDA decides to put the oral

formulation of ALA on the 503A bulks list. You go through the rulemaking and you do that, so the issue of final rule, putting it on the list in the oral formulation. What are the implications for the IV formulation at that point? As I understand, FDA's considered both formulations, and you're recommending only the oral, not the IV, placed on the list.

DR. BORMEL: Gain Bormel again, FDA. Once the final rule is promulgated, if the final rule only includes the solid oral dosage form, that would be all that could be compounded.

DR. VAIDA: All right. Thank you.

DR. BORMEL: And that means that the interim policy would be over, once the final rule is promulgated. I'm sorry to interrupt, but until that time, until there's a final rule, the interim policy would allow compounding to take place for the substances that are on category 1.

DR. GANLEY: This is Charley Ganley. I just want to clarify that further. You're going to see a presentation from McGuff. We've been going back

and forth with them trying to understand what's out there and how these are stabilized in currently marketed products.

We didn't have that information when we were doing our review, so part of this process is for compounders or other individuals to provide us information that supports an intravenous formulation.

There are issues related to stability, and we want to make sure someone's making a product that's put into a vial, and they're then putting it into an aqueous solution that we understand that it's stable; otherwise, you're injecting something that's -- and we're talking about a disease here that is particularly the diabetic neuropathy, which is an important disease.

So if it's being used for that and you're putting this into an aqueous solution, we'd like to understand that that's going to be stable in that solution. How fast do you have to give that infusion? Are there complications associated with that infusion?

There is information that we're trying to confirm from the German label that suggests the infusion rate becomes important. These are all issues that we haven't sorted out, and the burden also falls on the compounders and other clinicians to provide us information.

So I think if we were going to put out a rule, we would take the information that we get from this meeting, from the compounders, and subsequent information, and try to incorporate that into the proposed rule in making a decision.

That would then end the day there, and people would have the ability to comment on it. But the issue is if you're going to make a drug that is injected and you're putting it into D5W, and there are questions about its stability in an aqueous formulation, that issue needs to be addressed.

DR. VAIDA: Thank you.

We have one nominator and we'll take their presentation right now, Dr. Arthur Berkson from Integrative Medical Center of New Mexico.

Nominator Presentation - Arthur Berkson

DR. BERKSON: Hi, everybody. My name is Arthur Berkson, and I'm a family doctor from Las Cruces, New Mexico. I did an additional 2-year fellowship in integrative medicine at the University of Arizona, and thank you for letting me speak today.

Dr. Brave, thanks for your excellent presentation on lipoic acid.

What I'm going to speak to specifically is intravenous lipoic acid and how essential it is in the treatment of diabetic neuropathy. FDA has already told us that it's safe, and there does not appear to be significant adverse effects associated with its use, and that it's effective, and that ALA appears to show symptom improvement in the treatment for several weeks in diabetic neuropathy from their report.

I'm going to show that there are really no available equivalent treatments in terms of safety, efficacy, and mechanism of action for this important condition. There are promising uses that

can be subjects of future controlled trials. That's beyond the scope of the 15 minutes that I have. Furthermore, intravenous alpha lipoic acid has been proven over decades to be safe, effective, and stable. And I'm going to just give you a couple of case reports at the end.

I think all of us who are trained in the medical profession could do a literature search, and we could talk about safety and efficacy of different therapeutic agents. In my office in Las Cruces, we have patients who travel all over the world for our expertise in this particular substance.

I look back at our data, and we've administered over 75,000 doses of intravenous lipoic acid. In that time, we've seen zero serious adverse events. We do see some mild adverse events like hypoglycemia, so we make sure to keep amps of D50 on hand and snacks, because with diabetic patients you run into that risk. Additionally, we see headaches, somnolence, nonspecific symptoms that usually resolve within an hour or two.

Here's a partial list of diseases that you could find in the literature. I really challenge all of you to do a thorough literature search, and I appreciate FDA's effort on this behalf. But there are a lot of promising uses that I could get into, but I'm not going to.

I'm going to really focus on where the best evidence is, and that's in intravenous lipoic acid with diabetic neuropathy. This is an important condition because after 20 years of having diabetes, almost 90 percent of the patients will have diabetic neuropathy. Forty percent of those patients won't know that they have it because it's not the pain that affects them, but it's the lack of sensation and the risk of having other complications.

Briefly, the pathophysiology is hyperglycemia causes reactive oxygen species synthesis in the mitochondria, and that leads to endothelial damage to nerve cells.

As a primary care doctor, what are my treatment options? Well, first of all, I have to

achieve good glycemic control with lifestyle and available pharmaceutical agents. Also, I have to be sure that patients are having proper foot care so that they're identifying lesions early and hopefully preventing them so it doesn't lead to amputation. And finally, I could treat the pain.

Here is a slide that's adapted from the 2011 guidelines from the American Academy of Neurology, and it summarizes the evidence on available substances for neuropathy, pharmaceutical agents. The only FDA-approved agents are pregabalin, which is a derivative of the anticonvulsant gabapentin; duloxetine, the antidepressant; and tapentadol, which is an opioid pain medicine.

There are other anticonvulsants on this list. There are other antidepressants that have evidence of efficacy. And there are opioid pain medicines. These are agents that have high risk of misuse and abuse, and 2 of the 3 FDA-approved drugs are actually controlled substances as well.

So what do all of these available treatments for diabetic neuropathy have in common? All of

these agents change the perception of pain. They don't do anything to treat the underlying causes of pain. Why not treat the cause, especially when we have an agent that has the potential to do so? And that is alpha lipoic acid.

So again, very briefly, pathophysiology of diabetic peripheral neuropathy and oxidative stress from hyperglycemia leads to external damage and demyelination of these nerves, and you wind up with the neuropathic symptoms.

Dr. Brave talked about the chemical structure of lipoic acid in depth, but lipoic acid is fat soluble, it's lipophilic, and also in certain conditions, it's water soluble. This is a very potent antioxidant and mitigates that free radical damage. It also recycles other antioxidants like vitamin C and vitamin E and glutathione to further mitigate that damage. And finally, it's an insulin mimicker and also reduces insulin resistance. So it really goes after the underlying cause of disease, not just masking symptoms.

But I'm a clinician. I'm not a basic scientist. So when I treat patients, I want to know that what I'm using is safe and efficacious in people, not in rats. Here's a 1995 study. This is the ALADIN study, 328 patients with diabetic neuropathy. This was intravenous; I want to clarify that. And half of the patients got IV alpha lipoic acid, 600 milligrams a day. They actually ramped up that those, too, but they found that that was the optimal dose. Half of them got placebo.

In conclusion, it said, IV alpha lipoic acid using a dose at 600 milligrams a day over 3 weeks, superior to placebo in reducing symptoms of diabetic peripheral neuropathy without causing adverse reactions.

Another randomized double-blind, placebo-controlled trial 4 years later looked at 509 patients. This was the ALADIN III trial. In this trial, they used IV lipoic acid or a placebo followed by -- and that was over 3 weeks, too, followed by -- I think that was 6 months of oral

lipoic acid or placebo. This study was not as -- the results weren't as convincing in decreasing the Total Symptom Score. In other words, the pain of diabetic neuropathy, but it did show a reduction in neuropathic deficits, again, without adverse effects.

The SYDNEY trial from 2003, that looked at 120 patients; again, 3 weeks of IV alpha lipoic acid versus placebo. In conclusion, these authors stated that intravenous alpha lipoic acid, rapidly and to a significant and meaningful degree, improved positive neuropathic symptoms like pain, and the improvement of these symptoms was attributed to improved nerve pathology. It reversed disease; it didn't cover up pain.

This is a meta-analysis of the randomized controlled trials that were available for intravenous lipoic acid. It looked at over 1200 patients. I think there were 1258 patients. And it included 4 trials, which looked at 600 milligrams intravenous lipoic acid and 15 treatments over 3 weeks.

In conclusion, the authors summarized that the results of this meta-analysis provide evidence that treatment with IV alpha lipoic acid 3 weeks is safe and significantly improved, both the positive neuropathic symptoms, in other words, the pain, and the negative neuropathic deficits, the lack of sensation to a meaningful degree, and it did so safely.

Next slide. Here's a study I included of IV alpha lipoic acid from 2004. This was in 46 type 1 diabetics with autonomic neuropathy. In the treatment group, they found that the autonomic neuropathic indicators improved in that group, so they looked at orthostasis, dizziness, erectile dysfunction, neuropathic edema, and in the control group, there was no improvement.

I've talked about intravenous lipoic acid. In oral alpha lipoic acid, this is an interesting study out of Germany. They looked at just under 300 patients who had been on oral lipoic acid for 5 years and had some control of their symptoms. They switched the patients either to no treatment

or to gabapentin, which is one of the most commonly used drugs for this condition, as we all know.

Within 2 weeks, the untreated group began to develop symptoms again. In the gabapentin group, 45 percent of the patients stopped treatment because they couldn't tolerate it due to sleepiness and brain fog. All of us as professionals eventually become patients. If I'm going to be treated for my medical condition, I want to know that the treatment that I'm taking isn't going to affect my cognition. It's very important that we're all sharp, and alpha lipoic acid may actually improve cognition.

I'm going to skip that. In response to FDA, FDA states, which I appreciate, that it's safe, and they mention that there has been extensive literature reporting clinical evaluation of ALA. There do not appear to be significant adverse effects associated with its use.

In terms of efficacy, FDA states, "Alpha lipoic acid appears to show symptom improvement with the treatment for several weeks in the

treatment of diabetic neuropathy." They also stated, "No trial has shown ALA to improve diabetic autonomic neuropathy," which I disagree with because I mentioned that small trial, which I presented.

Furthermore -- and this has been addressed a little bit -- they mentioned that a search of the British, European, and Japanese pharmacopeia didn't show any monograph listings for ALA. Well, it's been a known pharmaceutical agent in Germany I think since the 1980s. Additionally, it's a pharmaceutical agent that's available in Columbia.

What about the stability of ALA in aqueous solution? Well, I think, again, I'm a clinician, not a pharmacist, not a basic scientist, and the Doug Tram [sic] is here, a pharmacist from McGuff, who will address this further. But there has been extensive experience with IV alpha lipoic acid since the 1970s.

There are also multiple studies of alpha lipoic acid as an IV preparation. I presented some of those studies and Dr. Brave presented some of

those studies in his presentation. It's also available as an IV drug in different countries around the world.

As far as data, I had sent an email to a South American drug company who produces alpha lipoic acid, and they actually graciously sent me back to stability data, which I'm happy to share with you guys, that showed that their solution was stable -- their alpha lipoic acid was stable in solution over 2 years, which exceeds our requirements. But I think McGuff will more articulately discuss this.

In the FDA statement, the aqueous formulation they state is likely to be much more unstable than solid dosage form. And due to lack of this precise information supporting solution forms of ALA, the stability can't be determined. There's no citation on this, so I think this is more speculation and doesn't reflect experience of clinicians in the literature.

I think about my patients first and foremost, and I don't know how I'm going to go back

and explain to a patient who's been safely and effectively receiving alpha lipoic acid, IV in some cases, 10 years, and explain to them that their product is no longer available.

Doug Tram [sic] flew here from California, and I'm going to let him present these slides in a little bit. But in closing, I want to say that at the Integrative Medical Center of New Mexico, we treat diabetic neuropathies and other neuropathies with IV alpha lipoic acid every day.

I want to address something, too, in that alpha lipoic acid is not an FDA-approved drug, and it's expensive and time consuming to get IVs in a doctor's office. So frequently, I'll start my patients on oral alpha lipoic acid, and after about 3 months, I'll reassess them. Some of my patients have benefits, but the majority I would say, maybe 50 percent, don't, and they'll switch to intravenous lipoic acid. Usually within 8 to 10 IVs, they usually start to notice sensation again.

Also, I have patients -- I have a patient that I saw 2 or 3 days before I came out here with

ocular pharyngeal muscular dystrophy, and her neuropathic symptoms have improved with intravenous lipoic acid. She can't take oral lipoic acid because capsules get stuck in her throat, and as an acidic substance, it causes burning. So that's really her only treatment.

Again, I want to give you a couple of patient examples. I have a patient, Wendy, who's had type 1 diabetes for 15 to 20 years. She runs an architectural firm, and she needs to be sharp and on point. She has very painful peripheral diabetic neuropathy. She's tried the available pharmaceutical agents, and every one that she's tried has caused cognitive problems to the point where she feels sleepy and can't function at work. She's had relief of her symptoms with intravenous lipoic acid.

Diabetes is a chronic disease, so one IV series is not a cure. It mitigates the damage from this debilitating disease. She comes about every 3 months from southern California to our clinic for a week of IV therapy, and she's able to function in

the interim. And she says, cognitively, she's actually improved.

I have another patient, Lisa, who has ovarian cancer, and it's actually in remission from heavy doses of chemotherapy appropriately prescribed by her gynecological oncologist. But it left her with debilitating neuropathic deficits from toxin-induced neuropathy. Her oncologist sent her to our clinic to try to have some improvement in her symptoms. When I saw her, she said, "My passion is really dancing, and I can't dance because I keep tripping over my feet."

After 8 to 10 treatments of IV lipoic acid, she said she began to notice return of some of her sensation. She did IV lipoic acid once or twice a week for 6 months, and after that 6-month period, she had about 80 percent return. And she's in dance classes and doing much better. There are no treatments available for neuropathic deficits.

So again, where do we stand? Well, I agree with FDA, lipoic acid is safe and effective for neuropathy. And again, I emphasize, for some of

this, there's no equivalent treatment. Even the FDA-approved drugs aren't equivalent in terms of how they work and what we're asking of those drugs.

Furthermore, intravenous lipoic acid by experience, by data, by studies, is safe, effective, and stable. And I really thank you all for your time and attention. But I want us to really make sure that we stand up with my patients like Wendy and Lisa.

Again, stand up for our families, for ourselves, because if I developed painful or neuropathic deficits with neuropathy, if my family did, IV lipoic acid would be my first therapeutic option. So please follow the science, and I know that we'll come to a positive conclusion.

These are the Oregon mountains outside of Las Cruces, and if you have any questions, I welcome them. Thank you very much for your time.

Clarifying Questions from the Committee

DR. VAIDA: Thank you. We'll now take a few clarifying questions. Again, remember to make clarifications just on what was presented.

I'll start with one on, you said you've administered over 75,000 IVs since 2002. Was that by different compounding pharmacies or do you get them all from one pharmacy?

DR. BERKSON: We've gotten them from at least three compounding pharmacies that I could think of. When you're administering something into an IV, you have to be extremely careful about quality control, and we ask a lot of questions. So the majority of our IVs do come from McGuff.

DR. VAIDA: Mr. Mixon?

MR. MIXON: Bill Mixon. I'd like to see that stability data that says that it's stable for 2 years. I'd like to evaluate that.

DR. BERKSON: I have that in a packet, so I'd be happy to provide that to you. It's in Spanish, but I think the scientific data is pretty easy to pull out of it.

MR. MIXON: Were you able to evaluate it? Did they do forced degradation and true stability indicating assays?

DR. BERKSON: I believe so. But again, I'm

a clinician, not a pharmacist, so I leave that to an expert like you to look at it and see.

MR. MIXON: Thank you.

DR. BERKSON: Yes, ma'am? Oh, sorry.

DR. JUNGMAN: This is Elizabeth Jungman, and I apologize to be coming back to this. I have some questions, but I understood Dr. Dohm's response to be that this is actually -- and I'll start with saying I appreciate the presentation, and I appreciate you coming all the way out here to give it. But my understanding of the response to my earlier question was this is not actually the meeting where we're considering IV formulations of alpha lipoic acid, and that a vote for the solid dosage form is not a vote against the IV formulation.

So I just want to -- I'm still finding myself a little bit confused about the question on the table given this presentation.

DR. DOHM: So we did consider aqueous or liquid formulations of ALA based on the information that we had before us. That's the subject of our

review, and based on the information we had at that time, we were recommending that only oral solid dosage forms of ALA be placed on the 503A list. That's where the review stands.

As Dr. Ganley mentioned, since then we've been having additional information come in from McGuff and hopefully information from this advisory committee that we'll take into consideration. But at this time, we're recommending only oral solid dosage forms based on the information provided before us.

If, as kind of Dr. Carome's follow-up said, we take all the information we have from this committee meeting, any information that is received subsequent to it, and when we go to actually propose a rule, we continue to feel that it is not appropriate to place aqueous or liquid formulations of ALA on the list, we'll be explicit about that in the proposed rule. So at that time, we'll have a proposed rule to put only oral solid dosage forms if that's where we end up on the list.

So I think as far as your vote's concerned

and where you end up, what I would recommend is that you'll vote on the issue of whether or not you recommend solid oral dosage forms of ALA to be included on the list and then subsequently provide commentary on your views as to whether or not the aqueous or liquid formulations of ALA should or should not be placed on the list. And then we'll take that commentary into consideration as well as we continue to consider this issue.

DR. JUNGMAN: So this is the meeting where -- this is the only meeting where this committee will consider the aqueous formulation. Is that right?

DR. DOHM: I think that is currently our plan.

DR. JUNGMAN: That's super. That's helpful. Thank you.

DR. BERKSON: May I have a comment to that? Again, I think that there's efficacy with the oral form, but I do not think it's equivalent in terms of efficacy to the IV form. In no way it has been my clinical experience, and I think the data

reflects that.

I think also in the studies that have been presented by FDA, in their report, there are no safety concerns with aqueous alpha lipoic acid. So in these long-term studies and data that I hope Doug will bring forward, I hope that further clarifies any lacking information.

DR. VAIDA: Dr. Ikonomidou?

DR. IKONOMIDOU: Hi. Chris Ikonomidou. Thank you very much. The FDA review basically concluded that ALA does not alter the course of diabetic neuropathy and does not have an effect on autonomic neuropathy. Would you object to that?

DR. BERKSON: I'm not saying I object to that. You know, a lot of these studies weren't designed to look at long-term use. I did mention the study out of Germany, 300 patients had been on oral alpha lipoic acid for 5 years. And again I reiterate, alpha lipoic acid is not a cure for diabetic neuropathy.

So if you get 3 weeks of alpha lipoic acid at point zero, and then you reevaluate those

symptoms five 5 years down the road, I would expect they would progress because the patients still have diabetes. So I don't think it's a one-time treatment, and I think there need to be longer-term studies to really evaluate what that looks like.

The other thing is I'm not objecting that -- I'm not giving my opinion whether it works or doesn't work for autonomic neuropathy. It's not my opinion. I'm just saying in my search of the literature, I'm presenting a study which showed the potential of benefit.

Does that answer your question?

DR. IKONOMIDOU: Yes, in some ways. Thank you.

DR. BERKSON: Okay.

DR. VAIDA: Dr. Wall?

DR. WALL: Two questions for you. One, since you've had so many patients that you've been administering this to, what do you share with your patients, before they ever start this, about an explanation behind this drug and its side effects and in its adverse event profile? Then number two,

with that many patients for diabetic neuropathy, can you share any experiences you've had within patients with renal insufficiency or failure?

DR. BERKSON: Yes. Thank you for the question. First off, I think it's very important that we're explicit with any medication that we give as far as risks and benefits. It's very difficult. I work in community health as well. I worked at a community health clinic in rural New Mexico, first full time, then part time since 2006. Sometimes I see 30 patients a day, and sometimes 35, in that context.

How could any of us really fully explain risks and benefits of treatment in that system? I think as a profession, we're all doing a bad job of that. That's one. Two, in my office now, I see about 8 to 10 patients in a full day. So I have about 2 hours with new patients and about an hour with follow-ups, 45 minutes to an hour. So it's a little bit of an idyllic situation, so I really get into the risks and benefits of any treatment that I'm providing to them.

My discussion about intravenous lipoic acid is basically based on the literature, one, there really haven't been any reported serious adverse events. I think it's fairly safe. But two, I always tell patients you need to eat a good meal because there's a significant chance of developing hypoglycemia with the IVs.

I mention all the nonspecific symptoms that sometimes our patients can experience like nausea, somnolence, mild headache, those kinds of things. But I also do mention with every patient that this is not an FDA-approved drug. So we're very careful about any kind of adverse event that are our patient experiences.

Does that answer?

DR. VAIDA: Dr. Desai?

DR. BERKSON: Oh, the renal insufficiency?

DR. IKONOMIDOU: And the renal failure.

DR. BERKSON: Yes. With diabetics and with other patients, we see a lot of renal insufficiency. I have never seen an adverse effect on kidney function. And actually in some cases,

I've seen improvements because a lot of the damage that happens with diabetes is oxidative damage from hyperglycemia in reactive oxygen species synthesis.

So theoretically, it should be helpful, but I think theory always needs to be supported by data, and I don't have the big study to back that up.

DR. VAIDA: Dr. Desai?

DR. DESAI: DR. Berkson, I just wanted to clarify, in terms of the oral formulation of alpha lipoic acid, clearly you have so many more cases of IV use in your practice, but do you still use oral formulations in any of your patients exclusively?

DR. BERKSON: Yes.

DR. DESAI: And if so, when do you use oral over your IV?

DR. BERKSON: I would say, personally, I actually use more oral than IV just because of the expense and the difficulty, the intrusiveness in people's lives of coming in to get IVs. So very frequently, I'll start with oral alpha lipoic acid, and I will use alpha lipoic acid supplements for

other indications as well.

I feel reassured when a reputable compounding pharmacy is making my product because there are so many issues with supplements, so I have to be very, very careful also before I recommend a supplement, because I find that me just saying go to your local pharmacy and buy an over-the-counter supplement sometimes -- it's my responsibility to also research reputable formulations of those things.

DR. VAIDA: Mr. Smalley?

MR. SMALLEY: Thank you, Dr. Berkson. In order to understand what I believe will be a follow-on presentation on stability, I want to ask you something about the dosage form.

DR. BERKSON: Okay.

MR. SMALLEY: I notice in your presentation that two versions of the formulation are 600 milligrams and 24 mLs and 600 milligrams and 15 mLs. Is this injection prepared like in water for injection and given an IV push? Do you use a solubilizing agent or a stability agent along with

that?

DR. BERKSON: Yes. So as far as the specific formulation from the pharmacy, I think that's best addressed by the pharmacist. In our clinic, if you just give it as a dilution -- I think the dilution forms are 40 milligrams per mL or 25 milligrams per mL, but that would be way too concentrated to inject in a patient's vein, so we dilute it out in D50 typically or normal saline. And we give it slowly over about 45 minutes.

So I think the point about looking at duration of treatment, the logistics of giving the IVs, I think that's an important point.

MR. SMALLEY: Thank you.

DR. CHELIMSKY: I have a question. I was just looking in detail at the abstract. I couldn't get the whole paper on the autonomic -- I'm an autonomic neurologist by the way, so I --

DR. BERKSON: Oh, good. So you should answer this question probably, but go ahead and ask it.

DR. CHELIMSKY: No. I think you'll be able

to answer it better than I can. How many studies -- first of all, the results here were very impressive. They had 46 patients that were treated with IV alpha lipoic acid and 29 controls. And it's really unheard of, so I have to go back and look at this paper in detail. It's just unheard of to improve the vagal function from 3 beats per minute to 10 beats per minute, where there was no improvement in the control group. In fact, their orthostatic pressures changed positively.

My question to you is, most of the trials that I'm aware of alpha lipoic acid in autonomic neuropathy, mostly diabetic, are with oral. How many are you aware of that use IV?

DR. BERKSON: I think there's a paucity of evidence with IV, but I think this study is impressive enough to include in a presentation. And I think my clinical experience reflects the impact of IV lipoic acid. I have to be cautious using my clinical experience to say this is what happens. But in my clinical experience, patients do have improvements in orthostasis, at least. I

ask them about that.

DR. CHELIMSKY: Okay. But my question was, how many studies are you aware of --

DR. BERKSON: I don't know --

DR. CHELIMSKY: Is this the only one or are there others?

DR. BERKSON: In my search of the literature, it was a brief search. This was the only study that I came across.

DR. CHELIMSKY: It's amazingly impressive. So it's either we're missing a very effective agent or this data are made up, but this is incredible.

DR. BERKSON: Here's something, too, is I think that more evidence is with peripheral neuropathy in diabetes, but the pathophysiology of autonomic neuropathy and painful peripheral neuropathy is the same. Theoretically, it should help, but we have to see bigger, longer-term studies.

DR. CHELIMSKY: Well, we can go offline and talk about that, but I actually don't agree with you.

DR. BERKSON: Okay. Like I said, yeah, thanks.

DR. VAIDA: Thank you. Dr. Ganley wants to make a comment.

DR. GANLEY: Charley Ganley. We have a copy of a label, which we believe is a translation, the German label. And in that, it suggests that with rapid infusion, you may end up with anaphylaxis or hypoglycemia. In the course of our review of the literature, these issues really didn't come up a lot.

Now, it's interesting to hear you say that you are aware of the hypoglycemia. And our question I think has to do with a compounded drug doesn't have a label. How is a clinician supposed to know the rate of infusion if there's no label that's going to warn them if you infuse it too quickly? And this includes the studies that we referred to in the diabetic neuropathy. There's no mention of this.

We haven't had reports of hypoglycemia reported to FDA, so it's just a little

disconcerting that you've experienced this. There's not much in the literature. The Germans seem to know it.

DR. BERKSON: Yes.

DR. GANLEY: So you understand the dilemma here. We're talking about compounded drugs that don't have a label. How's a clinician who may want to try it for a patient, which may be a very reasonable thing to think about --

DR. BERKSON: Right.

DR. GANLEY: -- how are they going to know that I can't infuse it over a certain period of time?

DR. BERKSON: Well, I do think that's a responsibility, as part of the education, of a compounding pharmacy when taking out a substance that is not FDA approved, that there's an educational component to it. I also think that any time a clinician takes on a treatment for a patient, they are taking on that responsibility, and they should fully understand and have a -- they should have a comprehensive understanding of what

they're prescribing, whether it's an FDA-approved drug, whether it's an off-use drug, or whether it's a compounded substance.

I don't know that that answers your question, but I think we have a huge responsibility as pharmacists, as physicians, to understand every agent that we're prescribing to them.

DR. VAIDA: Dr. Patel? Dr. Khurana?

DR. KHURANA: Thank you for the presentation. I just have a slightly different question. When you talk about giving infusions, are these covered by the insurance companies or are they paid out of pocket?

DR. BERKSON: They're paid out of pocket.

DR. KHURANA: Thank you.

DR. VAIDA: Dr. Sun?

DR. SUN: Thank you for your presentation. I just had two questions on the administration of it. I think some of the studies you cited, it was a daily injection for 3 weeks, and then some of the case studies you presented was an injection 2 to 3 times a week over several years. Can you comment

a little bit on that?

DR. BERKSON: I can. We have patients who fly from all over the country to come in. When they have an intake, when we talk to them, we tell them we recommend for diabetic neuropathy to stay for 3 weeks and get IV alpha lipoic acid daily. Because of cost issues, some of our local patients have been doing the infusions 2 to 3 times a week, and they seem to have similar effects. So just logistically is why we changed that protocol.

DR. SUN: My second question is, I know that you alluded to a later presentation on stability, but typically how much time elapsed between when something is compounded and when you finally administer it to a patient?

DR. BERKSON: You know what? I'm going to defer that to Doug Tram [sic] in his pharmacy presentation.

Open Public Hearing

DR. VAIDA: We're going to move on to our open public hearing. And again, if we have some

other questions that come up during the vote, if we have questions to bring --

DR. BERKSON: Thank you.

DR. VAIDA: We have three speakers, and I'll make the opening statement.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product and if known its direct competitors. For example, this financial information may include payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at this meeting.

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

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided could help the agency in 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.

Our first speaker?

MR. FILOSI: Good morning. My name is Mark Filosi. Thank you for having me here today. I am a technical advisor for MEDISCA. I also own my own compounding pharmacy in Plant City, Florida, and I'm also a teacher of three different compounding pharmacy programs.

I'd like to talk to you about alpha lipoic acid. Alpha lipoic acid is a very simple molecule that happens to be sensitive to heat and light as described by Dr. Brave. Also, it exists as two enantiomers.

Although likely to be stable when compounded, appropriately stored as the solid. Dosage forms, as we discussed, in the aqueous formulations are less stable. This is because the salts that are used in aqueous solutions to improve solubility have the tendency to polymerize, and therefore the drug substance is unlikely to be stabled when compounded in an aqueous solution if using those salts.

Now, that's not the only choice compounders have to make a preparation for their patients. To

circumvent this process, the preparation can be prepared and lecithin. If we look at some evidence of soy in lecithin palmitate oil, we can prepare ALA in a lipophilic vehicle. And compounders use lipophilic vehicles all the time to move formulas from one place to the next.

This topic addresses the carrying capacity of the drug in the delivery system, so it's directly correlated to the solubility in its base. Of course solubility in its base in a carrying capacity is inversely proportional to driving force, and that would be LogP [ph] over the drug partitioning out of its base.

In a study, Takagchi investigated the use of cyclodextrin to improve aqueous and thermal stability of alpha lipoic acid. This gives formulators an alternative to lipophilic substrates to carry the molecule. Cyclodextrin acts as a protector of the molecule that it hosts. It acts like a host and a guest. Dextrin molecules will arrange themselves in a cylindrical pattern, and the molecule, the guest, would become complexed

with the inner part of the structure. So that's also a possibility for compounders to used cyclodextrin.

Looking at the mechanisms of action, they call ALA the universal antioxidant. We have ascorbic acid for hydrophilic antioxidants. We have alpha tocopherol for lipophilic antioxidants. Alpha lipoic acid is both. It's known to be an amphipathic molecule because it has both a polar and a non-polar region in the molecule. As discussed previously, it cycles back and forth between its oxidated and reduced forms and functions as an antioxidant in both forms.

One of its activities is to improve glucose in ascorbate handling. It also increases endothelial nitrous oxide and improves nitrous oxide at the neuronal endothelium, and might be responsible for decreasing the oxidative stress on the axon due to diabetes. Proposed also, it could lower the expression of MMP-9 and VCAM-1 for the repression of NF-kappa 8 [ph], which is an incorrect expression, and it has been associated

with cancer. ALA may provide some protection.

Historical uses, it was discovered back in 1951. It was found to be a coenzyme in the Krebs cycle. Of course, the Krebs cycle or the citric acid cycle is the pathway for pyruvic acid in the production of ATP for cellular energy. In the '80s, it was recognized by the scientific community as a powerful antioxidant. And ALA has been used in countries like Germany for over 50 years safely. In Germany, it's used as a therapeutic option for diabetic peripheral neuropathy and retinopathy.

As far as historic uses, there's a study by Hermann in 1996 that characterized the pharmacokinetic profile of ALA in three different dosage forms. A study used both the R and S enantiomers and also used the racemic mixture of that substrate, and the study included the use of oral tablet solutions and intravenous solutions, and all three demonstrated adequate bioavailability.

With respect to safety, we've looked at studies with the previous speaker, Dr. Berkson, and

he looked at both the ALADIN I, II, and III studies and the SYDNEY-1 and 2 study trials. And if you look at the amalgamation of all those studies together, you can see the intravenous doses as high as 600 milligrams a day for 3 weeks with no significant adverse reported events, and doses of up to 1800 milligrams per day for 6 months didn't show any illicit adverse events.

In an Italian study, Parente et al., in a retrospective study in 2017 analyzing the safety data of ALA in 610 pregnant women, ALA was found to be completely safe. Noted in the study, the Italian Ministry of Health had no established upper limit for the dietary supplement, which means that it was deemed safe at relative doses.

The study demonstrated that ALA had a protective effect on the fetus and may indicate that ALA could ward off threatened miscarriage and prevent preterm delivery. Obviously, this particular group is a very sensitive patient group, that of the pregnant female and the developing fetus, and the data and study from Parente seemed

to indicate that it's reasonable to administer ALA.

To demonstrate that ALA has a positive effect on diabetic neuropathy, the ALADIN I and II studies both showed significant improvement in both nerve conduction and superior to placebo. The alternative therapies for those who lived with this disease caused the patient to feel disconnected. And in my experience, many patients that I see in my practice often discontinue use of oral gabapentin and pregabalin due to the side effects of these mainstays in peripheral neuropathy treatment.

The ORBOL [ph] study showed a reduction in diabetic polyneuropathy symptom after 3 weeks of ALA therapy at 600 milligrams 3 times a day. The SYDNEY study used ALA at 600, 1200, and 1800 milligrams for 5 weeks, and the SYDNEY study also showed improvement in neuropathic endpoints.

In another study by Bertoletto and Massone, a study conducted in Italy again, demonstrated that the combination of superoxide dismutase and alpha lipoic acid improved both physiological attributes

such as nerve conductivity and also sympathomimetic improvement such as improved sensory scores. Patients were treated with both alpha lipoic acid and the SOD at 140 international units per day for a period of 4 months.

Combining two drugs with different pharmacological mechanisms has the potential to provide superior relief over monotherapy without increasing side effects. A recent trial has demonstrated greater analgesic efficacy with pregabalin and duloxetine combination versus monotherapy alone without an increased side effect profile.

Although this was a positive finding, the additive benefit was submaximal because these two agents caused some similar adverse events, and doses must be reduced during the combination therapy to maintain safe tolerability. Thus, we hypothesized that analgesic combinations containing at least 1 non-sedating agent would provide greater additive benefits because of additive pain relief but not having the additive adverse events.

Both pregabalin and alpha lipoic acid are approved by Health Canada and proven for the treatment of neuropathic pain. An important pharmacological mechanism of pregabalin is the blockade of anti-voltage gated calcium channels resulting in decreased calcium influx in neurotransmitter release.

ALA has been studied in both preclinical and clinical neuropathic pain conditions in rat models of streptzotocin induced diabetes. ALA delayed the onset of polyneuropathy. Mechanistic studies suggest that decreased nociceptive sensitivity by inhibition of T-type calcium channel distinct from that of pregabalin, which inhibits N-type calcium channels, suggesting a potential for the synergy at these two different sites of action, making pregabalin and ALA possibly a good choice to use together.

While this is an old report -- and I believe that Dr. Brave also touched on this -- in the Western Journal of Medicine in 1976, there's also use of ALA in mushroom poisoning. In this

particular study, there were only 11 cases reviewed by the Western Journal of Medicine Study. Phalloides mushrooms can produce life-threatening symptoms as soon as 6 to 24 hours after initial ingestion.

The problem is most patients don't always show up within that time frame, and some of the support medications that we have to use to support the patient, such as the activated charcoal, might not be effective at that point because of the delayed ingestion of the mushroom. In that particular study with the 11 patients that were followed, 10 of them survived. The 11th patient may not have fared so well because of his late reporting of the symptoms to the hospital.

Lastly, we've got symptoms of burning mouth syndrome, which there really are not any great ways to treat this. With burning mouth syndrome, using ALA combined with gabapentin at 300 milligrams seems to show efficacy.

DR. VAIDA: Thank you. Our next speaker?

MS. WALL: Good morning. My name is Tammy

Wall, and I'm a food and drug law attorney, and I also work on legislative matters on behalf of several 503A compounding pharmacies and 503B outsourcing facilities. My statement concerns the composition of this committee and not the substance of the discussion. This is just where I was placed in queue.

There are only 12 voting seats on the Pharmacy Compounding Advisory Committee, and each voting member must bring relevant expertise and impartiality to the work of the committee. PCAC is tasked with making critical recommendations to FDA on individual bulks substances and in identifying demonstrably difficult-to-compound substances. The recommendations made by PCAC will directly impact both 503A and 503B operations, and most importantly will impact a patient's access to medications.

My concern regarding the composition of PCAC is twofold. The first is the lack of the expertise of a compounding pharmacist from a community healthcare setting. This perspective is imperative to fully understand the pharmacy compounding model

and the valuable role pharmacy compounding plays in our healthcare system and in the daily lives of individual patients.

The second concern is the appearance of any conflict held by voting members. For example, there's a current voting member, Pew Charitable Trust, that has in times past been on the Hill alongside commercial interests with the less than neutral message on pharmacy compounding by co-hosting a briefing and signing off on joint statements to Congress.

Healthy debate and hearing perspectives from all angles will result in stronger recommendations to FDA, however, the voting seats must be held by impartial interest to maintain the integrity of PCAC and to ensure the recommendations made to FDA are independent of commercial influence. I make this statement to underscore the need for and the importance of a balanced committee with objective, diverse, and relevant expertise. Thank you.

DR. VAIDA: Thank you. And our final speaker?

DR. TRAN: Good morning. Thank you for allowing me the opportunity to speak. My name is Doug Tran. I am a compounding pharmacist, and I work for McGuff Compounding Pharmacy Services, Incorporated in California. I'm here to address any concerns that the panel has regarding the aqueous stability of our compounded ALA injections.

We are probably the only compounding pharmacy that conducted a formal stability study for our compounded lipoic acid injection. Yes, of course, alpha lipoic acid is very poorly water soluble, however, according to the ALZ chemical, SDS, safety data sheet, alpha lipoic acid is water soluble in sodium hydroxide solution. And if the sodium hydroxide and the hydrochloric acid composition is optimal, alpha lipoic acid is stable in aqueous solution. We compound two strengths, one, 25 milligrams per mL and 40 milligrams per mL.

All the information that I'm presenting we have uploaded to the docket, so you have it. And I also emailed it to Dr. Fajiculay and Lieutenant Hallman.

When we conducted the stability study for our compounded lipoic acid injection, we assessed the appearance of the solution, the appearance of the vial, the appearance of seal. We also assessed for visible particulate. We performed endotoxin tests. We performed enhancement and inhibition method suitability to validate our endotoxin test.

We conducted sterility tests at time zero and at BUD. We also conducted the bacteriostasis and fungiostasis to validate our sterility test. We performed potency assay at time zero and post-BUD using the HPLC method. We also conducted container closure integrity test, which is the dye immersion test according to USP, at post-BUD, and it passed.

For the multiple dose formulation that contains an antibacterial, we also assayed the concentration of the antibacterial at time zero and at BUD. We also conducted the antimicrobial effectiveness test for the multiple dose injection.

We conducted a real-time study to support the BUD. According to our study, the one that we

just presented, our assigned BUD is at least 180 days. We know that it's stable in aqueous solution for our compounded lipoic acid injection for at least 180 days. We could have extended it, but then the California Board of Pharmacy regulation, we cannot exceed 180 days for the labeling, so there's no reason for us to conduct a longer study.

As you can see, the two concentrations that we compound, these are the tables for the result of the lot assays for our 25 milligrams per mL and 40 milligrams per mL. The reason we have two concentrations, the 25 milligrams per mL is for the physician who uses lower doses of the injection, and the 40 milligrams per mL, it makes it easier for the physician that uses 600 milligrams per mL. All they do is just withdraw 15 mL to get the 600-milligram dose. It's just for convenience and to facilitate the administration in the office.

This is the table that summarizes our stability study over the 180 days, all the attributes that we assess, and those are the core numbers for our study. Again, the study that we

conducted was real-time data from day zero to 180 days and longer.

As Dr. Berkson has mentioned, he has administered several doses of alpha lipoic acid infusion. From late 2011 to the present day, we have dispensed more than 70,000 doses or vials of lipoic acid injection, both concentrations, and we have received no reports of precipitation, color change, or other signs of chemical instability, or ever received by the pharmacy.

To address Dr. Ganley's concern, on our label for each vial, we have a cautionary statement for the physician. Consult a pharmacist for chemical compatibility and incompatibility with lipoic acid injection.

For the physician, prescriber, and end user, for the first time they get lipoic acid injection from us, myself and other pharmacists, we go through a -- we call it a counseling session. We inform the physician, and we advise them how to dilute, what to dilute; for example, a normal saline, D5W, to cover the bag with aluminum foil or

amber plastic and use it as soon as possible or within an hour. Also, we advise on what to mix with and what not to mix it with. We advise them not to mix it with any other ingredients, just lipoic acid and D5W or normal saline.

In conclusion, we cannot speak for other pharmacies, but the McGuff Compounding Pharmacy, for McGuff compounded lipoic acid injection, we do have stability information that support 180 days BUD.

May I add a personal statement? My sister has chronic fatigue syndrome, and my brother in law, who's married to my sister, he has idiopathic peripheral neuropathy. Six years ago, his neurologist told him that he would be wheelchair bound, but he's been on lipoic acid treatment for 6 years. He's still running and he's still walking. So it is a viable option. And I would not make something that's not stable for my loved ones. Thank you.

Committee Discussion and Vote

DR. VAIDA: The open public hearing portion

has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion of alpha lipoic acid. And the question before us is the FDA is proposing that alpha lipoic acid solid, oral dosage form be included on the 503A bulk list. Should alpha lipoic acid solid oral dosage forms be placed on the list?

I'll now entertain any discussion before we take the vote? Dr. Desai?

DR. DESAI: Just a procedural question, and I think I should direct it to Julie. And thank you for clarifying earlier because I had a comment similar to Elizabeth.

Is there a mechanism in this PCAC setting that if we vote just on oral, which is what is before us today, that another formulation of the same ingredient then be brought back to a subsequent advisory committee meeting for review? So for example, today we vote on oral. Could intravenous then be brought back since we're technically not voting on intravenous?

DR. DOHM: I think what would be helpful is if you could vote on the issue before you today and include in your comments your current assessment and whether or not you'd recommend that it be brought back to the PCAC.

DR. DESAI: Thank you, Julie.

DR. BORMEL: You could also comment on your thoughts about other formulations.

DR. VAIDA: All right. No further discussion?

DR. BOGNER: Thank you. Robin Bogner. What do we know about the degradation products of alpha lipoic acid in aqueous solutions? If it's degrading to this DHLA, and we know they interconvert, is this as big of a problem as we're trying to guard against?

DR. ZHANG: This is Ben Zhang from FDA. We know that ALA was degrading to DHLA in aqueous solutions, and the DHLA will further going through polymerization to form oligomers or polymers in the aqueous solutions.

DR. BOGNER: And are the oligomers or

polymers reversible?

DR. ZHANG: It is unlikely it will go back to ALA.

DR. BOGNER: Do we know anything about the timeline, the kinetics of that?

DR. ZHANG: We have some data showing that at 100 percent humidity, at 25 degrees, 20 percent of the ALA decompose after 48 hours.

DR. BOGNER: That's in the solid state. That's not an aqueous formulation.

DR. ZHANG: That's in the solid state. We have limited access to any stability that are in aqueous solutions.

DR. BOGNER: Thank you.

DR. VAIDA: Okay. Thank you. We'll now proceed to the vote. Each voting member has three voting buttons on their microphone.

You have more discussion?

DR. GHANY: I just had one quick question. This particular compound is being asked for I think 4 or 5 certain clinical indications. Are we to consider that if we vote yes, it will be approved

for each of those indications?

DR. BORMEL: Gail Bormel, FDA. We're not approving any drug here, but what you're voting on, again, you're balancing the criteria. We do not put -- when we put a drug on the 503A bulks list, we don't specify the condition or disease that it's to treat. So once you put it on the list, it can be used, provided it goes through rulemaking and we have a final rule. It can be used for what the clinician determines it should be used for.

DR. VAIDA: Thank you.

Each of the voting members has three buttons on their phone, yes, no, and abstain. Please vote by pressing your selection firmly. After everyone has voted, the vote will be complete.

The question, once again, is FDA is proposing that alpha lipoic acid solid, oral dosage forms be included on the 503A bulks list. Should alpha lipoic acid oral dosage form be placed on the list?

If you vote no, you are recommending that 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 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

If there is no further discussion, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you have made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again. Thank you.

(Voting.)

DR. FAJICULAY: For the record, the results are 17, yes; zero, no; zero, abstain.

DR. VAIDA: Thank you. We'll now begin for the voting members -- and we'll start with Dr. Ghany -- to please state your name, your vote, and any comment.

DR. GHANY: Thank you. This is Marc Ghany. I voted yes, and I do have a comment. I would

suggest that this compound not be used for patients with chronic hepatitis C. We have a very effective, safe therapy for chronic hepatitis C, and I would argue that it's probably unethical to use this drug in someone with hepatitis C when effective therapy exists.

DR. VAIDA: Next? Dr. Chelimsky?

DR. CHELIMSKY: I had no comments. Do I need to explain why I voted yes?

DR. FAJICULAY: Your name and your vote.

DR. VAIDA: Your name, your vote, and if you have any comment, please.

DR. CHELIMSKY: Yes. My name is Tom Chelimsky, my vote was yes, and I have no comment.

DR. VAIDA: Thanks.

DR. KHURANA: I'm Sandeep Khurana. I voted yes. I just have a couple of comments, too. Even though the bulk of the data was based on IV drug formulations, I just want to be clear that we are not voting on that. We are voting on the oral formulation.

Number two, I do agree that there is no

evidence so far to support its use in any kind of liver disease, chronic or otherwise, due to the lack of drug trials. And number three, that I'm voting this yes only primarily for the diabetic neuropathy indication. Thank you.

DR. IKONOMIDOU: I'm Chris Ikonomidou. I voted yes. I would also like to comment that of this compound, I'm not voting for this compound to be used for cancer, fibromyalgia, or liver disease because there are no supporting data. And I would also like to comment that I would recommend that the IV formulation be brought back for discussion. Thank you.

DR. SUN: Jeanne Sun. I voted yes. I would like to comment that -- I would suggest that this bulk substance be added to the list without any qualifications on the dosage forms, especially with the compelling efficacy and stability discussion that we had on the liquid and IV formulation.

DR. DESAI: I'm Seemal Desai. I also voted yes. I also would like to comment, similar to my colleague Jeanne Sun, that I do think the

intravenous formulation should also be brought back for discussion. I was particularly impressed with the data presented by Dr. Berkson of over 75,000 cases of patients that have been treated with no major adverse events.

Further, I think I was impressed that the representative from McGuff who presented more specifics to answer our questions on how this product was really infused and how the clinicians are really instructed to use this gave me a good amount of confidence that this is being done in a controlled way, especially with the number of patients that have been treated. So I would encourage us to look at the IV formulation again also.

DR. JUNGMAN: This is Elizabeth Youngman from the Pew Charitable Trust. I voted yes. With respect to the IV formulation, I understand FDA is continuing to evaluate that. I think it will be interesting as part of that evaluation to understand whether -- if some compounders are able to resolve some of the production concerns and

stability concerns if you have some assurance that that would be generally applicable or something that only a specialized few are able to do.

I share Dr. Ganley's question about how physicians are going to know about the risk of the product. But that said, there were a number of factors weighing in favor of including the aqueous formulation as well. I don't know that I have an opinion about whether it comes back to the committee. I understand that FDA has a ton of bulk drug substances to work through, and that there are public health benefits to going ahead and completing that process.

One option to consider might be that if FDA decides to recommend including it, depending on how this conversation goes, that you go forward. And if you decide that you're not going to and were going to cut off patient access to that formulation, that that would be a circumstance where you'd want to bring it back to the committee.

DR. WALL: Donna Wall. I voted yes. I think that we have a product here that looks like

it may be advantageous to many of our folks. I really appreciate Dr. Berkson's comments on educating the patient and working with the pharmacy and the patient to make sure that everybody is transparent and knows exactly what everyone is getting into.

I appreciate his comments, too, on some of the side effects that he has seen with the hyperglycemia. Things like that need to be more quickly reported so that we all can make appropriate decisions going forward.

I also agree with the comments on the IV formulation. I think it needs a little bit more study, but if it can be shown that it can be stable and work well for patients, we should go forward.

DR. CAROME: Mike Carome. I voted yes. I think there's sufficient data to show that the safety benefit profile for the oral formulation for use for diabetic neuropathy, it's appropriate to have it be on the list. For my colleagues on the committee, once it's on the list, it can be used for any indication. So you voiced your desire for

its restrictions for certain uses, but a physician can prescribe it for anything and have a compounding pharmacy make it for anything once it's on the list. So it's important to understand that.

In terms of the IV use, I ultimately would want to hear FDA's independent assessment of the stability and safety of the IV formulation before I would have an opinion on whether it should be put on the list for that formulation. Whether it should come back to the committee or not, I'm sort of neutral on that. If FDA does an in-depth, independent evaluation and perhaps they were to articulate that in a detailed Federal Register Notice, that might be an appropriate route.

DR. BOGNER: Robin Bogner. I voted yes, and I agree with Jeanne that there be no restrictions on the dosage form. I looked up the article on beta cyclodextrin that was referred to, and it does seem that there's an equilibrium between DHLA and alpha lipoic acid, but the degradation, the polymerization of DHLA seems to be quite slow. So I suspect some have figured out how to use this. I

can look and show you the basis of my very quick kinetic analysis at another time. I was also influenced by Dr. Desai's discussion of the use topically.

DR. VAIDA: Thank you. Allen Vaida. I voted yes. My only comment is if it does come back for a review of the IV, I think it was presented well that the oral is safe. But the one thing with the IV is I think, as already mentioned, with the indications, we would have no control over the indications. And this drug was -- also, some of those indications that were mentioned were cancer and hepatitis.

So my concern would be we would really want to look at the IV because that could be then used for a lot more than what was shown here at the meeting today.

DR. PATEL: Kuldip Patel. I voted yes to the oral formulation for the reasons, safety and efficacy data shared by the FDA. For specifically the indication of diabetic neuropathy, especially in patients who are intolerant to the standard

therapies that are available or experiencing adverse events, I was impressed with the data shared by Dr. Berkson and McGuff Pharmacy.

Just as a comment, if the IV form is brought back, one of the things that I struggled with -- and I don't know if there's a specific answer to this. But one thing that should be considered as a difficulty in extrapolating experiences like that is, while the data was extensive, how do you apply that to the broader general population, especially in a disease state that's growing? That's all for my comments.

MR. HUMPHREY: William Humphrey, and I voted yes for many of the same reasons already explained. I do recommend that there be continued review and evaluation of the injectable forms.

DR. HOAG: Steve Hoag. I voted yes, and I agree with the use in the oral. And also, I think the valuation of the IV should be continued. Things like compatibility, how is it administered with this drug, obviously if you change the pH or something, it would precipitate. So there needs to

be a little bit -- it probably could be formulated as an IV, but there needs to be some guidelines for that.

DR. VAIDA: Thank you. And now our two members on the phone, beginning with Dr. Gulur.

DR. GULUR: Hello. Thank you. This is Dr. Gulur, and I voted yes for the oral formulation. As a pain physician, I treat these painful neuropathies myself. And while there's an adjunctive role for this medication, as we start to consider the intravenous formulation with concerns for stability, which hopefully will be allayed by more formal presentations or FDA review, indication would still be something we're looking at as has been indicated by other members on the committee. My comment would be to review it more carefully and ensure that it's brought back to the committee, hopefully. Thank you.

DR. VAIDA: Dr. Venitz?

DR. VENITZ: Jurgen Venitz. I voted yes; a few comments. First of all, as one of the outgoing veterans of the committee, this was probably the

most persuasive presentation of evidence to support a positive risk-benefit and extensive use bulk for the oral and the IV formulation.

Number two, I am very positively inclined towards the IV formulation, and my suggestion would be that FDA, with the benefit of the additional information that they now have on stability and the additional clinical information that Dr. Berkson presented, that they reinitiate their review. And if they are inclined to do so, include the IV formulation as well.

If they have concerns, only then would I suggest that it come back to the committee for a second review. But unless the FDA finds any problems with stability or safety of the IV formulation, I think it should be included.

My last comment is to some of my fellow committee members. Yes, we do not approve indications; we approve drug products. And I'd like to point out that that is not really that much different for NDA-approved drugs. They are approved for indications, but they can be used in

practice by the physician for any indication that they like to use them for. Thank you.

DR. VAIDA: Thank you. We'll now take maybe a 5-minute break to 11:35, and please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience.

DR. CHELIMSKY: Could I add a comment?

DR. VAIDA: Let's try to reconvene about 11:35.

DR. CHELIMSKY: Is it possible to still add comments or no?

DR. FAJICULAY: No, we're done.

DR. CHELIMSKY: I had made no comment before, and I wanted to add one. Is that still possible? Afterwards?

DR. VAIDA: It's too late. I'm sorry. You could let us know.

DR. CHELIMSKY: My comment basically was that the findings in the autonomic neuropathy were very dramatic, and that really should be followed up for the IV form. And I just wonder if the IV

form has a different impact than the oral form. But I've never seen anything like that.

DR. VAIDA: Okay. Thank you.

(Whereupon, at 11:29 a.m., a recess was taken.)

DR. VAIDA: We'll start with Dr. Susan Johnson to present from the FDA on Coenzyme Q10.

(Pause.)

DR. JOHNSON: I'm happy to proceed with the paper slides if you'd like.

DR. VAIDA: Do you want to start? It is in your handout that we could follow along until we bring it up. Thank you.

FDA Presentation - Susan Johnson

DR. JOHNSON: We're starting with slide 1 on the paper slides in your handouts. I'll give everybody a chance to get that.

Good morning. My name is Susan Johnson, and I'm from the Office of Drug Evaluation IV in CDER's Office of New Drugs. I will now be discussing coenzyme Q. Thanks for arranging for the slides, fixing that up.

I'd like to recognize the entire review team and note that the folks named in this particular slide have worked on each of the substances that are being discussed today. I'd also like to welcome Dr. Sophia Hufnagel, a pediatric geneticist from the Division of Gastrointestinal and Inborn Error Products, who's here to help us address any clarifying clinical questions regarding the rare diseases that we'll be discussing this morning.

Coenzyme Q10 has been nominated for inclusion on the bulk drug substances list under Section 503A and is proposed for oral use in the treatment of mitochondrial disorders. Coenzyme Q10 is a term that refers to one of two different molecules, either ubiquinol, which is the fully reduced form, or ubiquinone, the fully oxidized form.

Each of these molecules is a benzoquinone with 10 isoprenoid units in its side chain. The all-trans isomer of ubiquinone is the substance that's under consideration today and is the substance most often referred to as CoQ10, so

that's the term that I'll be using.

It's an organic molecule with a well characterized structure. Ubiquinol was previously reviewed and presented to this committee in May 2017, and as we move forward with rulemaking for both ubiquinone and ubiquinol, we'll be considering discussion from today's meeting.

CoQ10 is not soluble in water. For this reason, we recommend that it not be used in intravenous formulations, but we note that only oral formulations were proposed in the nomination. The structure of CoQ10 suggests that it will have a good stability profile under ordinary storage conditions in oral formulations. Industrial production is likely via microbial fermentation. In conclusion, CoQ10 is well characterized and likely to be stable in oral formulations under normal storage conditions.

In healthy humans, CoQ10 is endogenously synthesized, and the normal body pool is estimated to be around 1 gram. CoQ10 is found in all plants and animals, so we also have an exogenous supply in

our foods. It's estimated that we normally ingest about 20 grams per day.

CoQ10 has many uses in the body, and it's most well known for being an electron transporter in the oxidative phosphorylation process that generates ATP. This process generates more than 90 percent of the energy needed by the body. CoQ10 is also a cofactor and contributes to many other essential processes, including cellular apoptosis.

Much of the understanding of CoQ10 pharmacokinetics is based on animal studies. Because of CoQ10's insolubility, the formulation in which CoQ10 is administered can substantially affect bioavailability. In a study using a rat model, administration of emulsion formulations resulted in higher AUC and Cmax than did administration of a crystalline CoQ10. Still, the bioavailability is only about 2 to 3 percent of an administered dose. In a dog model, it was shown that Cmax and AUC increased to a plateau after 7 weeks of dosing, and there appeared to be no further accumulation.

In humans without CoQ10 supplementation, CoQ10 is measurable in the plasma and is found in tissues like skeletal muscle where energy requirements are greatest. With supplemental CoQ10, a small portion of the dose is absorbed via both passive and active transport across the intestinal wall.

A 3-compartment pharmacokinetic model best fits the available data with Tmax occurring within 6 to 8 hours of dosing, followed by a 6- to 12-hour distribution phase, and then a long-term elimination phase of 33 hours. Steady state is reached in 3 to 4 weeks, and supplementation leads to higher plasma concentrations than are seen in the absence of supplementation, as you would expect. The metabolism of CoQ10 has not been well established.

Turning to nonclinical safety, repeat oral dose toxicity studies have been conducted in various species for a period of up to 52 weeks. Given the limited bioavailability of ubiquinone, we don't know how to characterize the systemic

exposure from these studies, but no toxicities were seen.

There was no evidence of genotoxicity in standard in vitro assays. No adverse events were seen in reproductive toxicity studies in rats and mice, but no developmental studies were found. CoQ10 had no impact on the lifespan or tumor formation in a 2-year mouse senescence study.

Clinical safety data include 19 FAERS cases. Among these, there were 2 deaths in pediatric patients with mitochondrial disorders, but both appeared to be related to the underlying disease. CoQ10 is currently marketed as a dietary ingredient in dietary supplements, and there are 837 reports in the CAERS system.

There were 8 deaths among the CAERS reports, none of which appeared to be related to CoQ10. The 22 cases in which CoQ10 was the only supplement or drug reported to have been used, showed no apparent safety signal.

In three studies of CoQ10 in healthy individuals with oral doses up to 3000 milligrams

per day, non-severe gastrointestinal symptoms were the most commonly reported symptoms.

We found no studies designed to assess safety of CoQ10 in patients with mitochondrial disorders. It's been reported that CoQ10 has been associated with a urinary marker of oxidative stress at doses of 1200 milligrams per day and that the safety of CoQ10 dosing for prolonged periods in patients with mitochondrial disease has not been well studied.

In a crossover study comparing treatment with CoQ10 and nicotinamide in patients with mitochondrial disorders, one patient died on the 39th day of CoQ10 treatment. This death was reported by the investigators to have been unexpected. An autopsy revealed cardiomyocyte degeneration and active fibrotic changes in the myocardium.

A second patient died during this study while on nicotinamide treatment after completing the CoQ10 arm of the trial and washout period. Three additional patients died within 24 months of

the end of the trial. The authors did not attribute the deaths to active treatment but did observe that safety of CoQ10 may be dependent in part on the severity of a patient's mitochondrial dysfunction.

In general, CoQ10 appears to be associated with non-serious adverse events, although most safety data are derived from healthy individuals. There's much less information available about the safety of CoQ10 in patients with various mitochondrial disorders.

This slide shows the synthesis of CoQ10 in mitochondria where oxidative phosphorylation occurs. It consists of a complicated series of steps that provide for the sequential addition of the 10 isoprenoid units, but you can see by the question marks that has not been fully characterized.

We looked at the efficacy of CoQ10 in the treatment of primary CoQ10 deficiency. This is an autosomal recessive rare disease that directly affects CoQ10 biosynthesis pathways as shown on the

previous side. The presumed mechanism of CoQ10's action is to reduce dependence on the CoQ10 synthesis process.

Primary CoQ10 deficiency has been associated with 5 main clinical phenotypic groups and 9 genetic mutations. The clinical presentation is highly variable, and diagnosis involves an extensive systematic evaluation process.

Although we found no clinical studies of CoQ10's use in primary CoQ10 deficiency, the literature contains multiple reports of CoQ10's effect in the treatment of this rare disease. In addition, the Mitochondrial Medicine Society issued guidelines in 2015 that recommend CoQ10 use in the treatment of primary CoQ10 deficiency.

There are numerous other mitochondrial disorders that do not directly affect the biosynthesis of CoQ10. The current clinical approach commonly identifies patients based on their phenotypic presentation, and then genetic evaluations are conducted to confirm diagnoses.

In the one randomized, double-blind,

placebo-controlled study that we identified, a dose of 600 milligrams of CoQ10 given twice daily for 60 days for a total of 1200 milligrams per day was compared with placebo in a crossover design. Thirty patients were included, and among them, there were 5 different mitochondrial diseases represented. Although it was established using plasma levels that CoQ10 levels increased with supplementation, the authors concluded that CoQ10 lacked effect on most of the variables that they measured.

The Mitochondrial Medicine Society 2015 guidelines say that evidence of CoQ10's effect is sparse, but they recommend that CoQ10 be offered to patients with a diagnosis of mitochondrial disease. We note that prior to the MMS publication of their 2015 evidenced-based guidelines, MMS conducted a survey of treating physicians and found that the use of CoQ10 in patients with mitochondrial disorders was common.

In conclusion, based on the small amount of data, CoQ10 is recommended for use in the treatment

of primary CoQ10 deficiency. And while there are no compelling data to establish the efficacy of CoQ10 in the treatment of other mitochondrial disorders, we note that in the absence of FDA-approved therapies for these rare diseases, CoQ10 is widely used.

It's noted that the various genotypes and phenotypes for mitochondrial disorders create a wide set of clinical presentations, and the effectiveness of CoQ10 for particular uses or at particular doses has not been established.

We found that CoQ10 has been compounded in oral and other dosage forms since at least 1999, but we don't have information to address the extent of use of these compounded products. CoQ10 is often one component of a mix of vitamins and supplements prescribed to a mitochondrial disease patient. The substances included in these mito cocktails are not the same for each patient and are tailored by the prescriber.

In summary, CoQ10 is well characterized and likely to be stable in oral formulations at normal

storage conditions. It's considered generally safe, although there is little safety information derived from patients with mitochondrial disorders. Based on literature reports and current guidelines, CoQ10 is effective for the treatment of primary CoQ10 deficiency and is used in the treatment of other mitochondrial disorders. CoQ10 has a history of having been compounded since at least 1999.

A balancing of the four evaluation criteria weigh in favor of Coenzyme Q10 ubiquinone for oral administration being added to the list of bulk drug substances that can be used in compounding under Section 503A. Thank you, and I'm happy to take questions.

Clarifying Question from the Committee

DR. VAIDA: Thank you. We'll now have any clarifying questions from the committee. Any questions?

(No response.)

DR. VAIDA: No? Thank you, Dr. Johnson.

We'll now have time for the nominators, and we have one presentation, Dr. A.J. Day from the

Professional Compounding Centers of America.

Nominator Presentation - A.J. Day

DR. DAY: Good morning, everybody. First, as we get started with this presentation, I'd like to acknowledge the FDA for both inviting to this meeting, but as well as having a greatly enhanced level of communication with the compounding industry to notify us about this meeting as well as the contents of the meeting, so that we could prepare adequately and make sure that the stakeholders are adequately notified. And we're extremely grateful for that.

As we get started with coenzyme Q10, I'd like to acknowledge some of the findings that FDA elicited in their evaluation. Stability in physical chemical properties are well defined. To my knowledge, there are no compounded IV formulations of coenzyme Q10.

The safety concerns both from nonclinical data as well as from the FAERS and CAERS databases do not raise significant concerns. Historical use in compounding, the FDA has found evidence going

back to 1999. I've got a little bit of extra information on that side and on the efficacy.

While the FDA does balance the various criteria that are coming into play for the determination of the appropriateness of coenzyme Q10 on the 503A bulks list, they do identify some concerns regarding the level of data that is available for coenzyme Q10 in the treatment of mitochondrial disorders. So I'd like to spend a few minutes to address some of those concerns.

Now as we begin, we must acknowledge the limitations in generating level 1 evidence for mitochondrial disorders. And this is a conversation that FDA did point out in the briefing information. This is a rare disease. There are no treatments which are dramatically effective and small-scale trials exist.

There are a number of other bullet points that I'm not going to spend a tremendous amount of time because we are already quite behind on the clock. But suffice it to say that there are a number of challenges to developing and generating

clinical studies to produce level 1 evidence, and much of what we see in mitochondrial disorders is of level evidence of 4.

From the FDA's assessment, they do talk specifically about primary coenzyme Q10 deficiencies, and they cite the 2015 article by Parikh, which states that coenzyme Q10 does seem to produce some very remarkable outcomes in a short period of time for these patients.

Looking at the citations that FDA has gone through regarding primary CoQ10 deficiencies, these are all level 4 evidence trials, patient populations between 1 to a maximum of 13 patients. Something that I think should be pointed out is the identification of a primary coenzyme Q10 deficiency versus secondary is conducted via genotyping. And genotyping was not the standard of practice until recently. Around 2005-2007 is when the recommendations changed.

All of the studies that were cited, only two of them did genotyping that actually identified the patients as having primary CoQ10 deficiency

Syndrome. One of these studies that was identified in the FDA's reviewed -- in the article, data identified as a primary disorder. However, the disorder that they genotyped was ETFDH mutation, which is by definition a secondary CoQ10 deficiency.

What is notable about these studies is that all of these patients had remarkable outcomes from relatively short-term therapies with coenzyme Q10. The article from 2015 by Desbats and colleagues does specifically talk about secondary coenzyme Q10 deficiencies, again noting ETFDH mutations, and that although in these situations, CoQ10 deficiency is a secondary phenomenon, it probably exacerbates the symptoms caused by the primary molecular defect. These patients often benefit from oral CoQ10 supplementation even though the response is not as dramatic as in those with primary forms.

FDA and Dr. Johnson did a good job of talking about a lot of the different clinical studies that we look at regarding what are considered secondary CoQ10 deficiencies. The

Glover study particularly looked at 1200 milligrams per day of coenzyme Q10 for 60 days, and they noted that there were minor effects on cycle exercise aerobic capacity and post-exercise lactate, but the other clinically relevant variables were not significantly altered.

Additionally, the article by Chen and colleagues supported some of that but also concluded that improvement might be noted after 6 months of coenzyme Q10 therapy. This time frame to realize clinical outcomes and clinical benefit is something that you'll see consistently throughout all of the rest of the studies.

These were two specific studies. Both of them were double-blind, crossover design trials, relatively small patient populations that were utilized. And the duration of the trial was relatively short, 2 months for the Glover study and 3 months for the Chen study. Because of the study design, the level of evidence is a little bit higher, but again, the duration of therapy was relatively short.

The Bresolin study was another one that Dr. Johnson identified in their review of coenzyme Q10. This one did go for a longer period of therapy. It was a two-phase study. The first phase was for 6 months; the second phase was for 3 months. They did identify a number of patients who had long-term -- they ended up passing away either during the trial or after the trial. They specifically noted that this had to do with the severity of the disease that some of these patients were experiencing.

They also noted that any improvement brought by CoQ10 therapy is probably maximal after 6 months; that the 3-month time frame is probably too short at the time to show differences in the clinically relevant parameters. And I misstated my comments about the patient deaths. That was another study that we'll get to, the Remes study.

Longer term studies that analyze the utilization of coenzyme Q10 for 6 months or longer do consistently show that there are benefits in clinical outcomes. The Suzuki study from 1998

specifically studied a phenotype of mitochondrial disorders known as MIDD, and one of the hallmark symptoms of these patients is dramatic hearing loss.

It was a placebo-controlled trial where the patients with coenzyme Q10 therapy after the 3-month and 6-month follow-up period did not note significant benefits, but after 6 months, 1 year, 2 year, and 3 year noted significant benefits in preventing further loss of hearing. You can see that in the graph on the far right. Your treatment group stayed relatively flat, whereas your placebo group had further loss in pure tone averages.

There's a follow-up study by Angeli. This was a smaller scale, but again were looking at MIDD patients, and they confirmed the results that were found in the Suzuki trial. This was a 1-year study, and they showed that you did not get further deterioration of your hearing with CoQ10 as opposed to placebo.

We do have a few different trials that are looking at therapy at or longer than 6 months.

Most of these are open-label designs. But when we're looking at appropriate time frames for therapy and follow-up with our patients, we do see consistent trends towards positive outcomes in clinical response.

Again, Dr. Johnson identified the Remes study as one that was particularly concerning. And in the conclusion from the Remes study, they do note specifically that the high mortality was likely to indicate the fact that severely affected patients were selected for the trial. The deaths were not directly attributed to the CoQ10 therapy.

There are a number of other studies in mitochondrial disorders. Most of them are open-label trials, small patient populations, and we see, again, consistent outcomes in clinical response with coenzyme Q10 therapy. One interesting study is the one at the very bottom of this chart, the Sacconi from 2010. They had a two-phase trial design as well.

They had 8 patients in this study that were low in intramuscular CoQ10 levels and 15 patients

who had normal intramuscular levels. And they noted that the patients who had low endogenous intramuscular CoQ10 levels, 7 of the 8 patients had ll positive clinical outcomes with muscle fatigue and exercise tolerance, whereas only 1 of the 15 patients with normal endogenous CoQ10 intramuscular levels saw significant improvement.

Now, in preparation for this meeting, we wanted to make sure that we had a thorough understanding of clinical impact on real-life patients, so as part of that, we worked with some pharmacies, compounding pharmacies, who tend to specialize in this field, who work with a lot of practitioners who are specialists in this field, and we wanted to hear from the practitioners and the patients.

This specific survey was sent to us by a patient parent. The patient was a 6-year old male who has been on compounded coenzyme Q10 for 1.7 years, specifically to treat mitochondrial disorders that were not specified further, and they're doing oral dosage forms of CoQ10.

Their statement is that CoQ10 has made a huge difference in our son's quality of life. He is less tired and can focus much better. We tried to use the over-the-counter coenzyme Q10, but it just made him hyper, and then he would crash.

Once we started using the compounded CoQ10, he was like a different child, attentive and needing less naps during the day. Gavin [ph] has a G-tube and needs his supplements compounded to go in the G-tube since he has severe acid reflux and sometimes vomits after the meds are given if by mouth.

It's a little bit difficult trying to juggle the slide's transitions because I don't have that screen right here. So I apologize for that.

In conclusion, from the evidence that we see from the primary literature, we do see that there is consistent positive outcomes in studies that are 6 months or longer, effects in an increasing exercise tolerance by reducing serum lactate levels, and it does show benefits in MIDD patients by preventing hair loss and maintaining serum

calcium levels in patients with mitochondrial disorders.

Now, that's the primary literature. Again, there are a number of expert opinion papers and guidelines on the appropriate therapy for mitochondrial patients. Natural Medicines Comprehensive Database specifically identifies that it is likely effective for mitochondrial encephalomyopathies. It has a number of different literature citations as well as getting into the safety profile for orally administered coenzyme Q10.

In 2017, we have the guideline for the diagnosis of pediatric mitochondrial disorders, and they specifically look at the oral use of coenzyme Q10 as part of this. And they say that empiric therapy with thiamine, biotin, riboflavin, and coenzyme Q10 at 15 milligrams per kilogram per day might be considered in patients with rapidly progressive or potentially life-threatening course of disease.

In the Journal of Molecular Genetics and

Metabolism, we have another study by Camp et al. in 2016, where they say that CoQ10 should be administered to most patients with a diagnosis of mitochondrial disease and not exclusively for primary CoQ10 deficiency. The five most frequently used supplements were CoQ10 at 28 percent, followed by levocarnitine, vitamin D, Riboflavin, and vitamin C. All participants who were taking CoQ10 believe that this supplement was the most beneficial in improving their or their child's symptoms.

The 2017 summary paper from the Mitochondrial Medicine Society states specifically, if you look to the right-hand column, "A combination of CoQ10 and riboflavin should be considered for ETFDH related myopathies." The current understanding of diagnosis and treatment of rare mitochondrial disorders, published by Bhaskar and colleagues in 2016 identified coenzyme Q10 as one of the mainstays of treatment for several of the top 30 mitochondrial disorders.

FDA itself has acknowledged the value of

coenzyme Q10. They have given orphan drug designation, although it is not an orphan drug-approved status to this molecule, orphan drug designation to an oral formulation of coenzyme Q10 for the treatment of mitochondrial cytopathies.

In conclusion, we do see that CoQ10 has demonstrated some beneficial effects in various mitochondrial diseases regardless of endogenous coenzyme Q10 levels. Patients with an underlying deficit in CoQ10 status may be more responsive -- and this is our primary CoQ10 deficiencies -- to therapy. Factors such as disease severity, dosage, and duration of CoQ10 therapy may influence the efficacy of treatment. And it is extremely difficult to predict how responders will respond.

It has been used in compounding since at least 1993. As I went through our files in looking for our earliest request for a. for a formulation of a customized CoQ10 dosage form, I came across a 1993 request for a pediatric patient who had difficulty swallowing liquid formulations and who

couldn't swallow oral capsules or tablets. So they wanted it into a chewable dosage form, so that was the earliest record that I have been able to find in our records. And we also do see that treatment guidelines for the population of mitochondrial patients consistently recommends CoQ10 therapy for patients with mitochondrial diseases.

So once again, I thank the FDA for their review and for their recommendation in favor of CoQ10 for the 503A bulks list, and I thank all of you for the opportunity to speak. And at this time, I'm done with my presentations. We're open for questions.

Clarifying Questions from the Committee

DR. VAIDA: All right. Thank you, Dr. Day.

There's opportunity now for the committee to ask any clarifying questions of Dr. Day. Dr. Wall?

DR. WALL: Thank you; a question about one of the studies. It was the studies in the mitochondrial disorders, the less than 6 months, and you had the Glover and the Chen.

DR. DAY: Yes, ma'am?

DR. WALL: And at the conclusion of the Glover, it said very high doses of coenzyme Q10 would be unlikely to show additional benefit and in fact may be deleterious when taken for prolonged periods. Do you know what they found; what kind of side effect profile they found in those products?

DR. DAY: I don't recall off the top of my head what the specific findings were on the side effect profile. They did not have patient dropouts due to the adverse events. And it was relatively short therapy, so in terms of how they came to that conclusion, I don't recall. It's been a little while since I've read that primary, the citation.

We do have a practitioner who has specific experience in treating these patient populations, short term and long term, so perhaps he'll be able to expand a little bit about his findings.

DR. VAIDA: Dr. Sun?

DR. SUN: Thank you for your presentation. I just have a clarifying question. You had a lot of primary literature. Are all these oral dosage forms?

DR. DAY: Yes. All of this is oral dosage forms, the CoQ10, and specifically ubiquinone.

DR. VAIDA: Before we go to Dr. Ghany, Dr. Johnson, you had something.

DR. JOHNSON: I just wanted to address Dr. Wall's question. The Glover article didn't describe adverse events, but at doses of 600 milligrams twice daily for 60 days, CoQ10 treatment was found to be positively associated with urinary levels of 8-hydroxy-2-deoxyguanosine, which the authors interpret as a marker of oxidative stress.

Their comments were that long-term high dose with high dosing with CoQ10 for prolonged periods may be deleterious. And that may be related to the mitochondrial disorder itself, so the severity of the mitochondrial disorder may impact the relationship or the therapeutics of CoQ10 and its ultimate safety. But again, because of the low number of patients, and these are anecdotal reports, but that was a suggestion.

DR. VAIDA: Dr. Ghany?

DR. GHANY: Yes. I had a couple of

questions. First, thanks for the exhaustive literature review. I noticed in your presentation that most of the studies were uncontrolled. Did you come across any placebo-controlled studies, and can you tell us whether there were any safety signals identified from such studies?

Then the second question is, can you give us a sense of how widely used this compound is in the general population? Your presentation was focused mostly on individuals with mitochondrial disease, but what about its use for other indications?

DR. DAY: Sure. So let me address the last question first because that's something that we consider when we're making the nominations to begin with. So as we nominate these substances, we understand that CoQ10 and a number of other ingredients that might be coming before the committee might be utilized in formats for a variety of conditions.

So our question that we ask ourselves is who are the patients who really require this to be compounded? Why is a manufacturer product, why is

a dietary supplement version of this product not appropriate for a particular patient or patient population?

So it is for these patients with mitochondrial disorders that we're really compounding it for. There may be other small-scale requests where a patient is on a statin and there's a drug nutrient depletion, and somebody wants to reduce pill burden. So they say, well, can we can combine things or can we do something for them or customize a dose? Those are few and far between. The vast majority from our records and our research of the requests for compounding CoQ10 are for patients with mitochondrial disorders.

So that's why this is the focus of our nomination. That's really what we're compounding it for. In my personal experience, I've never gotten a request to compound it for any other patient population.

Could you repeat your question about placebo-controlled studies? Right. The Glover trial and the Chen trial were both double-blind

placebo crossover design studies. As Dr. Johnson stated during the FDA's presentation, the studies are not typically designed to identify adverse reactions or designed to identify safety signals.

They're looking at clinical outcomes, and they may mention, and they any may identify within that what kind of safety signals there are. But if you go back into some of these charts, the outcomes and the primary measurements for these trials, primary, secondary, or even tertiary, are typically not related to the safety signals. They're looking at different biomarkers, or different physical functioning mechanisms, or parameters for these patients.

DR. VAIDA: Dr. Chelimsky?

DR. CHELIMSKY: That was a great presentation of CoQ10 for mitochondrial disorders. I was just curious, following up with Dr. Ghany's question, why did you restrict yourself -- I know that CoQ10's been published as effective in cyclic vomiting syndrome, for example, which is thought to have a mitochondrial origin. And also, you

mentioned that CoQ10 sometimes utilized, just now, to prevent statin-induced muscle symptoms.

I'm just curious. To me, at least I see the CoQ10 utilized in very large quantities in these kinds of disorders or other functional autonomic disorders. I'm just curious. Did you come across any literature on this, and can you comment on what that literature says? Or if not, if you didn't focus on it, why not?

DR. DAY: Sure. So CoQ10 has a broad spectrum of potential benefits for a number of different patient populations. I myself take CoQ10 supplements, 100 milligrams a day, nowhere near the doses that these patients are. And I can take manufactured, over-the-counter supplements.

The patient populations who really require compounded dosage forms of CoQ10 tend to be the patients with a variety of forms of mitochondrial disorders. That's where we focus our nomination because that's where we see the requests coming in specifically for compounded versions of CoQ10.

There are a lot of other patients who may

inquire about it, but once we can point them and help them identify other sources for it so it doesn't have to be customized -- there's an expense with having something tailor made for you, whether it's clothing or medicine. So once we help them identify that there are alternative options for them, then they tend to go for one of those. But it's the patients with mitochondrial disorders who don't have another choice. There is no other option.

DR. CHELIMSKY: So when you compound it, what is the difference between what they're receiving versus if I went to Costco and got the 300-milligram pill? What's the difference?

DR. DAY: So the primary difference is the dosage form and the dosage strength. A lot of these might be put into a liquid form, as you saw from the patient story where they have a G-tube or others swallowing difficulties, acid reflux, things like that. They may have malabsorption issues, so they have different routes of administration that come into play, as well as the dosage form.

I talked about that 1993 where they needed something that was a chewable. That's not available, for the most part, in manufactured dosage forms. We may have other patients who need it as liquids that are more or less concentrated.

Oftentimes -- and our open public hearing speaker may be able to speak more about this -- we don't treat patients with just CoQ10. We may initiate them on CoQ10, but mitochondrial patients, they're often treated with a combination of therapies as you saw from some of these treatment guidelines towards the end of my presentation.

So you have combination therapy that's often referred to as a mito cocktail, so the compound brings all of this together because at a high dose in combination with other medications, taking a variety of supplements, whether it's 600 milligrams a day, 300 milligrams a day of CoQ10, plus your various forms of B vitamins, and creatine, or any other supplement that might be part of your cocktail that is patient specific, it becomes very difficult to manage.

DR. CHELIMSKY: Thank you.

DR. VAIDA: Dr. Carome?

DR. CAROME: Mike Carome. In a clarification letter sent to the FDA about the nomination, PCCA asserted that coenzyme Q has a monograph with USP and the National Formulary. I'm assuming that's incorrect or we wouldn't be entertaining this nomination. But can someone clarify, the FDA or the nominator, whether that's true?

DR. SUN: I can comment on that. USP does have a dietary supplement monograph for that substance.

DR. BORMEL: So it would not be an applicable monograph.

DR. DAY: So to clarify, the statutory requirement is that there is an applicable monograph. It is FDA's interpretation the dietary supplement monographs are not applicable, but that is their interpretation. That is not written into the statute.

DR. VAIDA: Last question, Dr. Bogner?

DR. BOGNER: Robin Bogner. Thank you. You had mentioned other dosage forms. Are we talking about non-aqueous dosage forms, emulsions and maybe self-emulsifying systems? And if those are also prepared, is there a difference in dose? Does it affect the bioavailability of the coenzyme Q?

DR. DAY: No. Our compounded formulations would be considered crystalline formats, whether it's putting it into a liquid form or not making nanoemulsions, microemulsions. We're not dealing with the technology that's required to produce those on a consistent level. We're talking about utilization of coenzyme Q10 powders with specific formulations that we test and validate for the formulation process as well as the stability of those formulations.

DR BOGNER: Thank you.

DR. VAIDA: We have one final question from Dr. Venitz on the phone.

DR. VENITZ: Yes. Jurgen Venitz.

Dr. Day, I enjoyed your presentation as always. A question about the formulation. I think

you answered part of it, but the studies that you tabulated carefully -- and the study indicated the dose that was used. What formulations did they use? Were they standardized or is it reasonable to assume that the formulations could explain some of the different results that they found in those various studies? Thank you.

DR. DAY: Sure. It's an excellent question. Many of the studies utilized weight-based dosing, so each patient is going to have a custom calculated dose. These are all oral dosage forms. There are some studies that utilized a standardized dose per day, such as the 150 milligrams or 100 milligrams per day. So there is a little bit of variance in how these researchers approach the dosing protocols for their studies.

If you look to the guidelines and expert opinion sections, the 2017 recommendation was weight based. The 2016 recommendation was -- let me pull that slide up. I believe that one was standardized. So there's a little bit of a variance in how some of these opinion papers are

published and what kind of dosing they're recommending.

DR. VENITZ: But did they use the same formulation? Because it looks like the formulation very much determines bioavailability and [indiscernible].

DR. DAY: None of these studies specifically identified using nanoemulsion or microemulsion formulations, so we are operating under the assumption -- unless FDA or Dr. Johnson has other information, we're operating under the assumption that these were all utilizing the crystalline formats of coenzyme Q10.

DR. VENITZ: Thank you.

DR. VAIDA: Dr. Johnson?

DR. JOHNSON: Sue Johnson. I have a backup slide to show one study that compares various formulations of ubiquinone and ubiquinol if you'd like to see it.

There isn't a lot of pharmacokinetic information from humans about CoQ10 as it's an endogenous substance. Most of the pharmacokinetic

information that's out there, and there isn't very much, comes from manufacturers who are trying to establish whether or not their formulations have improved bioavailability.

In this slide, it was one company who makes formulations A, B, and C, and D was from a different company. It was an off-the-shelf product. In part, this addresses ubiquinol versus ubiquinone administration interests. The MMS guidelines actually recommend that ubiquinol be used as opposed to ubiquinone because ubiquinol may have slightly higher bioavailability. As we said before, ubiquinol was presented to the PCAC in May 2017, and its proposed use was as an adjunct in glycemic control, but again for oral use.

Single doses of 180 milligrams using these various formulations were administered. And what was measured was total coenzyme Q in the plasma, so that's ubiquinol plus ubiquinone. And if you look at formulation A and C, those are ubiquinone, and they were solubilized using emulsifying agents or an oil-based vehicle. A was a liquid; B was a soft

gel capsule.

Treatment B was ubiquinol in soft gel capsules and treatment D was a solubilized powder, so there wasn't -- oh, sorry, a non-solubilized powder. So there wasn't an effort to increase solubilization of the powder contained in a hard capsule. Because there were only 9 subjects, the statistical power was not very great. But you can see for the concentration in plasma at 12 hours, formulation A and formulation B exceeded the levels of formulation C at p less than .05.

I think Dr. Ganley's observed that A, B, and C look quite a bit alike, but if you notice the numerical trend, B, ubiquinol, is slightly greater in each of the realms. In A, B, and C, ubiquinones that are solubilized and ubiquinol exceed the levels of ubiquinone in a non-solubilized powder. So that tells us a little bit about ubiquinol versus ubiquinone and the effect of formulation.

Open Public Hearing

DR. VAIDA: Thank you. We'll now move to the open public hearing portion, session 2. And I

think we have one speaker.

DR. KORSON: Hi. My name is Dr. Mark Korson. I'm a metabolic or biochemical geneticist from VMP Genetics and spent the last 25 years working in the area of metabolic and mitochondrial disease.

Identifying the patient for whom coenzyme Q10 is appropriate is still a challenge given the limits of what we know in the field of mitochondrial medicine. In some cases such as coenzyme Q10 deficiency, the biochemistry defines the problem, the treatment is clear, and the patients respond as one might predict. But for the greater than 200 different mitochondrial disorders, mitochondrial disease is not a single entity. The benefit of CoQ10 is not always clear.

True. All these disorders result in some net deficiency of energy production, and yes, coenzyme Q10 helps to transfer high-energy electrons through the electron transport chain, the final common pathway of energy production. It also functions as an antioxidant, which is important

given the role of oxidative stress in this patient population, among other functions.

Are all these patients suitable candidates for CoQ10 then? No. But given the absence of therapies for this cluster of diseases that address the root problem, given the dramatic impact of these disorders on functioning quality of life and the low incidence and transient nature of the side effects associated with supplementation, this is a consideration.

While the consensus reports by the Mitochondrial Medicine Society and/or its members identify the use of CoQ10 in the majority of patients with mitochondrial disease prescribed by experts in this area of medicine, I'm speaking here to a particular symptom set to focus on.

Supporting a trial of CoQ10 in patients with disease, especially when it's associated with fatigue or weakness that impacts functioning like self care, participating in home life, learning at school, or working and staying productive, this doesn't mean that it doesn't also have a positive

impact in other aspects of mitochondrial disease, but it's harder to appreciate the benefit given the slow course of the disease.

In my practice, we have treated over 250 patients, patients with documented mitochondrial disease or who have significant evidence to support such a diagnosis, recognizing that genetic confirmation of a diagnosis only occurs about 60 percent of the time. These patients may or may not have a demonstrable deficiency of leukocyte coenzyme Q10.

The dosing was obtained by consensus reports of mitochondrial disease provider practices. These patients are provided a trial of CoQ10 for at least 3 months given the time it takes to raise blood levels and the time needed to assess improvement or side effects. Since a cocktail usually involves more than one supplement, it's not always practical to provide a separate period of introduction for more than a few months.

Assessing the benefits of CoQ10 -- since ongoing therapy is a commitment, a disease that is

already incredibly burdensome medically, psychologically, and financially -- is important. We do look at biochemical levels of CoQ10 to assess compliance with the supplement but don't generally see a correlation between levels and benefits. And in general, only one supplement is started at a time to avoid confusion.

Relying on patient accounts or even parental observations, while important, is not sufficient. As a matter of protocol, I recommend to parents that they not inform teachers, physical or occupational therapists, activity leaders, or others who observe the patient on a regular basis that the patient is beginning the supplement.

People like to see a child do well, and if informed beforehand, they might be biased in monitoring a child for improvement. If kept informed, and if they observe a sustained change in activity, attention, or stamina, that could be significant. And based on responses, the majority of patients and families through observers noted improvement of functioning while on the supplement.

Why do I place importance on the observation, individuals who are not medically trained? Because these observations are generally more balanced than the assessment done by a physician who sees a patient for only 20 or 30 minutes in his/her office. That time limited observation may not at all be representative of a patient's normal activity level, especially when it occurs in an intimidating medical office.

Around the area of weakness and fatigue, I look for improvement in activity, stamina, and attention, prospectively once the supplement is started. Sometimes the benefit is not observed after starting the supplement and only when it's taken away. The improvement is more apparent in retrospect.

I have prescribed CoQ10 in the morning and midday because too close to bedtime or too large a daily dose can result in difficulty falling asleep or staying asleep. When there's GI upset, is it due to the supplement or is it due to the presence of pills in a stomach that doesn't empty properly?

Gastroparesis is a common symptom in patients with mitochondrial disease. Following the recommendations of Tarnopolsky of McMaster University, we also utilize CoQ10 in conjunction with other mitochondria relevant supplements in an attempt to impact different stages of energy production, looking for a synergistic effect.

In summary, there are few therapeutic options for this group of disorders. It is well tolerated, and here's an opportunity to impact a particularly troublesome day-to-day feature of the disease. Thank you.

Committee Discussion and Vote

DR. VAIDA: Thank you. That now concludes our open public portion of the meeting, and we'll no longer take comments from the audience. We'll now have committee discussion and a vote. The vote will be FDA is proposing that coenzyme Q10 for oral administration be included on the 503A bulks list. Should coenzyme Q10 for oral administration be placed on the list?

If you vote no, you are recommending FDA not

place the bulk drug substance on the 503A bulks list. It is now open for discussion before a vote. Any discussion or on the phone?:

(No response.)

DR. VAIDA: Hearing none, remember, you have the three options on your device: yes, no, or abstain. Please press firmly on your microphone that corresponds to your vote. You have approximately 15 seconds to vote. After you made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again.

(Voting.)

DR. FAJICULAY: For the record, the results are 17, yes; zero, no; zero abstain.

DR. VAIDA: All right. Thank you.

We'll now go around the room and please state your name, how you voted, and any comment. I can start on my left. Dr. Hoag?

DR. HOAG: Steve Hoag, and I voted yes for the reasons given by the FDA and the nominators. I thought that the data and information they

presented made sense to put this on the list.

MR. HUMPHREY: William Humphrey. I voted yes. I think the presentation showed that it met the evaluation criteria.

DR. PATEL: Kuldip Patel. I voted yes. Clearly, it has a place in therapy for treating mitochondrial disorders.

DR. VAIDA: Now, our two committee members on the phone, beginning with Dr. Gulur.

DR. GULUR: This is Dr. Gulur. I voted yes for the reasons already stated by other members.

DR. VAIDA: Dr. Venitz?

(No response.)

DR. VAIDA: I'll start again. Allen Vaida. I voted yes for the reasons stated.

DR. BOGNER: Robin Bogner. I voted yes. It was a compelling case. I have some comments, though.

In general, in the recommendations section of the evaluation by the FDA, the physical and chemical characterization portion is not very detailed. I see words like "stable" versus "not

stable" and it's never one or the other, with no delineation as to whether it's physical or chemical. For those of us that that's our field, more detail would be helpful in determining whether the substance is well characterized.

Also, particularly for these poorly soluble substances, when the oral doses are given, when showing bioavailability or efficacy, it would be helpful when something is known about the formulation, that that also be included so that we could understand it better.

DR. CAROME: Mike Carome. I voted yes for many of the reasons already stated.

DR. WALL: Donna Wall. I voted yes for the reasons stated.

DR. JUNGMAN: Elizabeth Jungman. I also voted yes. It seems to meet a need for a patient population that doesn't have a lot of options without significant safety concerns.

DR. DESAI: Seemal Desai. I also voted yes for the reasons already stated.

DR. SUN: Jeanne Sun. I voted yes because

it's well characterized, and the USP have a dietary supplement monograph for it, and I think there is very compelling efficacy and safety data around it.

DR. IKONOMIDOU: Chris Ikonomidou. I voted yes for all the reasons stated.

DR. KHURANA: Sandeep Khurana. I voted. yes.

DR. CHELIMSKY: Tom Chelimsky. I voted yes. I'll just add a comment, my own personal experience. I see a lot of mitochondrial disorders, and I have seen superb responses to CoQ10. They're few and far between, but they really are impressive.

DR. GHANY: This is Marc Ghany. I voted yes. I think the risk-benefit analysis favors continued use of this compound in patients with mitochondrial disorders.

Adjournment

DR. VAIDA: Thank you. We'll now take a break for lunch. And if we could all meet back here by 1:15.

DR. VENITZ: Can I add a comment? I got cut

off.

DR. VAIDA: Please, Dr. Venitz, your vote?

DR. VENITZ: So the -- [inaudible - audio gap].

DR. VAIDA: Could you give your vote and any comment?

DR. VENITZ: Yes. A comment got cut off after my vote. I did vote yes. Just like Dr. Bogner, I'm concerned about solubility and bioavailability of a poorly soluble drug like CoQ10. There is evidence to show that the formulation has a major impact on its systemic levels, systemic exposures.

What comforted me in terms of my decision, though, was the fact that in practice, treating patients seemed to measure levels of CoQ10 to assess the oil absorption. Thank you.

DR. VAIDA: Thank you.

Remember, we'll convene back here at 1:15.

(Whereupon, at 12:40 p.m., the morning session was adjourned.)