FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Tuesday, October 27, 2015

10:00 a.m. to 12:30 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

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Division of Advisory Committee and

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Office of Executive Programs

Center for Drug Evaluation and Research

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Tarrytown, New York

William Mixon, RPh, MS, FIACP

Owner-Manager

The Compounding Pharmacy

Hickory, North Carolina

TEMPORARY MEMBERS (Voting)

John Cush, MD

(Participation in methylsulfonylmethane discussion via telephone) October 27th only

Professor of Medicine and Rheumatology

Baylor University Medical Center

Director of Clinical Rheumatology

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Dallas, Texas

Antonio Fojo, MD, PhD

(Participation in germanium, curcumin, deoxy-d-glucose, rubidium discussions via telephone)

October 27th only

Professor of Medicine

Division of Medical Oncology

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P R O C E E D I N G S

(10:00 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning. Welcome to the Pharmaceutical Compounding Advisory Committee meeting. I would like, first, to remind everyone present to please silence your cellphones, Blackberries, and other devices if you have not already done so.

I would also like to identify the FDA press contact for this open session meeting, Ms. Lyndsay Meyer. If you are present, please stand. Right there in the back.

Let me then officially call the meeting to order. Good morning. My name is Jurgen Venitz. I'm the chair of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee to order.

I will now ask those at the table, including FDA staff and committee members, to introduce themselves starting with the FDA to my left and

moving along to the right side, ending with one of the industry representatives, Dr. Ned Braunstein. So let's start to my left.

MR. PACE: Hi, my name is Brad Pace. I am a health fraud branch chief in CDER's Office of Compliance.

DR. LEE: Hi, my name is Sau Larry Lee. I'm the associate director for science from the Office of Pharmaceutical Quality.

MR. FLAHIVE: Good morning. My name is Jim Flahive, and I am a regulatory counsel in CDER's Office of Compliance.

MS. AXELRAD: I'm Jane Axelrad, the associate director for policy in the Center for Drug Evaluation and Research and the agency lead on compounding.

MS. BORMEL: I'm Gail Bormel. I'm the acting division director for the Division of Prescription Drugs in CDER's Office of Compliance.

DR. HONG: I'm Cindy Hong, acting designated federal officer for PCAC.

DR. VENITZ: I'm Jurgen Venitz, clinical

pharmacologist and a professor at Virginia Commonwealth University.

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

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

MR. HUMPHREY: William Humphrey. I'm the director of pharmacy operations at St. Jude Children's Research Hospital in Memphis.

MS. DAVIDSON: I'm Gigi Davidson. I am USP's representative to the Pharmacy Compounding Advisory Committee, and I'm the director of pharmacy at North Carolina State University, College of Veterinary Medicine.

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

DR. WALL: I'm Donna Wall. I'm NABP's representative, and I am a clinical pharmacist at University Hospital in Indianapolis, Indiana.

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

MR. MIXON: Good morning. Bill Mixon from Hickory, North Carolina. I own The Compounding Pharmacy. I am a non-voting industry member.

DR. BRAUNSTEIN: Ned Braunstein. I'm senior vice president and head of regulatory affairs at Regeneron Pharmaceuticals. I'm the pharmaceutical and biotech industry representative on the committee.

DR. VENITZ: Thank you all for attending the meeting. Let me read in the record the official introduction to this meeting.

DR. CUSH: On the phone?

DR. VENITZ: Okay.

DR. CUSH: Would you like us to introduce ourselves?

DR. VENITZ: Yes, please go ahead and introduce yourself.

DR. CUSH: My name is Dr. John Cush. I'm a rheumatologist. I'm director of clinical rheumatology at the Baylor Research Institute in

Dallas, Texas.

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

DR. FOJO: I'm Dr. Tito Fojo. I'm a medical oncologist at Columbia University Medical Center.

DR. VENITZ: Thank you for introducing yourselves. Now, let's go through the official introductory proceedings.

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

at hand take place in the open forum of the meeting.

We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Over the next two days, we will cover nine drug substances. On the morning of the first day, today, we will discuss two bulk drug substances nominated for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug and Cosmetic Act: methylsulfonylmethane and curcumin.

During session 1, we will hear presentations from FDA, ask clarifying questions, and hear nominator presentations. This afternoon, we will continue discussing the two bulk drug substances discussed in the morning, and hold an open public hearing, and have committee discussion and voting

on each of those two substances.

We will also discuss three additional bulk drug substances nominated for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A of the FD&C Act: germanium sesquioxide, rubidium chloride, and deoxy-D-glucose. Additionally, we will hear nominator presentations, hold an open public hearing, and have committee discussion and voting on each of the three substances.

Let us begin. We will now have Dr. Cindy Hong read the conflict of interest statement. Dr. Hong?

Conflict of Interest Statement

DR. HONG: The Food and Drug Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of Boards of Pharmacy, the United States Pharmacopeia, and the industry representatives, all members and temporary voting members of the committee are

special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found in 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the

government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

On October 27, 2015, the committee will discuss five bulk drug substances nominated for inclusion under Section 503A bulk drug substance list. FDA intends to discuss the following nominated bulk drug substances: methylsulfonylmethane, curcumin, germanium sesquioxide, rubidium chloride, and deoxy-D-glucose. The nominators of these substances will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which specific matters related to the five bulk drug substances will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the bulk drug substances at issue.

We would like to note that Dr. Donna Wall is a representative member from the National Association of Boards of Pharmacy and Ms. Gigi Davidson is a representative member from the United States Pharmacopeia.

Section 102 of the Drug Quality and Security Act amended the federal Food, Drug, and Cosmetic Act with respect to the Advisory Committee on Compounding to include representatives from the

NABP and the USP. Their role is to provide the committee with the points of view of the NABP and the USP.

Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue. Instead, they serve as a voice of the NABP and USP, entities with a financial or other stake in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein and Mr. William Mixon are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals and Mr. Mixon is the owner of The Compounding Pharmacy.

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

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

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

DR. VENITZ: Thank you. Just to point out, we do have two voting special government employees that have already introduced themselves by phone, and that's Dr. Cush and Dr. Fojo.

We will now proceed with the FDA introductory remarks from Ms. Jane Axelrad, the associate director for policy in the Center for Drug Evaluation Research and the agency lead on compounding. Ms. Axelrad?

FDA Introductory Remarks - Jane Axelrad

MS. AXELRAD: Good morning. I'd like to welcome you to the third meeting of the Pharmacy

Compounding Advisory Committee. It's been a very busy year for all of us, and I think the committee has accomplished quite a lot.

You've provided us with advice on 29 drugs that are under consideration for the list of drugs that may not be compounded under the exemptions provided by Sections 503A and 503B because they or their components have been withdrawn or removed from the market because they have been found to be unsafe or ineffective. As you may recall, there is a list of drugs that have been withdrawn or removed from the market at 21 CFR 216.24, and we propose to amend it.

You also provided advice on modifications to the listings of two drugs that are already on the list. We are continuing our work on the two rulemakings that would amend the list. One would be the final rule regarding the 25 drugs that were proposed for inclusion on the list in July 2014 that you discussed in the February meeting, taking into consideration the public comments that were received on that proposed rule and your input at

the first meeting of the committee, and also on the modifications to the list.

We're also working on a new proposed rule with regard to the four substances that we discussed at the last meeting of the committee. As you know, as I've talked about before, rulemaking takes quite a bit of time, but I wanted you to know that we are actively working on these.

At the last two meetings, we also discussed the list of bulk drug substances that can be used in compounding by entities seeking to qualify for the exemptions under Section 503A, and this is going to be the focus of our meeting over the next two days.

Just to refresh your recollection, under Section 503A, a licensed pharmacy or a licensed physician can compound a drug product using bulk drug substances that comply with the standards of an applicable USP or National Formulary monograph if a monograph exists and the USP chapter on pharmacy compounding.

If such a monograph doesn't exist, they can

compound with drug substances that are components of drugs that are approved by the Secretary; or if a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, it appears on a list developed by the Secretary through regulation issued by the Secretary under subsection (c) of Section 503A. This is the list, of course, that we've been discussing.

At the first meeting of the committee, we discussed the criteria we proposed to use to evaluate the nominated substances. Over the course of the first and second meetings, we discussed 10 of the nominated substances and obtained your recommendations on this. We are also working on the rulemaking that would begin the process of creating the list, taking into account the advice that you gave us.

To continue with what we've covered at our last meeting in June, we also discussed the criteria that we propose to use to evaluate drugs and categories of drugs that would be included on

the difficult-to-compound list and should not be compounded under either Section 503A or 503B.

One of the conditions under 503A is that to qualify for the exemptions under that provision, a compounder cannot compound a drug product that is identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding, that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.

We had a thoughtful discussion at the last meeting of those proposed criteria, and you made recommendations about those criteria that we're considering. I had hoped to be able to discuss one or more categories of drugs that we were considering for inclusion on that list at this meeting. But because of the work required to prepare for that discussion and the full agenda that we already had for this meeting, we decided to postpone it. We hope to begin those discussions at the next meeting of the committee.

Over the next two days, we'll be discussing

nine additional bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding by entities seeking to qualify for the exemptions under Section 503A.

We had hoped to discuss another drug, quinacrine, at this meeting. We intended to discuss adding all forms of quinacrine for intrauterine administration to the withdrawn and removed list and also to discuss the nomination of quinacrine hydrochloride for inclusion on the 503A list of bulk drug substances that can be used in compounding.

We had announced our intention to present on quinacrine at this meeting for both lists in the federal register notice, and we put a placeholder for it in the background materials. However, because the issues raised by this drug are complex, not the least of which is because it's under consideration for the withdrawn and removed list and also nominated for the list that can be used to compound, we just weren't able to complete our work on the background materials in time to discuss it.

So we decided to postpone its consideration to a future meeting.

I'm really sorry for any confusion that this might've caused with regard to the change in the agenda and the background materials. But I heard that some members of the committee were not sorry to be starting at 10 o'clock. We decided to start at 10:00 so that we didn't have to redo the entire agenda and the announced public hearing sessions and everything.

In addition, I want to provide an update about two draft guidances that we published yesterday. At the last meeting, I talked about our processes for developing the list of bulk drug substances that can be used in compounding by entities seeking to compound drugs that qualify for the exemptions under Sections 503A and 503B. I noted that we were working on guidance that would describe our interim policy regarding compounding with bulk drug substances while we're developing the list.

Yesterday, we published two draft guidances,

one that addresses the bulk drug substances that can be used to compound under Section 503A and one that addresses bulk drug substances that can be used to compound under Section 503B while we're developing the list. Although they are not a topic for discussion at this meeting, I really wanted to give you an update on them because of their relevance to the discussions today and tomorrow.

In a few minutes, I'm going to tell you about them. And then after I do that, we're going to provide some background information about botanical drugs and dietary supplements because some of the substances the committee will be considering today and tomorrow are botanicals and some are also marketed as dietary supplements. We hope that this background material will be useful to the committee during its discussions.

Back to the two draft guidances that describe our policies with regard to compounding from bulk drug substances while we're developing a list of bulk drug substances that can be used by compounders seeking to qualify for the exemptions

under Section 503A and 503B. I'm going to talk about the 503A guidance first. There's one for 503A and one for 503B.

As we've discussed before, approximately 740 unique substances were nominated in response to our July 2014 request for nominations for the 503A bulks list, including some that are already eligible for compounding under Section 503A and don't need to appear on the list, as well as some that are not eligible for use in compounding because they are biological products, radiopharmaceuticals, or on the list of substances that have been withdrawn or removed from the market for reasons of safety or effectiveness. In addition, one of the nominated substances is a Schedule 1 substance that has no currently accepted medical use.

Of the substances that may be eligible for use in compounding under Section 503A, about 390 substances were nominated without sufficient supporting information for FDA to actually even begin to evaluate them. Approximately,

65 substances were nominated with adequate support.

As indicated in the draft guidance, we published four lists of nominated substances on its website that are related to the 503A bulk drug substances list. List 1 is bulk drug substances that were nominated with sufficient support and therefore are under evaluation. List 2 will include bulk drug substances that raise safety concerns and that we don't think should be compounded in the interim while we're developing the list.

List 3 are bulk drug substances nominated without adequate support because we thought it would be helpful for people to see these are the ones that we thought had enough support and these are the ones that didn't. List 4, which will be developed in the future -- there's nothing on it yet -- is bulk drug substances that may not be used to compound drug products.

We are publishing two sets of lists with the same four categories. One of them is under 503A and goes with the 503A guidance. One is on 503B

and goes with the 503B guidance. The lists are going to include different drugs because there are different criteria for the 503A and 503B lists. Different substances were nominated for each, although there is some overlap. And different processes exist for developing the bulks list under 503A and 503B.

For example, as I said, the 503A list 4 will be developed through the rulemaking process required by Section 503A. When we propose drugs to be included on the list in the rulemaking, we'll also address the drugs that we've evaluated and decided not to put on the list. At the end of the rulemaking, they will appear on list 4. So that's what will happen there.

The draft guidance under 503A says that until a substance has been considered and is identified in a final rule as being included or in the preamble of the final rule as not included on the 503A bulks list, FDA does not intend to take action against the state licensed pharmacy, federal facility, or licensed physician compounding a drug

product, using a bulk drug substance that is not a component of an FDA-approved product or that's not the subject of an applicable USP or NF monograph, provided that several conditions are met, including that the substances may be eligible for inclusion on a 503 bulks list, was nominated with sufficient support for FDA to evaluate them and has not been identified by FDA as a substance that appears to present safety concerns.

So that's basically a long-winded way of saying you can compound with the things that are on list 1.

The draft guidance for bulk drug substances under consideration for the 503B bulks list is very similar but because this committee has not yet dealt with any bulk drug substances under consideration for the 503B bulks list, let me just remind you of what that list is.

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for the exemptions under Section 503B is that the facility does not compound drug products

using a bulk drug substance unless the substance appears on a list published by the Secretary identifying bulk drug substances for which there is a clinical need, or the drug product that's compounded from such a bulk drug substance appears on the drug shortage list in effect under Section 506E -- that's the FDA drug shortage list -- at the time of compounding distribution and dispensing.

For the 503B list, about 2600 unique substances were nominated in response to the July 2014 request for nominations. Some, like the 503A list, are not eligible for use in compounding because, as was the case for nominations for the 503A list, they're biologicals, radiopharmaceuticals, or on the list of substances that have been withdrawn or removed from the market for reasons of safety or effectiveness.

In addition, as I noted for the 503A list, one of the nominated substances is a Schedule 1 substance that currently has no accepted medical use.

Of the substances that can be used in compounding under Section 503B, 650 substances were nominated without sufficient supporting evidence for FDA to evaluate them. About 190 substances were nominated with adequate supporting evidence. Like we're doing for the bulk drug substances under consideration for the 503A bulks list, the draft guidance for the 503B bulks list says that FDA has published four lists of nominated bulk drug substances on its website. I'm not going to go over them. It's the same four lists, bulk drug substances.

List 1 is the key because it's bulk drug substances that had adequate support for evaluation. There are about 190 substances on there. Those are the ones that can continue to be compounded while we're developing the list. List 4 will be the list of substances that can't be used that we've evaluated, and it will be developed through the process that we have for evaluating drugs for the 503B list.

The policy is very similar. The draft

guidance says that until FDA publishes its final determination in the federal register that a bulk drug substance may or may not be used in compounding under Section 503B, we don't intend to take action against an outsourcing facility that's compounding a drug product using a bulk drug substance that appears on list 1. We've also said that list 1 is the one that was adequately supported.

In addition, to take into account, the other circumstances in which an outsourcing facility can compound from a bulk drug substance, the draft guidance says that FDA does not intend to take action against an outsourcing facility for compounding a drug product if the drug product compounded from the bulk drug substance appears on the FDA drug shortage list. There are two times that you can compound from a bulk under 503B and one of them references the shortage list.

These guidances are in draft and out for public comment, but we intend to apply an enforcement policy that's consistent with the draft

guidances during the public comment period.

In addition to publishing the two draft guidances and the lists, we're also establishing two public dockets where substances can be re-nominated with sufficient supporting information or where new nominations can be submitted of bulk drug substances that were not previously nominated for consideration for the two lists. One docket is for 503A and one is for 503B.

We're going to consider the re-nominated or new substances after completing the reviews of the substances that have already been nominated with adequate support to allow us to conduct an evaluation.

That brings you up-to-date on these recently published guidances and the federal register notices establishing the dockets. I know this is really complicated with four lists for each guidance, but I want to make a few points about this.

In the final guidance that we issued last March regarding compounding under Section 503A, we

stated that we would not allow compounding from bulks that were not on the 503A list while the lists were being developed. We flat out said you can't compound unless it's on the list. The interim policy we just announced is a significant relaxation of that policy because we are going to allow compounding with the bulk drug substances, or most of them, that were nominated with sufficient support and that are under evaluation until we make a final determination on whether to put them on the list through rulemaking.

Second, we gave nominators two chances to provide us with basic information about each nominated substance. Many nominators did give us sufficient information to conduct an evaluation; that's why we have the 64, 65 substances that we're evaluating and bringing to the committee. But we've determined that we shouldn't allow continued compounding with substances for which we have not received even the most basic information about the need to compound with those substances that we can even begin to do an evaluation.

Third, we provided a process through the two dockets to provide supporting information and to submit new nominations. We've stated that we're going to wait to review newly nominated or re-nominated substances until we complete the review of the 64 or 65 substances that have been adequately supported. We think that's only fair to the people who nominated those substances with sufficient support to get through those and bring them to the committee before we start on new things.

Fourth, we've provided list 2, which includes substances that should not be compounded in the interim while we're developing the list because we have significant safety concerns about the substances. So far, only one substance is included on that list and that's domperidone.

We first issued warnings about domperidone in 2004, and we've issued over 20 warning letters citing compounders for compounding with domperidone because of our significant safety concerns.

We're going to be discussing domperidone

with the committee tomorrow afternoon, and we look forward to hearing your views about it. But because the draft guidances and lists were published yesterday, before we had the committee's discussion and to be consistent with our past actions and our safety concerns that exist today as reflected in the briefing materials, we have placed domperidone on list 2 as something that shouldn't be compounded even while we're evaluating and going through the rulemaking to make the final determination.

With all of that and before I give you a little introduction about the next two speakers, let me ask if anybody has any clarifying questions about the bulk drug substance interim policy. I can take a few questions.

DR. VENITZ: Any clarifying questions for Dr. Axelrad?

(No response.)

DR. VENITZ: It doesn't look like it. Thank you very much.

MS. AXELRAD: Okay. I just want to

introduce what's coming up next. We're going to provide some background material, a short presentation about how we, in the Center for Drug Evaluation and Research, look at botanical drug products that are being considered for market approval. Two of those substances that you're going to be discussing today and tomorrow are botanicals, that is drug substances obtained from plants.

We have a group in the center that specializes in reviews of botanical drug substances, and they have been involved in the review of the botanical substances that were nominated for inclusion on the list. We thought it would be useful for you to hear a little bit about what we've learned about botanicals and some of the science behind demonstrating that a botanical is safe and effective for a particular use.

Although the information we're going to present is derived from our reviews of new drug applications, it's information that should be kept in mind when determining whether the botanicals

that we're going to discuss at the meeting should be put on the 503A bulk drug substance list.

The second presentation that you're going to hear is about dietary supplements and their regulatory status. Several of the bulk drug substances that we're going to discuss today are also marketed as dietary ingredients in dietary supplements.

At the last meeting, FDA presented to the committee two dietary supplements that were nominated for the 503A bulk drug substances list, N-acetyl-D-glucosamine and oxitriptan. There is a USP dietary supplement monograph for N-acetyl-D-glucosamine.

At the meeting, some questions came up about how dietary supplements are regulated, the USP dietary supplement monographs, and why being the subject of a USP dietary supplement monograph was not enough to allow a substance to be compounded without being on the 503A bulk drug substance list.

Mr. Pace is going to give you some information about how dietary supplements are

regulated and how they differ from drugs, and then I'm going to talk about the USP dietary supplement monographs relative to the 503A bulk drug substance list.

DR. VENITZ: Thank you. Dr. Pace, you're going to be next.

MS. AXELRAD: Dr. Lee first. (Off mic)

DR. VENITZ: Okay. Dr. Lee, please, go ahead and go first.

While he's getting ready for the presentation, I'll remind the committee, we hold back the clarifying questions until we have listened to both presentations. Dr. Lee?

FDA Presentation - Sau Lee

DR. LEE: Hello. Good morning, everyone. Welcome to White Oak. Today, I'm going to provide you some background information regarding our experience and our scientific perspective on botanical drug development and quality standards.

You may ask us what the botanical drugs are. From FDA's perspective, the term "botanical" means products that include plants, materials, algae,

microscopic fungi, or their combinations. Botanicals are complex or heterogeneous mixtures derived from a botanical source. Therefore, they do not include highly purified substances, fermentation products, and products derived from animals, minerals, or genetically-modified botanical species.

Botanical drugs can be available in various dosage forms such as a solution, powder, tablet, capsule, topical, or injectable. Currently, we have approved two botanical new drug applications, NDAs. The first one is the topical ointment, Veregen, which is used for the treatment of genital warts. The second one is the solid oral Fulyzaq, which is used for the treatment of HIV AIDS-related diarrhea.

As you can see here, these two pictures show the botanical raw materials or plants used to make these two drugs. The top one is the green tea leaves used to make Veregen and the bottom one is the Croton lechleri plant used to make Fulyzaq.

As I just mentioned, botanicals are

heterogeneous mixtures comprised of many or multiple chemical components. These botanical mixtures may contain more than one active component meaningfully contributing to the entire mixture, physiological, or pharmacological action.

In general, chemical components in a botanical mixture, as well as their potential biological activities are not well-characterized and understood. Furthermore, botanicals or botanical products exhibit batch-to-batch variability considerably larger than that for non-botanical products such as chemically synthesized small molecule drug products.

I also want to emphasize one more thing, is that a certain degree of variability is generally expected for botanical products as it is inherent to the seasonal variations in the botanical raw materials.

Based on what I just described, it is pretty clear that the complexity of botanicals is derived from the fact that they contain multiple or many chemical components, have no well-defined active

components, and exhibit a considerable batch-to-batch variation.

Nevertheless, for new botanicals intended to be marketed as FDA-approved drugs in the United States, these botanical products are expected to meet the same standards as non-botanical drugs such as the chemically-synthesized, highly purified, small molecule drug products for quality, safety, and efficacy.

However, there are some unique considerations due to their unique characteristics, as well as complexity. First, it's not difficult to imagine that the quality control of botanicals is very challenging as the entire mixture and its added components generally cannot be well-characterized by analytical means.

Therefore, the conventional quality control strategy for small molecule drugs under the NDA pathway, which is primarily based on the chemical testing, is not sufficient for ensuring the consistency of quality for botanical products. Because of this, we actually allow research and

really come up with a more practical approach to ensure the quality for botanical drug, which I will elaborate a little bit more later in this presentation.

Since botanicals have a long history of prior human use experience, for example, such as dietary supplement or traditional medicines in other countries, this information may provide some indication about the safety profile of botanical drug candidates for early phase trials, which may impact our early safety IND evaluation.

Finally, as I mentioned before, a certain degree of variability is expected for botanical products. Therefore, the late phase clinical studies should be designed in a way to gain some understanding about the effects of batch-to-batch variation, for example, in botanical composition on the safety and efficacy of botanical drug products. This information is particularly critical to our strategy for quality control, as I will elaborate a little bit more later in this presentation.

From a quality perspective, in order to

overcome our current limited ability to characterize the entire botanical mixture, as well as to ensure that the marketed botanical products deliver a therapeutic effect consistent with that observed for products tested in the clinical studies, we have developed a scientific approach, the so-called totality of evidence approach, that utilizes multidisciplinary information to ensure the consistent quality of botanical drugs in order to ensure they deliver the consistent therapeutic effect from batch to batch.

In this approach, in addition to the conventional quality data, including data from analytical testing and manufacturing process control, we also consider additional quality measures as well as evidence, including raw material control, clinically relevant bioassay, and other data, including clinical data on dose response generated based on multiple batch of botanical products and to really ensure the consistent quality for botanical products.

It is pretty difficult to explain this

concept without going through a real example, so let me just use the case study of Fulyzaq, which we just approved -- this is one of the botanical products we approved -- to illustrate the scientific concept of this totality of evidence approach.

Before I explain the scientific aspect of this approach, let me just give you some background information about this product. Fulyzaq is a delayed-release oral tablet containing 125 milligram of crofelemer. This drug substance, crofelemer, is derived from the crude plant latex of Croton lechleri. This botanical raw material, which is known as Dragon's Blood -- it's not difficult to see why they give this name if you look at the picture -- is commonly used as an herbal medicine for treating diarrhea in South Africa before they gained approval from the United States. This drug is the first FDA-approved drug for symptomatic relief of noninfectious diarrhea in patients with HIV and AIDS on antiretroviral therapy.

This drug substance, crofelemer, is a complex mixture of oligomers that can vary in composition, sequence, and length as illustrated in this chromatograph of corresponding botanical raw material.

One thing I would like to emphasize here is that the chromatograph of respective drug substance, crofelemer, although not shown here because of proprietary reasons, also share a very similar feature with many overlapping peaks. From the chemistry perspective, you can immediately see that the quality control of this botanical mixture is very challenging because the conventional HPLC method we usually use for the quality control of small molecule is not sufficient to provide adequate separation and quantification of each individual oligomer in the mixture.

Although we asked the manufacturer to use more advanced and multiple analytical methods to further characterize the structural signature of crofelemer for the purpose of quality control, we ultimately determined that these analytical data

were not sufficient to support the characterization and therefore, the quality control of this complex botanical mixture. Therefore, we need additional quality control measures and evidence in conjunction with chemical testing to really ensure the quality for this botanical product.

Since botanical raw materials collected from different regions or by using different practices may vary significantly in terms of their chemical compositions, it is pretty clear that the first control measure was to rely on botanical raw material control, including the implementation of good agricultural and collection practices, as well as restricted harvesting of botanical raw material to specific ecogeographic regions. This quality control can help to reduce dramatically the variability of the plant and raw material levels.

The second measure was to overcome our limited ability to characterize the entire botanical mixture by analytical means, was to develop a bioassay that reflects the well-known mechanism of action for crofelemers, which is based

on the inhibition of dual intestinal chloride channels.

Not only does this bioassay enable the establishment of clinically relevant specification for us to release the product to the public, but this could also help to provide more possibility for the manufacturer to make any further changes in the future, for example, expansion of cultivation sites to increase and diversify the botanical raw material supplies.

Because we do need this type of assay to ensure that if you move away from one cultivation site, we need to make sure that you can use these raw materials still to produce the products with the efficacy and safety expected from the one you observed in the clinical trials.

Although we have already imposed botanical raw material for Fulyzaq, as I mentioned earlier, a certain degree of variability is still expected for this botanical product even though their raw material collected is restricted to certain regions. Therefore, we also examined the

dose-response clinical data based on the multiple batches of crofelemers in order to understand the effects or impacts of lateral variations in crofelemers on the clinical effect.

From our dose-response data from 125 to 500-milligram b.i.d. dosing show that the drug's effects were not sensitive to the tested doses, meaning that the strength we approved is already on the top of dose-response curve. This is pretty consistent with our understanding of the drug concentration in the GI tracts leading to the drug saturation at the site of actions.

More importantly, the multiple batch clinical data did not show any noticeable clinical differences among drug product batches' manufacturer by using different batch of drug substances.

Let's just think about this. These data are actually very important because it's the first time we can collect from the clinical outcome to the quality. Collectively, this clinical evidence suggests that the lateral variation observed in

crofelemers from the restricted regions were unlikely to have significant impact on the efficacy and safety of Fulyzaq.

In summary, with all these quality controls and evidence, we are pretty confident that the manufacturer of Fulyzaq can consistently produce products with consistent quality that we expect.

I just want to show you in this slide from 2002 to 2014, we have reviewed and received more than 600 pre-IND and INDs in total, and we just want to let you know that we are very actively looking at this product because we think this is a very important product. As I mentioned earlier, we have successfully approved two NDAs for botanical drugs despite their complexity.

Before I conclude my presentation, I would also like to bring you the attention that we have published some key considerations of our scientific approach for botanical quality control described in this presentation in two journals, Science and Nature. With that, I conclude my presentation.

DR. VENITZ: Thank you, Dr. Lee.

Dr. Pace, if you go on to the next presentation, and then we're holding off our questions.

FDA Presentation - John Pace

MR. PACE: Hello. My name is Brad Pace. I am the health fraud branch chief in CDER's Office of Compliance. Today, I'm going to be discussing a little bit about how dietary supplements are regulated and how they differ from drugs.

Whether a product is regulated as a drug or a dietary supplement depends on several factors, including, but not limited to, what ingredients are in the product, the route of administration, as well as intended use. It's important to remember that a firm that produces dietary supplements must follow all dietary supplement legal requirements, including labeling and CGMP.

First, what is the definition of a dietary supplement? Under 201(ff) of the Federal Food, Drug, and Cosmetic Act, a dietary supplement is a product that is intended to supplement the diet, contains one or more dietary ingredients, is

intended for ingestion, is not represented for use as a conventional food or as a sole item of a meal or the diet, and is labeled as a dietary supplement. Certain ingredients studied under an IND or approved as a new drug are not permitted in dietary supplements under the Act.

As I stated in the previous slide, one of the requirements of a dietary supplement is that it must contain one or more dietary ingredients. A dietary ingredient can be a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet, or it can be a concentrate metabolite, constituent, extract or a combination of any of those previously mentioned ingredients.

It's also important to remember that under the definition of a dietary supplement, certain ingredients are not permitted in dietary supplements. Except in cases when the ingredient was marketed as a food or a supplement prior to the approval or authorization, a dietary supplement cannot contain active ingredients that are in

approved new drugs or active ingredients in products authorized for investigation with substantial clinical trials that have been made public.

Another important factor to remember when considering whether something is a dietary supplement or a drug is the route of administration. Dietary supplements must be intended for ingestion. This means it must be in form such as tablets, capsules, powders, soft gels, gel caps, or liquids. Dietary supplements cannot be, for example, sublingual products, injectables; they cannot be topical or nasal. Remember dietary supplements must be intended for ingestion.

Another factor when considering whether a product is subject to regulation as a drug or a supplement is the product's intended use. A dietary supplement can include claims to affect the structure or function of the body. A lot of times, these are referred to as structure function claims. A dietary supplement cannot include claims stating or implying that a product will diagnose, mitigate,

treat, cure, or prevent disease. These commonly referred to as disease claims. If a product is marketed with disease claims, it is likely subject to regulation as a drug.

Some examples of structure function claims that would be permissible for dietary supplements include claims like supports the immune system or promotes mental alertness. On the other hand, examples of claims that would not be permissible for supplements include things like relief of bronchospasm or treats or prevent Alzheimer's.

In producing dietary supplements, a firm must follow other laws and regulations related to dietary supplements. For instance, all firms that produce dietary supplements must register with FDA and are subject to dietary supplement CGMPs. The dietary supplement CGMP rule in 21 CFR Part 111 applies to all firms that manufacture, package, label, or hold dietary supplements. Compliance with these CGMPs are monitored by FDA by inspection.

This slide provides some examples of how a

specific product would be regulated and may help better understand this distinction between dietary supplements and drugs. First example, product X contains green tea extract, is intended for topical use, includes the statement "dietary supplement" and is marketed to maintain healthy joints. This product is subject to regulation as a drug because it is not ingested. As you can see, it's for topical use.

Product Y contains beta carotene, is intended for ingestion, and is marketed to prevent Alzheimer's. This product is subject to regulation as a drug because it makes a disease claim, prevents Alzheimer's.

Product Z contains Echinacea, is intended for ingestion, includes the statement "dietary supplement" and is marketed for mental alertness. Product Z could be marketed as a dietary supplement as long as the firm meets all other legal requirements for dietary supplements.

At times, a firm may want to combine ingredients into one product. Again, it is

important to remember that a dietary supplement cannot be legally marketed if it combines dietary ingredients with certain drug ingredients studied under investigational new drug applications or that are approved as new drugs under 201(ff)(3)(B) of the Act.

An example of this would be product A contains beta carotene and ibuprofen. It's marketed for ingestion, includes the statement "dietary supplement" and is intended to maintain healthy joints. This product would be subject to regulation as a drug because the product contains ibuprofen, which is the active ingredient in various FDA-approved drugs and which was not marketed as a food or supplement prior to this approval.

Thank you.

Clarifying Questions

DR. VENITZ: Thank you, Dr. Pace.

Any questions by the committee? Dr. Pace, I have question for you. You mentioned that dietary supplements are subject to CGMP. How is that

different from drugs in terms of the actual rules? What are the major differences in the manufacturing?

DR. WELCH: Hi. My name is Cara Welch. I'm with the dietary supplement program at CFSAN. The major difference between a dietary supplement CGMP and the drug GMPs is the dietary supplement GMPs are less prescriptive; it's all based on specifications that the manufacturer has established for the product and then testing that they've met the specifications there, some skip-lot testing that's allowed, some subset testing. So it's less prescriptive than the drug GMPs.

DR. VENITZ: But they still have to define potency and the usual -- characterize the ingredients?

DR. WELCH: Similar. The terminology is slightly different but there are specifications that are required on the finished product for identity, purity, strength, composition, and then limits on contaminants.

DR. VENITZ: Okay. Thank you.

Any other questions? Dr. Wall?

DR. WALL: A quick question. You have, let's say, a dietary supplement store and a patient or a person comes in and says, "You know, I really need these types of things in liquid; I can take it better." Is that, whoever works in that store allowed to mix those together in a liquid formulation?

DR. WELCH: If they are manufacturing dietary supplements, then they are still subject to the Good Manufacturing Practice regulations.

DR. WALL: But as an individual request from a customer who walks in, is there anything that restricts them from doing a little mixing and making in the back room?

DR. WELCH: They would be considering manufacturing a finished product at that point, so they could be subject to the GMP requirements.

DR. VENITZ: Dr. DiGiovanna.

DR. DiGIOVANNA: I actually have two questions. The first relates to this. Mr. Pace said dietary supplement GCMP rule applies to all

firms that manufacture, package, label, or hold dietary supplements. I'm not sure what "hold" means. Is that the grocery store that I go into to purchase it? Are they subject to inspections?

DR. WELCH: Retail stores are not, no. That's more for warehousing facilities, distributors mostly.

DR. DiGIOVANNA: I had a question for Dr. Lee. You mentioned there were more than 600 pre-INDs and NDAs for botanicals and said a third were commercial and two-thirds were research. I'm not sure what the difference between that is, commercial versus research INDs.

DR. LEE: For the research one, I think it's pretty much from academia. They want to look at some of the small research, some of the mixture to look at mainly for the research purpose very early in terms of development. For the commercial, I think they are a little bit more elaborate in terms of more like really try to -- tends to develop to the drug. But for the research, mainly for the academic purposes, may or may not be developed in

the product in the future.

DR. VENITZ: Dr. Carome?

DR. CAROME: A question for Dr. Lee. Was crofelemer marketed as a dietary supplement before the NDA came in?

DR. LEE: No, I don't think so. Jin-Hui, correct me if I'm wrong, but it has been -- as I mentioned it before, the raw material for crofelemer, which is known as Dragon's Blood, has been used in other countries as a herbal medicine for treating diarrhea.

DR. CAROME: But not marketed in this country as a dietary supplement; is that correct?

DR. LEE: Jin-Hui, can you --

DR. DOU: My name is Jin-Hui Dou. I'm a botanical reviewer working in Larry's botanical review team. I think the formulated product is not readily available, but the raw material and different abstracts are available as dietary supplements.

DR. CAROME: Okay. So in terms of the presentation of Dr. Pace, then someone can continue

to market those or put out new products as dietary supplements with crofelemer, right? Because you said if something is a drug-approved under an NDA, unless it was already on the market, it can't be marketed as a dietary supplement. But this one apparently was marketed, the botanical has a dietary supplement.

MR. PACE: So that's right. You could market it -- if that's true, then you could market it as a dietary supplement, but not for disease claims, of course.

DR. DOU: I would like also to add they will not be able to make crofelemer. They'll make different abstracts from Dragon's Blood or Croton lechleri because the crofelemer is associated with raw material control and the process control, and the more restrictive standards for the specifications. Thank you.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: You mentioned CGMPs and registration with FDA as requirements for production in marketing of dietary supplements in

botanicals, I believe. I didn't hear any mention of USP dietary supplement monographs. How do they relate to this? Do you use the standards in those? I noticed that all of the chapters that are called out in the dietary supplement monographs are enforceable chapters; they're numbered under 1000.

DR. WELCH: Sorry. I was just wondering if anyone else is going to address the question. USP monographs are not required for dietary supplement products and ingredients. They can be used, but they're not required.

MS. DAVIDSON: Just to follow up, all the chapters that are called out in the dietary supplement monographs are numbered below a thousand, so they could be enforceable. And I would assume FDA would be the agency to enforce those?

DR. WELCH: You're talking about a dietary ingredient monograph or a dietary supplement monograph?

MS. DAVIDSON: Yes.

DR. WELCH: Dietary supplement firms who

choose to use a USP monograph, that's their choice. If they put it on the label, then they must meet it. If they say they are using a vitamin C USP, then they must meet that monograph, but they don't have to meet it.

MS. DAVIDSON: Okay. So if a supplement or an agent of a dietary supplement monograph meets USP standards, then if it didn't, then those chapters could be used to enforce against that firm who is marketing that dietary supplement?

DR. WELCH: If they are saying on their label that they using USP grade or USP, enter ingredient here, then they must subsequently meet that monograph. But they don't have to meet the monograph if they don't say they meet it.

MS. DAVIDSON: I wanted to just make sure I'm understanding that correctly that they do not have to meet USP dietary supplement monographs to legally market dietary supplements?

DR. WELCH: Correct.

MS. DAVIDSON: Okay.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: No.

DR. VENITZ: Any other questions by the committee?

DR. CUSH: I have a question --

DR. VENITZ: Go ahead.

DR. CUSH: This is Dr. Cush. Can I ask any one of the two presenters, what are the limitations on a structure function claim? What needs to be in evidence for someone to say it helps mental clarity or helps maintain healthy joints? Is there any evidence required to make a structure function claim or is it a free for all?

DR. WELCH: This is Cara again. A structure function claim, you have to have substantiation for the claim that it is truthful and not misleading. What type of substantiation is not explicitly laid out.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: I had a question going back to the presentation about the guidance documents. Trying to understand the relationship between the docket that's being opened and list 1, do you

anticipate that the substances for which evidence that's provided to the docket, if FDA determines that those are kind of adequately supported that they will then be added to list 1 or are those sort of separate processes?

MS. AXELRAD: Yes. After we finish the list 1's, after we've done our thing with them and evaluated them and then presented them here, and probably while we're doing the rulemaking, we will start looking at things that have been re-nominated in the docket or new substances that have been nominated, and then we'll decide whether to add them to list 1. So list 1 can grow, but we're going to do the first 64 first.

MS. JUNGMAN: So it won't grow in the interim, though. There will be a time period where --

MS. AXELRAD: It probably will not grow in the interim because people are so tied up, we really just aren't going to be able to sort of be looking at those.

MS. JUNGMAN: Okay. Thank you.

MS. AXELRAD: I will have some more stuff to say about --

DR. VENITZ: I was going to turn it over to you.

MS. AXELRAD: If we could just go back to the slides that I had up because I have one slide on this. You've just heard how FDA views dietary supplements, and I want to sort of connect up what you've heard with what we're talking about here in terms of compounding with bulk drug substances, and also about why the fact that a substance as a subject of a USP dietary supplement monograph isn't enough, as we said at the last meeting, to allow it to be compounded without being on the 503A bulk drug substances list.

Just to remind you, one of the conditions that have to be met for a compounded drug product to qualify for the exemptions in Section 503A of the Act is that licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that comply with the standards of an applicable USP or National Formulary monograph,

if a monograph exists, in the USP chapter on pharmacy compounding.

If such a monograph does not exist, the bulk drug substances or components of drugs approved by the Secretary, or if such a monograph doesn't exist and the bulk drug substance is not a component of a drug approved by the Secretary, it appears on our list.

Under the law, a bulk drug substance is defined in part as a substance that becomes an active ingredient or a finished dosage form of a drug, but it doesn't include intermediate use and the synthesis of such substances.

FDA has interpreted applicable USP or NF monograph to mean an official USP or NF drug monograph. FDA doesn't consider USP monographs for dietary supplements to be applicable USP or NF monographs within the meaning of Section 503A because they are monographs for dietary supplements. As you've just heard, dietary supplements are regulated very differently than drugs.

A dietary ingredient or dietary supplement is subject to regulation as a drug if it's intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease. Compounded drugs are used in the diagnosis, cure, mitigation, treatment, or prevention of a disease, and they are often accompanied by disease claims. In fact, all of the things that have been nominated here have disease claims.

Therefore, a dietary ingredient or a dietary supplement used to compound a drug is considered a drug and the applicable USP or NF monographs are those that are applicable to drugs.

This is consistent with the way the monographs are listed in the USP NF compendium. The monographs for drug substances, dosage forms, and compounded preparations are located in the USP monograph section; excipient monographs are in the NF; and monographs for dietary supplements and dietary ingredients appear in a separate section entitled "Dietary Supplements."

As you've just heard dietary supplements are

intended for ingestion only. The standards contained in the monograph -- a drug in the dietary supplement monographs are appropriate only for ingestion. Drug products can have different routes of administration, for example, intravenous, intramuscular or topical, and that's reflected in the drug product monographs. The standards in a dietary supplement monograph may not be appropriate for all routes of drug administration.

The USP limits for elemental impurities are different for drugs and dietary supplements. For example, the permissible daily oral exposure for arsenic in drugs is 1.5 micrograms per day, and in dietary supplements, it's 15 micrograms per day.

In addition, there are limits for many more elemental contaminants for drugs than there are for dietary supplements. There are 15 elemental impurities for drug products dependent on route of administration, and there are only four elemental impurities for dietary supplements, which are always for administration by ingestion. That's where there are standards for these.

Certain dietary supplements are difficult to characterize. Related substances can be present in a single dietary supplement monograph even though they have different compositions. For example, the dietary supplement monograph for Boswellia serrata extract describes the use of different solvents, and the reference standard identifies four different molecules, any of which could meet the dietary supplement monograph.

We don't think that it would be in the best interest to public health to consider applicable USP or NF monograph to include the USP monographs for dietary supplements. Doing so would allow any substance that has a dietary supplement monograph to be compounded and marketed as a drug for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease even though the standards of the monograph only contemplate the substance's use for ingestion as a dietary supplement.

When considering a bulk drug substance for inclusion on the 503A list, the FDA and the advisory committee are using the following factors:

the physical and chemical characterization of the substance; any safety issues raised by the use of the substance in compounded drug products; historical use of the substance in compounded drug products, including information about the medical conditions that the substance has been used to treat and references in peer-reviewed medical literature; and the available evidence or lack of effectiveness of a drug product compounded with the substance, if such evidence exists.

It's very important that FDA and the advisory committee consider these factors for substances that have dietary supplement monographs because, as stated previously, the dietary supplement monograph contemplates the substances use as dietary supplement and not a drug. These criteria help FDA and the advisory committee to determine whether a dietary supplement or dietary ingredient is appropriate for use in drug compounding.

FDA is evaluating the nominated bulk drug substances, including dietary ingredients and

dietary supplements, that were nominated with sufficient information to permit evaluation for use in a drug product and presenting them to the advisory committee.

As you can see, several of the nominated substances are also the subject of a dietary supplement monograph in the USP. So the fact that these dietary ingredients were nominated is consistent with FDA's interpretation that substances subject to the USP dietary supplement monographs need to be on the 503A list if they're going to be used to compound a drug.

The bottom line though is that if an entity decides to mix two or more dietary supplements or dietary ingredients together for ingestion, labels the product as a dietary supplement, and does not include a drug in the mixture, and does not make disease claims concerning the combination of dietary supplements or ingredients, then the final product is not considered a drug. And the act of combining the dietary supplements or ingredients is not considered compounding within the meaning of

Section 503A, and the substances don't need to be on the list.

That relates to the questions that were just raised. They're regulated differently. If you're just taking dietary supplements, you're putting them together, you're not adding a drug, you're not making drug claims, you're regulated by other groups; you're not really in our world here where we're talking about compounding of drugs.

DR. VENITZ: So can I then ask a follow-up question? By definition then, the moment you compound a dietary product, you're implying a health claim, and it becomes a drug?

MS. AXELRAD: No, I don't think that we would say that. You are writing a prescription for it, but I think that if -- I'm going to have my -- the expert dietary supplement people may need to help me out here. I think that it's just the fact that you're doing it doesn't imply it, but if you're adding a drug to it, if you're making any health claims about it, those are the things that we would look at in determining whether you're in

the compounding world or whether you stay in the dietary supplement world.

Do you guys, Cara or Brad, have something to add before --

MR. PACE: That sounds right.

(Laughter.)

DR. VENITZ: I still don't understand the difference there. If I have a natural product and I don't compound it, but I mix it in some way, and I don't make any health claims, it still remains a natural product and I can market it as such?

MR. PACE: When you're looking at intended use, you look at all the circumstances surrounding the sale. But if you're not making any claims about a product, then it potentially could be marketed as a dietary supplement, and it would not be a drug.

DR. VENITZ: So it does change the intended use if it becomes compounded rather than mixed? Because I mean you're using the term compounding now to indicate that you can only compound something to a drug, not to a natural --

MS. AXELRAD: Well, first of all, it has to be a dietary supplement or a dietary ingredient to begin with. If it's something else, if it's some drug-like thing and it doesn't meet the definition of dietary supplement or dietary ingredient, you got a problem from the get-go.

Assuming you're talking about a dietary ingredient or something that's been marketed as a dietary supplement, the mere fact that you're mixing it together with another dietary supplement or another dietary ingredient does not make it a compounded drug.

But if you mix it with a drug or you make health claims about it even if you're talking -- or it's for a route other than ingestion -- you know, suppose you mix two dietary ingredients or dietary supplements together into a liquid, and then it's injected. It's no longer a dietary supplement. It crosses the world into a drug, and it's a compounded drug.

DR. VENITZ: Thank you. Go ahead.

MR. MIXON: Forgive me if I'm missing

something here. But isn't 5-hydroxytryptofan considered a dietary supplement?

MS. AXELRAD: I'm sorry. Isn't what?

MR. MIXON: 5-HTP, isn't that considered a dietary supplement? Yet, last meeting, we voted to put it on the Do Not Compound List.

MS. AXELRAD: I'm not --

MR. FLAHIVE: I'm sorry, Mr. Mixon. Is that oxitriptan that we discussed --

MR. MIXON: Yes.

MR. FLAHIVE: -- at the June meeting? Yes, that's considered a dietary ingredient.

MS. AXELRAD: But it's being marketed as a drug with drug claims, and therefore it's a drug. If you take a dietary ingredient or a dietary supplement and make drug claims about it, it becomes a drug. If you do it for a route other than ingestion, it becomes a drug.

Things that are marketed that way are in our world, and we need to deal with them as to whether they can be compounded or whether they should be put on the withdrawn or removed list or the bulks

list.

MR. MIXON: Can I clarify something then? Did we vote on oxitriptan because it's being used intravenously?

MS. AXELRAD: Pardon me?

MR. MIXON: Some route besides oral? I'm sorry to be revisiting this, but I'm confused.

MR. FLAHIVE: Mr. Mixon, we discussed oxitriptan at the June meeting because it was nominated for two drug uses. It was nominated for treatment of insomnia and treatment of depression --

MR. MIXON: That makes it a drug.

MR. FLAHIVE: -- and we examined those uses. And those were drug claims and drug uses.

DR. VENITZ: We have time for one more question.

MR. MIXON: Thank you.

DR. VENITZ: Ms. Davidson?

MS. DAVIDSON: Just a point of clarification, when you say when you mix two dietary supplements together, does the "you" have

to be registered with FDA and do it under CGMP conditions or could a consumer do that?

MS. AXELRAD: When I say "you," I mean a compounding pharmacist --

MS. DAVIDSON: Okay.

MS. AXELRAD: -- mixes two things together.

MS. DAVIDSON: That's what I wanted to clarify. Okay.

MS. AXELRAD: Cara may address how they may view it if you do that.

DR. WELCH: No, you're right, yes. If a manufacturer -- if a business is mixing two dietary supplements together to make a product, then they are manufacturing a product. They would have to be registered under the Food Facility Registration Act, yes, and subject to CGMPs.

DR. VENITZ: Donna, last question.

DR. WALL: Who must make the claim that it's the drug? Is it the actual seller, or can it be a prescriber, or somebody goes on television? At what point is that thing actually moved from the dietary supplement to the drug? Who has that power

to do that?

DR. WELCH: If the firm marketing the product is making a disease claim, then they have moved their product from a dietary supplement into a drug, and probably a non-approved drug but a drug.

If an advertiser is making a claim about a third party product, then we would be taking action against the advertiser. And if it's a healthcare professional, I'm not going to regulate physicians and how they prescribe medicines or treatments for their patients.

Does that answer your question?

DR. WALL: We're saying that the seller is the one who's going to be ultimately responsible if they don't put the claim on it. But where I see is this process starts a lot further upstream with prescribers and folks who are working to make those patients better who may not be the ultimate seller.

I'm still playing with that piece to see at what point -- if the prescribers are saying it or -- he didn't even have to write a prescription;

he can stay, I think you need to go and get some of this whatever product it is because I think I think it's going to help your arthritis or do whatever. It's sort of a mixed message in there. At which point, he's using it for something he believes therapeutic, he or she, and yet the seller may not be part of that.

DR. VENITZ: Final, final question. Mr. Mixon?

MR. MIXON: This is more of a comment. I think this committee needs to understand the hands of the prescriber are now tied because if a doctor writes a prescription for a substance that includes 5-HTP, he's making that clinical decision for that patient, that that patient needs 5-HTP plus something else.

We're now tied -- we're now prevented from compounding that preparation for that patient pursuant to a valid prescription for an individual patient.

DR. VENITZ: Thank you. Let's move on to our first bulk substance for today,

methylsulfonylmethane. We have Dr. Angelina Pokrovnichka. She's going to present the FDA's summary.

MS. AXELRAD: Dr. Venitz? Before she starts, can I just mention that the National Community Pharmacy Association nominated methyl sulfone for the last -- which we didn't recognize as being another name for methylsulfonylmethane.

In our background package, we didn't list NCPA as one of the nominators of this substance, but they are. So we'll be making a correction to the package after the meeting. I just wanted to note that. I don't think they intend to present but I wanted people to know that they were also one of the nominators of this.

DR. VENITZ: Okay. Thank you.

FDA Presentation - Anjelina Pokrovnichka

DR. POKROVNICHKA: Hi. Good morning. My name is Angelina Pokrovnichka, and I'm a medical reviewer in the Division of Anesthesia, Analgesia, and Addiction Products.

My presentation today will cover the

physical and chemical characteristics, the nonclinical information, and the human data for safety, effectiveness, and historical use in compounding of methylsulfonylmethane, or MSM, that has been nominated for inclusion on the list of bulk drug substances for use in compounding.

The review team for this application included myself, the quality reviewer; Norman Schmuff; and the nonclinical reviewer, Nik Patel.

The most common use of MSM is to treat osteoarthritis pain. A variety of other uses were referenced in the nominations. However, scientific support provided by the nominees was only for the use of MSM in osteoarthritis.

MSM is a fairly simple and stable low molecular weight molecule with a structure depicted here. Although the exact synthesis of the molecule for the compounded product is not known, the mostly likely method is a simple oxidation of dimethylsulfoxide. Assuming this is the case, the most likely impurities would be DMSO and the residual hydrogen peroxide.

I will now briefly summarize nonclinical data available from published literature regarding the pharmacology and toxicology of MSM. Although MSM has been reported to possess antioxidant, anti-apoptotic, and anti-inflammatory properties, no clear mechanism of action has been identified for these effects.

There are no published safety pharmacology studies with MSM. Therefore, no information is available regarding its possible effects on the central nervous system, the cardiovascular system, and the respiratory system.

In single-dose acute oral toxicities studies in mice, rats, and dog, MSM was shown to have an LD50 of greater than 2 grams per kilogram. An LD50 is a dose that results in the death of 50 percent of test animals within a dose group. In a repeat-dose toxicity study, no adverse toxicities were identified in rats administered up to 1.5 grams per kilogram daily for 90 days, which is equivalent to a total daily human dose of 14.5 grams.

In published mutagenicity studies, MSM did not cause mutations in bacterial cells and did not induce chromosomal abnormalities in mammalian cells. In addition, MSM did not induce chromosomal damage in an in vivo mouse assay. In a rat developmental toxicity study, MSM was not teratogenic at doses of up to 1 gram per day administered orally to dams on gestational days 6 through 20. A dose of 1 gram per kilogram per day in rats can be considered equivalent to a total human dose of 9.6 grams per day.

Although no long term carcinogenicity studies with MSM are available, some studies in the published literature have indicated that MSM can delay the initiation of tumors in rats and that MSM can be toxic to cancer cells in vitro.

In a rat study looking at toxicokinetics of MSM, MSM was absorbed within 15 minutes following oral administration and persisted in plasma and tissues for up to 48 hours post dose.

The major route of excretion for MSM in rats was via the urine, blood, kidneys, testes, and eyes

contained highest levels of MSM. However, significant levels were also found in brain indicating that MSM can cross the blood brain barrier.

In conclusion, based on the limited nonclinical data that are available in published literature, no adverse toxicities have been associated with MSM. However, ideally, the studies listed here would enable a more complete nonclinical assessment of the safety of MSM for use in compounding.

Slides 9 and 10 provide a list of the six articles that describe the human randomized clinical trials related to MSM use in osteoarthritis. These articles were identified based on the sources cited in the 503A nominations for MSM use and independent literature search.

The safety of MSM use beyond 12 weeks has not been investigated in clinical studies. MSM doses of 500 milligrams orally 3 times daily, 1.125 grams orally 3 times daily and 3 grams twice daily have been administered in randomized

controlled studies.

The quality of the adverse event reporting appeared to be poor in the literature. Gastrointestinal events, including bloating, constipation, and indigestion, together with headache, fatigue, and insomnia were among the most commonly reported adverse events. There were no serious adverse events and the rate of discontinuations from the studies due to adverse events was low.

In addition to the literature, a search of the FDA Adverse Event Reporting System, FAERS, database, was conducted for reports of adverse events associated with MSM use. FAERS is a database of unsolicited spontaneous adverse event reports for approved drugs that may include reports for compounded products. The most commonly reported events were fatigue, nausea, headache, cough, difficulty breathing, difficulty sleeping, and increased INR.

INR is a standard laboratory unit that measures the time required for the blood to clot.

Higher the INR, the longer it takes for the blood to clot. Four cases of bleeding were identified. In three of them, in addition to MSM, subjects were taking other medications that increased the risk of bleeding such as the anticoagulant warfarin, a medication that interferes with the body's ability to make a blood clot and the pain medicine, ibuprofen.

It is difficult to make definitive safety conclusions based on FAERS because FDA does not receive all adverse events that may potentially occur with a product, nor has the sales data to calculate the frequency of occurrence for a given adverse event.

Three studies that compare the efficacy of MSM to placebo for the treatment of pain associated with osteoarthritis have been described in the literature. Two articles that critically discuss the results of these studies were also identified.

The assessments of pain in the controlled studies were based on accepted pain measurement scales. The improvement in pain was greater for

subjects taking MSM compared to those taking placebo.

However, the overall improvement was small and not considered to be clinically meaningful. In addition, many of the statistical tests failed to provide evidence that MSM was better than placebo for the treatment of pain associated with osteoarthritis.

Limitations of the osteoarthritis, MSM clinical studies include the small number of patients who received MSM, the variation of the doses administered, the unknown effect on efficacy findings of other pain medications if taken during the study when the pain was not adequately relieved, and the concerns about the statistical analysis used.

No information was found for the historical use of MSM in pharmacy compounding.

To summarize, use of MSM has been reported in many countries and appears widespread. However, we are not aware of any jurisdiction approving MSM as a drug. The physical and chemical properties of

the molecule are well-characterized. Nevertheless, the safety profile in animal studies is not adequately characterized.

The human safety of MSM as described in the literature consists mostly of non-serious adverse events. However, there have been events of concern reported that include increased blood pressure and increased effectiveness of anticoagulants that could lead to bleeding.

The evidence for efficacy is weak, suggesting only minimal reduction of joint pain associated with osteoarthritis. Notably, there are a number of approved alternative treatments for osteoarthritis that have been demonstrated to be safe and effective.

Based on the minimal evidence of efficacy, the possibility of a potentially serious interaction with anticoagulants and the risk of bleeding and the availability of approved alternatives, MSM should not be included on the list of bulk drug substances that can be used to compound drug products in accordance with

Section 503A of the Food and Drug Administration Act. Thank you.

Clarifying Questions

DR. VENITZ: Thank you. Are there any clarifying questions for the committee? Yes, Dr. Vaida?

DR. VAIDA: It looks like the trials or the studies that you did, it was on the oral?

DR. POKROVNICHKA: Yes.

DR. VAIDA: Okay. There wasn't anything on the topical, or injections or --

DR. POKROVNICHKA: No, these were oral -- administered orally.

DR. VAIDA: Okay.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: Do I understand correctly this is available as a dietary supplement; is that correct?

DR. POKROVNICHKA: Yes.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. Two questions, did FDA find any other data supporting other

nominated uses for the drug?

DR. POKROVNICHKA: No.

DR. CAROME: Okay. Is it fair to say based upon your presentation that MSM appears to present safety concerns? Is that FDA's view?

DR. POKROVNICHKA: Bleeding is a safety concern. There were cases from FAERS, reported four cases, in patients who two of them were taking warfarin; it's the so-called blood thinner. One patient was taking nonsteroidal anti-inflammatory drug, ibuprofen, and the third patient was taking nothing. There are three patients reported as bleeding.

Unfortunately, in the three controlled trials, the population selected was pretty healthy subjects, and patients who were on those drugs, for example, patients who were taking warfarin or taking nonsteroidal anti-inflammatory drugs or had bleeding disorders, were not allowed to participate.

They were excluded because of the signal of potential interaction, so we have no real data or

information how these would affect those people. To note, osteoarthritis is a disease of the elderly, and many of those patients, people will have many other comorbidities and will be on many other medications.

DR. VENITZ: Mr. Mixon?

MR. MIXON: You're asking this committee to vote on a substance that can be purchased over the counter, has very little data to say that it's unsafe, yet you're going to restrict the use of this drug upon prescription by a licensed practitioner for a patient, or you're asking this committee to vote on that.

You know, when we take care of patients, we don't treat clinical trials; we treat individual patients. And two of the alternatives you offer in here are ibuprofen and acetaminophen, both of which have clear toxicity. And opioids, that's absurd, to recommend that an opioid be used in lieu of MSM.

DR. VENITZ: Thank you.

DR. FIELDS: Hi. I'm Ellen Fields. I'm the deputy director of the division. I just want to

say we're asked to look at this not as a supplement but as a drug, and we're asked to review the data that's available. We're not recommending those other products; we're just saying they're approved.

The data that we had showed possibly minimal efficacy, and there was a safety signal. That's all it is, is a signal. We don't know the rate of it. I'm talking about the concern about interaction with anticoagulants.

So when we have a product where there is questionable efficacy and a safety signal, we're inclined not to recommend that for use. We're not looking at it as a supplement. We acknowledge it's a supplement. Ms. Axelrad had explained that earlier.

DR. VENITZ: Just one suggestion, let's keep it to clarifying questions because we have a discussion after the nominators later on. I have Dr. DiGiovanna next.

MS. AXELRAD: If you want to -- I guess I can address it during the discussion because --

DR. VENITZ: Okay, go ahead.

MS. AXELRAD: -- it went beyond the clarifying question, so my answer goes beyond that. I'll hold it until when you discuss it.

DR. VENITZ: Let's do that. Dr. DiGiovanna?

DR. DiGIOVANNA: I'm not sure if this is a clarifying question or not. But from what I understand, we identified four individuals from the literature who either had an issue with reported bleeding or a laboratory test of INR that's been abnormal. There's no discussion of the denominator of those four individuals.

In reading through the FDA information, they say there are approximately 87 proprietary names for products sold around the world that contain this preparation. It becomes difficult to make a reasoned assessment at what a signal means if one individual in the world has an issue and what the risk of that means as far as making an evaluation of what a practical assessment is.

On the other hand, what is the criteria for efficacy that the advisory committee should be thinking about? Is the same as an IND approval of

a drug, and should the criteria of what's in the literature be held to that standard, considering that this is not something that's mass marketed to large numbers of individuals, but from my understanding, requires a prescription for an individual patient.

I think there are a lot of issues in the way this has been presented that makes it difficult to interpret what the data actually is and how to assess it.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: Just a point of clarification. The primary precursor for this drug is DMSO and the major possible impurity is DMSO. Is DMSO still approved for topical installation in human bladders? It used to be under the brand name, Rimso.

DR. FIELDS: We believe so, yes.

MS. DAVIDSON: Okay. So it is approved as a drug already, the precursor and the impurities?

DR. FIELDS: Yes, but I believe that's for bladder cancer, which is different.

MS. DAVIDSON: Topical, yes, and I think that's the point I'm making, is there is an established use for topical potential use of these sorts of chemicals.

DR. VENITZ: Dr. Vaida?

DR. VAIDA: Just one more question. With this drug, you already said you only found studies for osteoarthritis and only in oral. Yet it looks like the two, in the nominations that were in our packet, it's for any use and injection, topical. Is that what we're -- I mean, if it was approved, it would be -- from what was nominated here --

MS. AXELRAD: Any use.

DR. VAIDA: -- for any use?

MS. AXELRAD: No. It would probably be for any use. What we did was when something was nominated for multiple uses, we looked at the ones that were well-supported, gave us something to go on to look at them.

If there was just like one article or nothing supporting another use, we didn't look at them. Obviously, some of these had many, many uses

that they were nominated for, and we could not look at all of them, so we made decisions about what we would look at.

But if you put it on the list, as we've said before in previous meetings, it's not clear we could restrict its use to a specific indication because in some cases, for example, the compounding pharmacist wouldn't know how it was being used, what the diagnosis was. So I think it would be very difficult to restrict its use.

We might be better able to restrict its route of administration. For example, it's obviously -- if it's topical, it's topical. If it's oral, it's oral. That's something that the pharmacist who's compounding it would know by and large. But we're not entirely sure that it could be restricted. If you vote to put it on the list, I think you could assume then it would be used for uses other than those for which it was nominated.

DR. VENITZ: Dr. Cush, you had a question.

DR. CUSH: Yes. Can you hear me? This is Jack Cush in Dallas. My concern is that this is

deemed intended for osteoarthritis, which affects 27 million Americans, so becoming a prescriptive product is actually quite important, and the standards are for that of a drug.

My concern is over the amount of data that has been presented here. I, too, could not find a lot, but this drug -- this compound I should say, MSM, is frequently used in combination with other products, other dietary supplements, so-called nutraceuticals.

Is there not more data? I mean to only look at data based on 168 patients and what's available through the adverse event reporting system is limiting, but more damning for the drug than more of a pest. What about when it's used in combination with other, again, dietary substances? Do we have any data there?

DR. POKROVNICHKA: We reviewed only the data in which MSM was only administered and compared to placebo. There were many other articles in which MSM was used in combination, but you cannot really assess what's the MSM contribution to efficacy,

neither to safety, when it's administered in a combination product.

DR. VENITZ: Okay. One last question, Dr. Pham, because we're running out of time.

DR. PHAM: Sorry. This is actually just a clarifying question to kind of frame the rest of the two days. But when we are noting if something should not be included and therefore does not -- you know, you can't come in with the prescription then, I guess, and say this is osteoarthritis, if we're talking about MSM as an example.

I'm concerned about the workaround of can then it be acquired as a dietary supplement, and then you actually lose the ability for a doctor to be monitoring for something, for the toxicities that they be concerned about because now is there a backdoor way to acquire the product without the prescription and therefore the appropriate medical monitoring.

MS. AXELRAD: That would be me, I think.

DR. VENITZ: Go ahead.

MS. AXELRAD: Because it's sort of a more general question, not specific to this. If it's marketed as a dietary supplement already, it can be marketed as a dietary supplement.

If I go to my doctor, and my doctor says I'd like you to take MSM, go to the health food store and get it, I could do that. They don't need to write a prescription for me to do that. They could just tell me I want you to take this, that, or the other thing in this quantity, and come back to me in two weeks and tell me how you're feeling. That's something that can be done.

As I said, what we're dealing with here are drugs that have never been approved in this country for any use, although they may be marketed as dietary supplements. And the question is whether they can be used in drug compounding for drug uses like osteoarthritis.

We can't change the backdrop of whatever might happen if it's not put on the list and somebody can already go to the health food store and get it as a dietary supplement. We have to

deal with what we are given in terms of the level of evidence that is out there and do the best we can to try and make judgments as to whether we're going to allow it for drug compounding.

DR. VENITZ: Thank you. Appreciate it. I think we'll move on to our next bulk substance, and that's curcumin. Dr. Casak is going to present the FDA summary to us.

FDA Presentation - Sandra Casak

DR. CASAK: Good morning. My name is Sandra Casak, and on behalf of the team listed on this slide, I represent our review of curcumin for its inclusion in the list of compounding products.

Curcumin, or Curcumin I, has been described as the active ingredient of turmeric and has been consumed as a dietary spice. Curcumin I occurs naturally along with Curcumin II and III in turmeric. Chemically, Curcumin I, II, and III are collectively known as curcuminoid or C3 complex. Several of the C3 complex products are available in the U.S. as dietary supplements.

Heavy metals, pesticides, aflatoxins,

residual solvents are impurities that have been identified in curcumin preparations. Curcumin is unstable at neutral to basic pH and undergoes hydrolysis in alkali solutions. This slide shows some of the degradation products.

Curcumin can be isolated by steam distillation or using extraction methods in different media such as methanol, ethanol, and acetone. In these organic solvent extracts, the total of curcuminoids is about 4 to 6 percent.

As mentioned before, curcumin is unstable at basic pH, and therefore, all solutions and topical preparations that include the use of order should be avoided because the product will be degraded.

Curcumin has been reported to have antioxidant properties. There do not appear to be safety pharmacology data to characterize the effects of curcumin on the brain, pulmonary, gastrointestinal, or cardiovascular systems, though data from one toxicology study suggests that curcumin exhibits a low order of toxicity.

In mice, the median lethal dose was

estimated to be greater than 2 grams per kilogram. However, curcumin exhibits poor oral bioavailability; thus, this data cannot be extrapolated to guide dose selection of curcumin.

In repeat-dose toxicology studies, doses greater than 2 grams per kilogram a day were associated with gastric ulceration or hyperplasia in rodents. In carcinogenicity studies, curcumin was considered equivocally carcinogenic based on an increased rate of hepatocellular adenoma and neoplasm of the small intestine in the mouse, and then an increased rate of clitoral gland adenomas in the rats.

Curcumin has been nominated for three medical conditions. Familial adenomatous polyposis, FAP, and its variants are caused by germline mutation in the APC gene. FAP is characterized by the development of hundreds to thousands of colorectal polyps, and the majority of patients are asymptomatic until they develop cancer. The mean age of polyp emergence is 16 years.

Colorectal cancer occurs in nearly 100 percent of individuals if untreated. And given the predictable development of colorectal cancer, treatment is surgical removal of the colon when polyposis develops.

Chemopreventive strategies have been studying FAP to delay the development of adenomas. However, none are recommended at this time. Although celecoxib has shown to reduce adenomas in FAP, celecoxib is a COX2 inhibitor with potential serious risks and is not recommended outside of a clinical trial.

Oral leukoplakia presents as white patches or plaques of the oral mucosa. Between 1 and 20 percent of lesions progress to carcinoma within 10 years. Leukoplakia can also be seen in inflammatory conditions not associated with malignancy.

The clinical significance of oral leukoplakia depends upon the presence and degree of dysplasia. Patients with high degree of dysplasia require ablation, and for other lesions, the

removal of the chronic inflammatory stimuli such as tobacco induces regression of the lesion.

The terms "gastric metaplasia," "metaplastic atrophic gastritis" and "atropic gastritis" have been used to describe chronic gastritis, that in addition to inflammation is associated with mucosal metaplasia. There are two main types, autoimmune and environmental.

Autoimmune metaplastic atrophic gastritis is associated with an immune response against gastric parietal cells and intrinsic factor. Affected patients can develop pernicious anemia, B12 deficiency, hypergastrinemia, achlorydia, iron deficiency, and in later stages, neurologic damage.

Patients with autoimmune metaplastic atrophic gastritis are at increased risk for gastric carcinoid tumors and adenocarcinoma. Gastric adenocarcinoma has been reported to develop in up to 3 percent of patients with autoimmune gastritis. However, the risk is difficult to determine as some of the reports come from Asia where the baseline risk of gastric cancer is much

higher than in the U.S.

There is no treatment for metaplastic atrophic gastritis, and a guideline issued by the American Society for Gastrointestinal Endoscopy suggests that patients at increased risk for gastric cancer, due to either background of family history, may benefit from surveillance, and if high-grade dysplasia is confirmed, gastrectomy could be considered.

Curcumin has been studied in multiple small clinical trials in a variety of clinical conditions, including both nonmalignant and malignant conditions. According to published reports, preliminary signs of activity related to curcumin were observed in different conditions. However, despite numerous clinical trials, there is no evidence of its effectiveness.

In general, the preliminary signs of activity involve effects on biomarkers that may not be related to clinical benefit or to effects on disease processes observed in uncontrolled or small studies.

In these studies of curcumin, exposure was limited by curcumin's poor bioavailability, limited duration of exposure to curcumin, and variety of doses and products used. Most of these studies were small and inconclusive.

In most literature reports, it appears that at doses below 8 grams per day and for shorter durations of time, curcumin is well-tolerated. Gastrointestinal adverse events have been reported. However, the safety of curcumin for longer-term use cannot be ascertained.

As mentioned before, exposure was limited by curcumin's poor bioavailability and limited duration of exposure to treatment. In addition, there is no established exposure relationship and the potential for prolonged exposure to impurities and drug-drug interactions have not been studied. In vitro data suggests that curcumin loses CYP3A enzymes.

Chemopreventive strategies have been studied in patients with FAP to delay the development of adenomas in the gastrointestinal tract, as well as

to prevent recurrence of adenomas in the retained rectum of patients after prophylactic surgery with colectomy and ileorectal anastomosis.

In a small study published in 2006, 5 patients with FAP who had undergone prior colectomy received combinations of curcumin and quercetin orally 3 times a day. The number and size of polyps were assessed at baseline and after therapy.

Quercetin is a flavonol that can be found in fruits, vegetables, grains, and is available as a food supplement. The number and size of polyps was reported to have decreased after 6 months of curcumin and quercetin. However, these results need further validation.

Weaknesses of the Cruz-Correa study in relation to the consideration in the bulk substances include the following: This was a small, unblinded study, and other reports have shown that a small percentage of diminutive polyps can shrink or completely regress without treatment. The study did not isolate the effect of curcumin.

Although the studies stated that patients were instructed not to take nonsteroidal anti-inflammatory drugs, the study did not report on the concomitant use of nonsteroidal anti-inflammatory drugs that have also been reported to have effects on polyps. Finally, the assessment was performed by a single observer without biopsy of the polyps to ensure pathological diagnosis.

In a phase 1 study of curcumin as a chemopreventive agent published by Cheng in 2001, although two patients with oral leukoplakia were reported to show signs of improvement, one of the seven patients with oral leukoplakia developed malignancy. Additionally, one of four patients with uterine cervical intraepithelial neoplasia developed malignancy.

Although this is a small study, 14 percent of the population with oral leukoplakia and 25 percent with uterine cervical intraepithelial neoplasia developed frank malignancy during the short study, raising concerns as the rate of

malignancy could theoretically be increased in addition to reduced or having no effect.

The experience of curcumin patients' treatment of metaplastic gastritis is limited, and there were no dedicated reports found in the literature. However, in the chemoprevention study conducted by Cheng, one of the six patients with metaplastic gastritis developed gastric cancer during the conduct of the study.

For the commissions for which curcumin has been nominated to be included in the list of bulk drug substances that can be compounded in accordance to Section 503A, there is insufficient evidence that curcumin is effective. Furthermore, curcumin use may delay the effective treatment of these conditions.

Familial adenomatous polyposis is a serious condition because virtually all patients will develop colon cancer if left untreated. Use of curcumin outside of a clinical trial setting where monitoring of the polyps is regimented may increase the risk of these patients of developing an

undetected cancer if they use curcumin in lieu of monitoring.

Although not all leukoplakia lesions are precancerous, medical supervision, diagnosis, and biopsies may be needed to determine if a particular lesion is nonmalignant, premalignant, or malignant. Any treatment without clinical monitoring increases the risk of patients to further develop malignant lesions, increasing the morbidity and potentially impairing the curability of an oral cancer.

Finally, limited data exists regarding the prolonged administration of curcumin that will be necessary for cancer prevention indications. At least one small trial reported development of malignancies in patients with cervical intrauterine neoplasia, oral leukoplakia, and gastric metaplasia.

Therefore, irrespective of any effects on biomarkers, an increased risk of malignancy could not be ruled out. Finally, it's important to communicate that large randomized trials of other antioxidant studies as cancer prevention agents

show that the incidence of cancer increase after the administration of the antioxidant substance.

In the current study, more than 18,000 participants at high risk of lung cancer were randomized to receive beta carotene and vitamin A , or placebo. The study was stopped prematurely because participants who were randomly assigned to receive the antioxidants were found to have a 28 percent increase in incidence of lung cancer and 17 percent increase in the incidence of death.

Although the results of the SELECT study exploring cancer prevention with vitamin E and selenium in prostate cancer were not as dramatic, the study also failed to demonstrate any benefit, and the incidence of cancer was higher in the group receiving antioxidants.

Therefore, we recommend that curcumin not be placed in the list of bulk substances allowed for compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act.

Clarifying Questions

DR. VENITZ: Thank you, Dr. Casak. We have

a few minutes for any clarifying questions by the committee. I don't see any arms raised. Okay. Dr. Carome?

DR. CAROME: Is it fair to say that -- I asked this question on the last drug -- FDA believes curcumin appears to present safety concerns?

DR. CASAK: The analysis I just presented is referencing specifically the strict conditions for which curcumin has been nominated. Our main safety concern in regard to these indications is that by doing this, patients may not be doing what they need to do.

DR. VENITZ: Any other questions?

(No response.)

Okay. Then thank you, Dr. Casak --

DR. CUSH: Oh, I have a question. I'm sorry. I have a question. This is Dr. Cush.

DR. VENITZ: Go ahead.

DR. CUSH: Yes. Can you explain to me, please, why there's no -- first off, why this has been limited to prevention of gastrointestinal

malignancies and why there's been no petition for its use in arthritis? Was that not requested, and that's why it's not on the list? But I'm curious with that because this compound gets a lot of use for arthritis.

Then secondly, why was there no discussion on the mechanisms of curcumin's effects? I mean you did largely discuss of an antioxidant and phytochemical when there was no discussion regarding its effects on cyclooxygenase, which I think are very clear, and largely its benefits. This is not working as an antioxidant, in my opinion; it's working as a cyclooxygenase inhibitor. Why was that not discussed?

DR. CASAK: In regards to the indication, we are discussing the indications for which curcumin has been proposed. That was what our analysis was based on.

DR. CUSH: Proposed by compounders or proposed by the FDA?

DR. CASAK: It was nominated for the treatment of FAP, oral leukoplakia and gastric

metaplasia.

DR. CUSH: By whom?

MS. AXELRAD: By compounders. I'm sorry. This is Jane Axelrad, Dr. Cush. We solicited nominations -- actually, it wasn't just compounders; it was various trade associations nominated substances, compounders that nominated substances; bulk drug substance producers also nominated substances. We're working off of the nominations that came from a variety of members of the public.

The ones that we looked at were the ones that were adequately supported. Although the nomination is one of the nominations for this mentioned, it's used in these other things. There was no literature cited or anything to support its use, so what we looked at were the things that were supported by some kind of literature that would give us something to start with in terms of doing the review.

MR. FLAHIVE: This is Jim Flahive. We made the cut largely by if a nomination both listed or

proposed a drug for a specific use and supported that use, that was usually what we looked at.

DR. CUSH: Again, my concern would be that in the real world, it's getting much larger and wider use despite the limitations of nominations. Again, move on to my other questions regarding why no discussion of curcumin's effect on cyclooxygenase.

DR. CASAK: I'll let Dr. Helms answer that question.

DR. HELMS: I think we did all of the literature searches ourselves, and we focused more on the safety than mechanism in this case. But many of these botanical type products have multiple potential mechanisms of action, and I think in this case, antioxidant was the one that we found to be most relevant to the indications.

DR. CUSH: Again, I would disagree because as you well stated, the efficacy of an antioxidant in ameliorating disease of any kind is almost nonexistent; hence, that's why the research has occurred, which has delineated the effects on COX2

for curcumin and actually other phytochemicals as well.

DR. HELMS: Well, there are COX2 inhibitors that have been looked at in this indication as Dr. Casak mentioned, so I think that we do have some information on that included in the presentation.

DR. CUSH: Okay.

DR. VENITZ: One last question. Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. On the briefing materials we got, I think I have it as page 83, 84 and 85, there's what appears to be the list of what was requested for the drug. There are some indications of arthritis, rheumatoid arthritis, and osteoarthritis, and other issues.

So again, I'm a little bit confused as to why we don't have information related to the other indications as kind of Dr. Cush has suggested. It seems that it's only focused on one particular condition here where I think it seems quite obvious that eliminating the standard of care therapy would

pose risks to that population.

But for other populations, perhaps with arthritis where other drugs might have been contraindicated, it would have been -- I, for one, would have thought it would have been helpful to have a better assessment as whether there were not any studies of efficacy and issues of safety in that population or those populations.

DR. VENITZ: Okay.

MS. AXELRAD: So when you look at the nomination for this, the ones that were, what is the proposed use for the drug in compounding and the ones that cited articles were FAP, oral leukoplakia, gastrometaplasia, and then is there any other relevant information, and there's a list.

Orally, turmeric is used for osteoarthritis, rheumatoid arthritis, dyspepsia, abdominal pain, hemorrhage, diarrhea, flatulence, abdominal bloating, loss of appetite, jaundice, hepatitis, liver and gall bladder conditions, headaches, bronchitis, common cold, and it goes on.

Obviously, we were not able to evaluate this

for all of those potential indications, so we selected the ones for which there was some support. If someone would like to ask that it be considered for the list for some other use and is willing to provide some support for it, then we could consider it. That's why we opened the two dockets.

DR. VENITZ: Okay. Let's move on because we will have a discussion after lunch. Now, we have our nominators giving their presentation. Our first nominator is Dr. Day from Professional Compounding Centers of America.

Nominator Presentation - A.J. Day

DR. DAY: Good morning. My name is A.J. Day. I'm the director of pharmacy consulting with Professional Compounding Centers of America, PCCA, located in Houston, Texas. As a conflict of interest disclosure, we are a chemical wholesaler who does sell MSM.

Now, a lot of this is background data that we're covering, so I won't spend a lot of time on it since have had a robust discussion about it within these walls here. These slides here that

are labeled "FDA Briefing Information," these are literally copy and paste from the FDA's briefing information that was published a couple of weeks ago. It goes through the stability and well-characterized physical status of MSM and that from the viewpoint of characterization and physicochemical properties, MSM is suitable for use in compounding.

Pharmacology, again, FDA does a good job of recognizing that this is naturally found in a lot of the foods that you and I have been consuming for decades, also going through a little bit of the potential mechanism by which it's exerting beneficial effects on osteoarthritis.

FDA also does point out the GRAS application and the details from Center for Food Safety and Applied Nutrition and that the CFSAN replied that they had no question regarding the submitter's conclusion that MSM is GRAS for use in foods under the conditions up to levels of 4 grams per kilogram in food bars such as granola bars and energy-type bars at levels up to 30 grams per kilogram.

The repeat-dose toxicity, this was the rat study, they had no observed adverse effect level that was noted at greater than 1.5 grams per kilogram and correlating that to a human equivalent dose of 14.5 grams per average 60 kilogram-person per day based on a body surface area comparison.

Now, the FDA's analysis did point out some concerns regarding potential toxicity due to transfer of MSM across the blood brain barrier. There were two articles cited. The first one in the toxicokinetic section of the briefing information looked at an article from Magnusun and colleagues at a dose of 500 milligrams per kilogram of radiolabeled MSM, where the sulfur was labeled with the radiolabel tag.

They did it on 8 rats. Interestingly, the test was not carried out on all 8 rats. They were only done on 6 of them; 3 rats were in the blood group, 3 from the urine and feces group.

The dose that was used represented 3 times the maximum reported dose -- this is the screen shot from the actual article -- 3 times the maximum

reported dose in humans of 182 milligrams per kilogram, approximately 5 times the dose of 6 grams per day used in adults in a recent clinical study. So at a significant level, we did see that there were some detections of the radiolabeled MSM or more specifically of the radiolabel.

The authors do go on to conclude that while we did note the presence of the radiolabel in the various tissues, including across a blood brain barrier, what they're actually detecting is not MSM. What they're detecting is the radiolabel. And this is a general weakness of radiolabeled studies, which is that you have the risk of the dissociation of that radiolabeled isotope from the parent molecule. So the fact that the administered radio activity remains in the animal's body does not mean it is present as MSM.

They have also acknowledged that studies have demonstrated that sulfur from MSM can be incorporated into tissue proteins. This is also substantiated by another article from 1986 also included in the FDA's analysis. Here, where they

show that not only is it likely, but almost 60 percent, 59 percent of that radiolabel was partly because of incorporation of the radiolabel from the MSM into proteins that have half-life of greater than 1 day.

The FDA's conclusion statement from that subsection says that the pharmacology studies have shown that significant levels of MSM are present in the brain following oral administration in humans and rats. The clinical significance is uncertain.

Now, the human study that they reference is an article from Lin and colleagues from 2001. That article had 4 patients, 3 of whom were only examined once. And the patient population were patients with Alzheimer's disease, cognitive impairment, stroke, brain tumor, Parkinson's disease, infections, CFS, hepatic and toxic encephalopathies.

Now, this study was designed -- it did an MRS study where they administered MSM to certain patients. Some patients had admitted that they had taken -- it was basically an interview style, that

they had taken large doses of MSM in the preceding days in current therapy. They essentially analyzed the MRS results to see could they identify peaks, and that's how they determined it.

I'm not a neuroscientist of any kind, so I'm going to take the assumption that this is the standard of care for how they're determining these studies to be accurate.

Despite the presence of the MSM that this study did find, they did also say that no adverse clinical or neurochemical effects were observed. The second study on rats was the Magnusun study that we previously discussed.

From a nonclinical perspective, this is from the FDA's document, there do not appear to be any data suggesting adverse effects. However, the data for oral toxicity is limited, and there are no data for other routes of administration.

What are the recommendations per the FDA when they're looking at alternatives? The approved therapies for osteoarthritis and joint pain include acetaminophen, NSAIDs, duloxetine, opioids, and

opioid combinations, and all of these therapies carry risk.

It is important that we look at some of these components because the criteria set forth for this process of the nominated substances, it looks at four different criteria, physical and chemical characterization. And historical uses of the substance in compounding, those are pretty well established. We've already discussed point 1. Point 3, well, we wouldn't be here talking about it if it hasn't been used historically in compounding.

The safety issues raised by the use of the substance, we talked about the nonclinical and the clinical assessment in the human studies as well and the available evidence of effectiveness or lack of effectiveness for this drug product. No single one of these criteria is dispositive. We're looking at all of these things in combination, and failure to meet all of our expectations in one category by itself should not be enough reason to dismiss any of this.

When we're looking at the alternatives, I

think that that is a very important factor to consider because without access to some of these substances, what are our patients going to be treated with?

Again, going back to the historical use of MSM, the bibliography from the FDA includes publications from 35 years ago. The FAERS database does not have significant risks associated. They do identify an increased risk of bleeding, increased INR, and as discussed in our previous comment period, that the data for the denominator on that has not been revealed.

What is the risk with the NSAIDs, acetaminophen, duloxetine, or opioids with regards to bleeding risk and INR? What are the interactions with warfarin? As you can see, this data comes from Clinical Pharmacology. It's a common drug reference used in pharmacies across the United States and Canada.

The drug-drug interactions between NSAIDs, duloxetine, and acetaminophen are not insignificant, specifically when it comes to

anticoagulants and the effect on INR.

The recommendation that opioid and opioid combinations be used as a therapy that is safe and effective for the treatment of osteoarthritis would probably not sit well with another government agency. This is from last month's Centers for Disease Control and Prevention, their recommendations for controlling prescriptions of opioids.

Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain, which I think we would all agree that osteoarthritis does fall under. So we have now a recommendation from two government agencies that are conflicting.

In addition, let's look at some of the other risks associated with NSAIDs specific to osteoarthritis. This is an article from 2010 where Hauser and colleagues looked -- and I'm going to give you a specific quote from the article.

"In osteoarthritis, there's a disruption in the homeostatic state and the catabolic processes

of chondrocytes. It is clear from the scientific literature that NSAIDs from in vitro and in vivo studies in both animals and humans have a significantly negative effect on cartilage matrix, which causes an acceleration of the deterioration of articular cartilage in osteoarthritic joints.

"The preponderance of evidence shows that NSAIDs have no beneficial effect on articular cartilage in osteoarthritis and accelerate the very disease for which they are most often prescribed and used.

"Some of the effects of NSAIDs on the articular cartilage in osteoarthritis include inhibition of chondrocyte proliferation, synthesis of cellular matrix components, glycosaminoglycan synthesis, collagen synthesis, and proteoglycan synthesis. The net effect of all or some of the above is an acceleration of articular cartilage breakdown."

I don't typically read slides out loud, but I felt this one was important.

Another article that looks specifically not

just at NSAIDs but included acetaminophen in end-stage renal disease, this was a 1994 publication from New England Journal of Medicine, 716 patients. Approximately 8 to 10 percent of the overall incidence of end-stage renal disease was attributable to acetaminophen use. They actually stratified by the quantity of these medications that was used.

A cumulative dose of 5000 or more pills containing NSAIDs was also associated with an increased odd of end-stage renal disease, odds ratio of 8.8.

The reason that I've taken the time to point out some of these details from these two other studies is that, yes, we do have some options that are commonly used and that are the standards of care. But it must be acknowledged that those are not without risk of their own, both of similar scope that the FDA presented with regards to MSM and beyond.

From the FDA's briefing document, they cite a number of trials showing a -- one of their

trials, they showed a 25-percent reduction in WOMAC pain score; another one that showed a mean pain decrease of 21 percent of the same, and that there were trends in all studies in favor of MSM in physical function, which means our patients are actually telling us, and we're actually able to observe an improvement in their physical function.

Based on minimal evidence of efficacy, the possibility of a potential serious interaction with anticoagulants and risk of bleeding and the availability of approved alternatives -- well, I think that we've done a good job of having a discussion on what is that actual risk, that potential serious interaction risk, and what is the safety profile of some of the approved alternatives. They're great medications. We all have them in our homes, but they are not without risk of their own.

What is happening in the real world? We know that MSM is commonly available. We know that we can go into any grocery store, into any corner drug store and to nutrition stores and buy MSM by

the truckload. In the world of compounding, it is not used monotherapy. If you need it monotherapy, you can go buy something like that over the counter.

In the world of compounding, it is used as an adjunctive medication, and it is important that we have appropriate screening in place for these patients. If it's not available as a prescription medication as an option, then we lose that ability to appropriately screen and counsel patients.

Typically, the combination therapies include glucosamine and chondroitin, but most commonly with an NSAID. As was very well stated by the FDA regarding the differences between dietary supplements and a compounded medication, it cannot be combined with an NSAID and still maintain its status as a dietary supplement. This would really tie the hands of your prescribers, as well as your treating team.

There are over 1600 products containing MSM sold in North America. There are 12 that claim USP, and those are verified to meet the compendial

standards of USP. Here is a quick screenshot from the doctor we're all familiar with, Dr. Google. You can see the various combinations that are often used with MSM in the manufactured CGMP dietary supplements. There are monographs both for the chemical, as well as for the tablets in the current version of USP.

Now, something that was very interesting in the discussion that came out earlier this morning is this notion that health or disease claims are made for compounds, and that is the scope with which we are evaluating the substances. The FDA asked about how these materials are used in compounding. That is the scope with which the submissions were made.

When you have MSM being submitted, the line on the form said something to the effect, how is it commonly used or what are the anticipated uses? I don't remember the specific verbiage, but it was not saying what is the indication for this. When these nominations were submitted, it was never indicated -- or never meant to be an indication.

To phrase that another way, for the substances that you all have voted yes on and that FDA has recommended that a substance be added to the list, is that saying that the yes vote for N-acetyl-D-glucosamine or Dibutyl squarate are indication approvals?

I would argue no, that is not the intent of FDA; that is not the intent of this committee. We must remind ourselves that when we're voting on these things, we're not giving them an approved indication.

The presence on the positive list, on the bulk drug substance list, does not give it a de facto indication of any sort. That is not in the DQSA H.R. 3204, nor is it in any of the documents set forth by FDA.

Placement of any of these substances on the list is not an indication approval. It means that with receipt of a valid patient-specific prescription, a compounding pharmacist can work with that physician to fulfill the needs of that patient. Thank you.

DR. VENITZ: Okay. Thank you. The next nominator presentation is from Dr. Gruber.

Nominator Presentation - Christopher Gruber

DR. GRUBER: My name is Chris Gruber. I'm with Fagron Group. I would like to provide the disclaimer that we sell MSM with our company.

Thank you, Dr. A.J. Day. I'd like to supplement his discussion about MSM, looking at the brief overview of the GRAS notification of MSM submitted by Bergstrom Nutrition in 2007, which also had an FDA response.

The notification provided an assessment by Bergstrom Nutrition for a potential total MSM supplementation from all sources, including the dietary supplementation of opti-MSM, which was the name of the product proposed, averaging 2.9 grams per day up to 4.8 grams a day at the 90th percentile.

Both foods and supplements containing MSM were discussed, so there's a lot of food and supplements on the market currently. I actually got a full page from the FDA review. The most

compelling information is from Kim et al., which was discussed earlier, where 50 arthritis subjects received MSM at a dose of 100 milligrams per kilogram per day for 12 weeks, noting there were no significant ADRs.

There were actually no abnormal changes in clinical chemistry, hematology, urinalysis, parameters for MSM ingestion, no changes in complete blood counts, differential white blood cell counts, hepatic and renal functions, lipid profiles, BMI, vitals, stool occult tests, swelling, and tendonitis in the knees.

Related to safety, the GRAS notification included animal studies, which showed an LD50 range of 2 grams per kilogram up to 20 grams per kilogram, where there were actually no significant adverse effects. But there actually was occurrence of death in one rat.

In the actual FDA review, it was stated there were no safety pharmacology studies found in literature for MSM on the impact of CNS and respiratory systems. However, it was noted in the

GRAS notification studies for both of those in humans in the GRAS dossier, and I'd like to read just a quick summary of these.

On the CNS effects in 2001, they investigated levels of MSM in the brains of individuals, both healthy and with memory loss, following daily administration of 1 to 3 grams of MSM for various periods of time. There was actually no adverse clinical or neurochemical effects of MSM.

It was stated from a nonclinical perspective that data for oral toxicity is limited, and actually Dr. Day had stated this as well. There was no data for other routes of administration.

I did want to point out that in the GRAS notification by Bergstrom that there was information on use of a topical ointment in rats with no irritation. There was actually information about intranasal use in rats with no irritation. There were actually some ocular studies in albino rabbits where there was a slight irritation, but it resolved in 72 hours. There was an intradermal

study in Guinea pigs where no ADRs were actually reported.

In the FDA review, it was stated that there was no systemic pharmacokinetic data for MSM. However, there is information on the serum levels and urinary excretions of MSM as a metabolite of DMSO.

In the GRAS notification, in a human clinical study, Egorin et al. 1998 investigated plasma concentrations and pharmacokinetics of DMSO and its metabolites that result from delivery of stem cell preparations. The infusions lasted for 20 to 120 minutes. Plasma concentrations of MSM were noted, and the urinary excretions of MSM were noted, as well as for DMSO.

Also, in another study, the oral administration of DMSO at doses of 1 gram per kilogram to 6 human subjects, the peak concentrations of MSM were noted after 72 to 96 hours. The serum levels were noted, as well as the urinary excretions in that. In summary, the pharmacokinetics of MSM in DMSO, which is a parent

compound of MSM have been studied.

It was stated there was not literature describing topical administration of MSM in the FDA review. However, under FDA guidelines -- and this was discussed earlier -- you may compound with an FDA-approved chemical or component of an FDA-approved drug where there may not be any data on other routes of administration.

In the FDA's response to GRAS notification, there was only a request for clarification of discrepancies related to the daily average consumption and the parts per million in milk. That was the only concerns they had initially.

The FDA concluded there could be significant issues with MSM in patients using anticoagulants relative to the FAERS reporting. I wanted to read this statement from the FDA website. I know we talked about occurrence, but there were a couple other items listed on the FDA website that weren't mentioned.

This is the statement, "First, there is no certainty that for a reported event, adverse event

or medication error, that was actually due to the product as far as causality, the FDA does not require that a causal relationship between a product and the event be proven. And the report does not always contain enough detail to properly evaluate an event."

Now, I will tell you that regarding anticoagulants, my spouse is a pharmacist at the VA, and she actually manages Coumadin clinics. Now, I'm not a professional by association, but I will tell you in the process that she describes and what I've seen as a pharmacist in practice, there are a lot of items that you have to be aware of when taking warfarin or Coumadin therapy. And you have to be aware of how those ingredients affect your INR in measuring those levels on a weekly or monthly basis.

In the FDA's response to the GRAS, which they did provide a formal response in 2007, they had no further clarifications under the intended conditions for use. The FDA has intended that it is the responsibility of Bergstrom Nutrition to

ensure the food ingredients that are marketed are safe, focusing on the word "marketed." However -- there were a few comments made earlier -- a pharmacist cannot compound with MSM under the direct supervision of a provider or prescriber.

After making these statements, I would like to recommend including MSM on the list because of the benefit it offers in compounding. I will say, as an additional disclaimer, that I did take my glucosamine chondroitin with MSM this morning when I woke up. And that's all.

Adjournment

DR. VENITZ: Okay. Thank you, Dr. Gruber. That does conclude our session, and we are going to break for lunch now. The meeting is going to reconvene at 1:30 sharp. Enjoy your lunch.

(Whereupon, at 12:32 p.m., the morning session was adjourned.)