FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Tuesday, October 27, 2015

1:30 p.m. to 4:24 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

**Meeting Roster**

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

**Cindy Hong, PharmD**

Division of Advisory Committee and

Consultant Management

Office of Executive Programs

Center for Drug Evaluation and Research

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**(Voting)**

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*(Consumer Representative)*

Director of Health Research Group

Public Citizen

Washington, District of Columbia

**Gigi S. Davidson, BSPh, DICVP**

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*(USP) Representative*

Director of Clinical Pharmacy Services

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**Padma Gulur, MD (via phone)**

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Senior Vice President and Head of Regulatory Affairs

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**William Mixon, RPh, MS, FIACP**

Owner-Manager

The Compounding Pharmacy

Hickory, North Carolina

**TEMPORARY MEMBERS (Voting)**

**Vincent Lo Re III, MD**

***(Participation in deoxy-d-glucose and glycyrrhizin discussions via telephone) October 27th and 28th***

Assistant Professor of Medicine and Epidemiology

Division of Infectious Disease, Department of Medicine

Center for Clinical Epidemiology and Biostatistics

Perlman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

**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

Department of Medicine

Columbia University

New York, New York

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:30 p.m.)

**Open Public Hearing**

DR. VENITZ: We will now proceed with the second session for today. Before I follow the schedule, just for the record, all committee members did receive the third nomination for MSM. It's a one-page document that everybody should have received.

All right. Let's get back on track. I will now read the following open public hearing statement into the record.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the

committee of any financial relationship that you may have with a product and, if known, its direct competitors.

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

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

The FDA and this committee place great importance in open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

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

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

I'm now calling our first open public hearing speaker to the microphone please.

DR. BENJAMIN: Good afternoon. My name is Bona Benjamin. I am director of medication use quality improvement at ASHP, the American Society of Health System Pharmacists. I have no conflicts of interest or financial relationships with any compounding pharmacy.

On behalf of ASHP, I would like to thank the FDA for the opportunity to provide comments to the Pharmacy Compounding Advisory Committee on substances considered for inclusion to the Section 503A bulk substances list.

ASHP believes that this committee plays an important role in the agency's decision-making process as it implements the compounding provisions

of the DQSA. Our organization represents pharmacists who service patient care providers in acute and ambulatory settings. Our more than 40,000 members include pharmacists, pharmacy technicians, and student pharmacists. For over 70 years, we have been on the forefront of efforts to improve safe medication use and patient safety.

ASHP's members work in organizations that perform sterile compounding every day. They also compound medications that are customized to an individual patient's clinical needs. But just for purposes of transparency, our members generally prefer to dispense ready-to-administer FDA-approved sterile dosage forms if commercially available.

The majority of our sterile compounding is preparation of sterile drugs for administration and only 1 of the 9 nominated substances, alanyl-D-glutamine, would likely be considered for formulary addition in most hospitals where our members work. Therefore, my comments today address our general perspectives and outline a few concerns about specific substances for the 503A list.

First, in our review of the nominations, we found that few of the ones that were submitted provided enough specific information to answer what we considered some fundamental questions: why is the compounded drug needed; does it effectively treat the stated indication; what are the precautions of use; what are the advantages over an FDA-approved product; what is done to ensure safe compounding?

We do understand and agree with the comments from the American College of Advancement in Medicine and others about the significant time commitment required to fill out the nomination form. However, absent even the minimal information I mentioned, we found it challenging to determine a case for adding any of the nominated substances to the list without doing our own research.

So we did that. In terms of evidence in the biomedical literature, we used ASHP's extensive drug information resources, as well as FDA's comprehensive review. However, sometimes we could not either confirm the information supplied by the

nominators or we found no relevant information at all.

We also found that of the studies that were available, many of them failed to rise to the rigor of a well-designed clinical trial, although we are still willing to consider them. But in the cases where we could find no information, we were not able to support adding substances to the list.

In terms of dietary supplements compounded as injectables, given serious adverse events in patient deaths from poor compounding practices, including one significant outbreak where intravenous nutrition was compounded from nonsterile components, ASHP has serious concerns about using oral dietary supplements as raw material for compounding intravenous medications.

We didn't find recommendations in the meeting background information nor our own research for assuring that compounding procedures for these dosage forms adhere to applicable USP compounding and quality standards. In these cases, we are not able to support addition of the substances to these

lists unless we would have this assurance.

In addition, we were unable to find in the compounding world that we don't deal with, the external compounding world, any suggested SOPs, or recipes, or compounding techniques that would help us understand how this might be done safely.

Fourthly and lastly, in terms of the use of unproven therapies for treating cancer and other serious diseases, according to the National Center for Complimentary and Integrative Health, and I quote from their website, "No complimentary health product or practice has been proven to cure cancer," and we would probably suspect that this is true for other serious diseases. Unfortunately, this concept often gets lost in the myriad of miracle cure claims that one can find in a casual stroll through the internet.

In general, ASHP recognizes and respects the desire of patients for access to complimentary or integrative treatments for cancer and other serious diseases. We note that academic medical centers have begun to offer complimentary therapies as

components of evidence-based integrative cancer care programs. In these settings, complimentary therapies are used to supplement rather than replace conventional treatment.

We also believe that collaboration between the patients' oncologists and naturopathic practitioner afford the patient the best chance for optimal outcomes. However, ASHP does not support the use of unproven medicinal substances to the exclusion of FDA-approved conventional therapies except in well-designed clinical trials with human subject protections in place.

In addition to these general perspectives, we offer the following specific comments. We concur with the position of the American Society for Parenteral and Enteral Nutrition that intravenous glutamine supplementation potentially benefits a selected small population of critically ill patients.

However, we are also concerned about formulating this substance in a sterile multiple dose form. Therefore, we recommend that the

compounding of this substance be left to 503B as drug establishments or that the FDA explore using its regulatory discretion to allow importation of dipeptiven, a foreign-approved glutamine infusion, if appropriate.

For MSM or methylsulfonylmethane, we could not find any data from either animal or human studies with which to evaluate the safety of IV MSM, including the studies provided by the nominators. Therefore, we support FDA's recommendation against adding this supplement to the list of bulk substances. We note that MSM is readily available as an oral dietary supplement marketed as a commercial product from a number of manufacturers.

For curcumin, we agree that the data suggests a significant therapeutic or maybe a number of significant therapeutic roles for curcumin, including the chemoprotective one. However, we agree with FDA that the use of this agent to treat precancerous conditions may delay turning to standard of care therapeutic options.

Poor solubility, and poor oral absorption, and the pharmaceutical manipulations required to increase bioavailability may present demonstrable difficulties for compounding for curcumin that we do not know can be overcome by techniques associated with traditional compounding.

The nominators have also proposed the IV route for this substance, which likely presents additional challenges for formulation. Therefore, absent sufficient information to resolve these questions, we, again, concur with FDA's recommendation to exclude this substance.

For germanium sesquioxide, rubidium chloride, and deoxy-D-glucose, which have not been discussed yet, again, we concur with FDA to exclude these substances due to their potential for use as treatment in lieu of standard therapies for cancer and the potential to delay seeking conventional treatment should disease progression occur.

We have no objection to the use of glutaraldehyde to treat warts. We do not comment on nonmedicinal uses such as the one for fixation

of cardiac tissue other than to note that in the case of compounding glutaraldehyde, it's considered a health hazard and workers have to be protected from occupational exposure.

Glycyrrhizin, we, again, concur with FDA's recommendations to exclude this substance due to the risk of compounding a sterile injectable from an oral food supplement and the use of an unproven therapy to treat a serious disease.

Lastly, for domperidone, ASHP concurs with FDA's recommendation to exclude this substance based on the enhanced risk of QT interval prolongation in the target population in women and the import ban that is still in effect for this product.

Again, we thank the agency for the opportunity to provide public comment in this forum and encourage the agency and the committee to forward any requests for additional information or questions to ASHP. Thank you.

DR. VENITZ: Thank you. Now, we have our second open public hearing speaker, I think. Maybe

we don't. Oh, we do.

MALE SPEAKER: I was scheduled for this afternoon [inaudible – mic off.]

DR. VENITZ: I thought we had two in this slot and one at 4:15. Are you at the 4:15?

MALE SPEAKER: Yes.

**Committee Discussion and Vote**

DR. VENITZ: Okay. It looks like our open public hearing is concluded unless I'm missing something. Okay. So the open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience until 4:15.

We will now begin the panel discussion portion of the meeting. We have two bulk substances to discuss, and I suggest that we go in order and start discussing and getting ready to vote on MSM.

Any comments, any questions? Dr. Vaida?

DR. VAIDA: Regarding the MSM, I think Dr. Day answered one of my questions on the indication that any drug that goes on the list,

we're not looking at indications. Once it goes on, you have a prescription, you could fill it for whatever you want, a valid prescription.

But the second is, once again, the form of the drug. It looks like -- and I mentioned before -- that this is actually being put forth for oral, topical, ophthalmic, and injection. And it looks like both presenters or supporters actually have that on their list, so I'm taking -- unless we say otherwise, if it gets on the list, it'll be open for any of those forms?

DR. VENITZ: I think that's a question for FDA, right?

DR. VAIDA: Right.

MS. AXELRAD: So the question is if it's put on the list without qualification, can it be used for any use including ophthalmic or whatever. Yes, the answer is yes unless you restrict it to some -- unless your recommendation is to restrict it to some dosage form or something like that where the compounding pharmacist is likely to know how it's going to -- you know, will know with the

dosage form is obviously. I mean if it's for topical use only, that's clear.

DR. VENITZ: I would suggest, for the record as we've done before, after we go through the vote, you all have a chance to provide comments. And if that's something that's important for your vote, you would want to express, for the record, what dosage form or what routes you find acceptable or not.

DR. CAROME: Mike Carome. Just a couple sort of general comments. As I said at the first meeting, under 503A, we have to remember that we're waiving all the requirements that are intended to ensure the safety and efficacy of drugs, so there's no new drug application; there's no labeling requirements that are typically found in a drug to ensure their safe use; there's no good manufacturing practice requirements.

For me, there has to be a significant amount of evidence to justify including a drug on this list, which is now part of an FDA-approved product and not covered by a monograph. Modern medicine is

evidence-based, and for the two drugs discussed this morning, I didn't see much evidence to support the effectiveness or safety of either product.

There were comments made about there are dietary supplements that may include these ingredients, and so why will we place limits on compounding these products?

I think I'd made several comments. One is there are many people who feel that the regulations of dietary supplements are inadequate; many of the uses of dietary supplements, there is a lack of evidence to support the uses for which they are often promoted.

Often when a dietary supplement is finally subjected to a randomized clinical trial, and there have been some funded by NIH, we often find that the evidence from those clinical trials finds that there is no evidence to support their safety and effectiveness for the proposed uses.

For me, the fact that these products may exist in a dietary supplement isn't relevant to considering whether they should be compounded as

drugs.

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

MS. DAVIDSON: Gigi Davidson, USP representative. I think it's been adequately discussed that oral use of MSM is provided for as a dietary supplement. That won't stop if we do not add it to the list.

If we do add it to the list, as Allen brought up, then that opens the gate for any indication, any route. And that concerns me because if we do add it to the list, then what incentive would there be to develop a USP drug monograph for it because the dietary supplement monograph that USP has already written has already been very well explained as to why that's not legally representative of a drug.

If there's no incentive for USP to develop a monograph because it's on the list, then by what standards will compounders choose these, for lack of a better term, dietary supplements to compound with? What standards are out there for purity,

identity, strength, and quality? That's what USP's mission is, is to determine those by virtue of monographs.

I would point you to the monograph for MSM that was provided in the nominators' notes. Look at the results for yeast and mold. There are 10-colony-forming units per gram of substance. If we use that to make an injection, we're already in dangerous territory.

I am honestly quite torn about whether to put this on the list or whether to not put it on the list. But I don't think that putting it on the list is going to guarantee quality materials will be used. That's already not an option for dietary supplement manufacturers. They can ignore dietary supplement monographs as it is.

DR. VENITZ: Any other comments? Yes, Mr. Mixon?

MR. MIXON: I would encourage the committee to approve the use of this drug for compounding for topical or oral use only and specifically eliminate the parenteral dosage form.

DR. VENITZ: Any other comments?

Dr. Jungman?

MS. JUNGMAN: I think I would add to what Dr. Carome was saying, that it seems like we have a decision to make as a committee about how we're going to deal with these substances that also have uses as dietary supplements. It is tricky and awkward, I think, to contemplate not including on the list of substances available as a dietary supplement.

But I'd submit that claims matter. And the fact that a substance is available as a dietary supplement, it's a big leap to go from there to saying that it should be available in a way that you can make drug claims about it and these treatment claims about it.

We do have a list of criteria that we all agree to for how we were going to evaluate these bulk drug substances, and I would just submit that we should look at those criteria. If under those criteria, we think that it's appropriate to include a drug on the list, we make that recommendation.

But the fact that it's available as a dietary supplement, that's really a separate consideration because we're talking about a different set of claims.

DR. VENITZ: I would second that wholeheartedly. I think we have a set of four criteria that were discussed in detail, and whether the product that we're looking at is a dietary product or not, that's a secondary consideration.

Yes, Dr. DiGiovanna?

DR. DiGIOVANNA: Yes, DiGiovanna. Could you reiterate -- maybe I could ask you exactly what you mean by if we put it on the list, then drug claims or therapeutic claims can be made about it? Because my understanding was not that, was that if it's on the list, that it can be compounded as a prescription for an individual patient, but that it did not permit medical claims to be made for it.

MS. AXELRAD: If you put it on the list, you're saying it's appropriate bulk drug substance for use in drug compounding. A person who is compounding it can offer it for sale. And many

compounding pharmacies do, on their website, say that we are offering MSM for arthritis and sinusitis and whatever -- you know, I'm not saying this specific, but they offer claims about that. If they do that, then the standard by which they're judged is whether they're false or misleading. Our law says that you can't make false or misleading claims about a compounded drug.

DR. VENITZ: Yes, Dr. Wall?

DR. WALL: A question to follow up your comment, Jane, are we allowed to make one of these products prescription only? And in that case, it wouldn't be on a website; it would be a prescription only.

MS. AXELRAD: We've had some questions asked of us in other contexts about compounding over-the-counter products, and we really haven't explored fully what the implications of an over-the-counter product is. Here, we're talking about a dietary supplement product.

Under 503A, as you know, 503A requires that it be compounded upon receipt of a prescription or

in anticipation of getting a prescription. 503A we believe already has a prescription requirement in it. I'm not sure whether putting "Rx only" on it, what effect that would have. We haven't really looked at the prescription requirements as being applied to a dietary supplement. If you are only talking about a dietary supplement, I really don't know what to say about that.

Do you know what I mean? I don't know what putting "Rx only" on would mean. 503A says you need to have a prescription for a compounded drug under 503A.

DR. WALL: I think my question goes back to if a prescriber believes that this is something that legitimately needs to have a prescription, the patient legitimately needs it and they write a prescription for it, does that eliminate the other concern of people doing marketing for mass of these things on the internet and allows it to be done in more of a structured, controlled environment? Or by us putting it on the list, it just nix it for many prescription and everything, period?

MS. AXELRAD: Well, for us, the fact that it has a prescription is important. We believe that is what 503A says, and we believe the prescription requirement is important. But I don't think that it prevents people from mass marketing it directly to consumers and patients and saying, you know, do you have this, that, or the other disease? If you do, contact us and we'd be happy to work with your doctor to have them write a prescription for you for it.

I think that it is some protection, but I really think that the way this is working isn't the way I think people think it works. It works this way in -- in some cases, a doctor has a patient who has unique needs, and they decide that a compounded drug is the best thing, and they write a prescription for it. But all too often, we see it's working the other way, that the demand for this is being generated by somebody who's doing direct-to-the-patient advertising and then talking to the doctors to write a prescription.

DR. VENITZ: Mr. Mixon?

MR. MIXON: I'm just trying to react to what Ms. Axelrad just said. Obviously, you know of circumstances that we don't know. I would hope that most compounders would be above trying to drum up prescriptions for compounded MSM. I mean clearly, it's illegal to -- and we know it's illegal -- to make medical claims for compounded medications.

I would submit that if somebody is putting on their website that they're compounding for over-the-counter use, you should take an enforcement action against them. I mean, in my mind and many other compounders, that's clearly an unapproved new drug.

DR. VENITZ: Okay. Are we ready for a vote then?

DR. CUSH: I'd like to --

DR. VENITZ: Go ahead.

DR. CUSH: -- make a comment if I could.

DR. VENITZ: Go ahead.

DR. CUSH: I just want to say that both these products are obviously in widespread use.

The issue before me, I guess, is should they be allowable or not allowable for compounding use. I can just say that MSM is not in the arsenal or menu of compounds that has any utility in arthritis, musculoskeletal pain, or osteoarthritis.

It's not in any major textbook on the topic of osteoarthritis as a reasonable choice. It's not in the Cochrane review showing any kind of efficacy. It's not in any guidelines in American College of Rheumatology or the European League Against Rheumatism, and nor is it an approved product in any way for use in arthritis.

Whether it's safe is sort of a moot point. It just isn't used and shouldn't be advocated solely or in combination. It sort of makes zero sense. And if there's any risk, then you've already gone over the threshold.

Again, I really fail to see the utility of MSM as a product for any sort of structure function claim or any kind of medical indication for the treatment of musculoskeletal pain or arthritis. Again, I spent time looking for information and

evidence that would support that. I could come up with nothing other than the 168 patients in two trials with basically negative outcomes.

I feel differently about curcumin. Although the evidence that was presented here was for GI indications, I think curcumin has utility and could have at least a structure function claim. If this moves forward and stays on the list, I think that could actually promote more research.

If you compare the amount of reports on both of these drugs in the literature, there's a handful, 20 or so, for MSM, but there is 40 times, 50 times that amount for curcumin in the amount of research that's being done on this.

So again, I just wanted to clarify what the rheumatologists' view would be on these compounds and their utility.

DR. FOJO: Can you hear me?

DR. VENITZ: Yes, go ahead please.

DR. FOJO: This is Dr. Fojo. I had questions about that as well, and that is -- he spoke briefly about curcumin; he had before. But I

imagine that the question -- I haven't seen the question yet -- in the voting will be with regards to the three indications that were being considered because it's not for us to decide whether or not, oh, this might have some use in a disease; let's approve it, that then it would be widely available for other things and then could be used for these three indications for which, in my opinion, there is no good evidence that it should be used.

Am I correct in that? We are going to be deciding about the particular indications, and we should not think that because they are possibly valuable in another situation they should be approved. Correct?

DR. VENITZ: Dr. Axelrad?

MS. AXELRAD: Yes. Let me address that because you have not had the benefit of our discussions and background that we presented at previous meetings.

Basically, if a drug substance is put on the list of drugs that can be compounded under 503A, unless we limit its dosage form, generally, it can

be used for anything that people want to use it for. If we just simply put the substance on the list, they can use it for cancer, or they can use it for arthritis, or they can use it for whatever they choose to use it for.

What we have said in the past is that just because something is not put on the list does not mean that it's never available. What we're basically saying is that patients shouldn't be given what is basically an unapproved drug. If it's going to be used to treat someone, it should be done under an investigational new drug application, where the patient can be advised that it's an unapproved drug, that it hasn't been shown to be safe and effective for anything in particular about any other issues associated with it like warnings, and precautions, and drug interactions, and things like that, and patient monitoring.

The consequences of not putting something on the list doesn't mean that nobody can ever get it. It means that it needs to be provided under an IND with controls that are designed to protect the

patient.

DR. FOJO: But then, what you're basically saying is that off-label use is allowed. This seems to me an incredibly difficult and almost not manageable situation because for curcumin itself, you or someone read the list of the 20 potential applications, bloating and chronic abdominal pain and all sorts of things.

If one kept coming back to all of those one at a time, one would say, well, this isn't a life-threatening disease. Sure, when chronic, this is an important problem to the patient, and curcumin has possibly a reasonable side effect profile that maybe it could be tried in this situation. At some point, if it gets approved for bloating, you're saying that then it could be used off-label for the three indications that today we might decide unindicated for. Is that correct?

MS. AXELRAD: Yes, that's correct. These are unapproved drugs. If someone got an approval for curcumin for something, then under our statute, it can be used to compound for other uses.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: Just a point of order. If, as has been discussed, MSM was added to the list but restricted to a dosage form, remind the committee how that happens in the voting process.

DR. VENITZ: There will be the official vote by pushing the button, and I'm going to instruct you painfully, slowly in a minute how that works. And then we go around the table. Everybody can tell us how they vote for the record, and then add anything that you wish to justify your vote to qualify it any form that you choose.

Dr. Carome?

DR. CAROME: Just to clarify, I wasn't sure the name of the individual who was just speaking on the phone, but he asked, I think, whether we're voting for each of the indications discussed for a particular drug. He may have said it but I -- but no, we're voting whether to include the drug on compounding list, the 503A list.

MS. AXELRAD: Just to be clear, we're asking, Should the drug be put on the list or not

put on the list. If it is an unqualified yes, it should go on the list, then it can be used for anything. This is really different than a drug approval. It's not being approved at all, and it's not being linked to any specific indication in the sense of a new drug application.

There will be no labeling like there is in a new drug application that would be informed by the clinical trials in which you study the drug. In fact, it's likely there would be very little labeling at all on one of these products. It's basically a yes or no.

As Dr. Venitz is going to instruct you and sort of mentioned just now, you can, in explaining your vote, qualify it in some way. In the past, the committee voted to put tranilast on the list, I believe, for topical use but not oral use. In a previous meeting, you did qualify your vote that way.

DR. VENITZ: Let me just add to that. We have four criteria that we've been using in the past and we have to learn to live with in order to

have some semblance of consistency over time. If we're not approving drugs, we are putting bulk drug substances on a list according to four criteria that we have agreed on.

Mr. Mixon?

MR. MIXON: I'm sorry. Just for clarification, are we having discussion about curcumin and MSM or just MSM? Thank you.

DR. VENITZ: Dr. Pham?

DR. PHAM: I wanted to ask about labeling, so that was a better clarity point. I thought in previous discussions, there were opportunities to comment on how certain things could be commented in labeling. Was that because of the different list of things that could be compounded? And now we're talking about the list of Do Not Compound, and that's why we don't have the same potential for labeling?

MS. AXELRAD: We're only talking about the bulk drug substances that can be used to compound, but basically we don't prescribe any real labeling requirements for compounded products. Under the

law for 503B outsourcing facilities, the law says that certain things need to be on the label of those compounded products, but there are no comparable provisions in Section 503A for what goes on the label for a compounded drug.

In no way would a label for a compounded drug ever look like the label for an approved product where you have the physician labeling, the package insert with all the detail that's informed by the clinical trials that you had that supported the approval of that drug because you don't have those in these cases.

DR. VENITZ: Let me propose then that we move to our vote. I'll read the instructions once, but we're going to apply them at least for the rest of this afternoon. The voting instructions are as follows.

The panel will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone: yes, no and abstain. Please vote by pressing your selection firmly three times. After everyone has

voted, the vote will be complete.

Voting will be on four products, but we will do that one at a time. All vote questions relate to whether these products should be included on the withdrawn or removed list. And I think we're going to get a slide to show that everybody knows what they're voting on.

After the completion of each vote, we will read the vote from the screen into the record and then hear individual comments from each member.

Can we have the first voting question? Okay. I'll read it aloud for the record.

FDA is proposing that MSM NOT be placed on the list of bulk drug substances that can be used in pharmacy compounding in according with Section 503A of the FD&C. The question that you are voting on, should methylsulfonylmethane be placed on that list? If you vote yes, it will be place on the not to be compounded list.

(Chorus of nos.)

DR. VENITZ: So if you vote yes, you agree with FDA.

(Chorus of nos.)

(Laughter.)

DR. VENITZ: We always have that problem. Okay, so if you vote yes, you disagree with FDA --

MS. AXELRAD: If we can just put it, if you vote yes, it goes on the list; if you vote no, it does not go on the list.

DR. VENITZ: So a yes vote is disagreeing with FDA's recommendation and a no vote is agreeing with it.

MS. JUNGMAN: But can we be clear, too, that it's a list of bulk substances; it's not a Do Not Compound List. It would be a list of things that it's okay to compound as opposed to a list of things --

DR. VENITZ: Yes.

MS. JUNGMAN: Right.

MS. AXELRAD: The question is, should methylsulfonylmethane be placed on the list of drugs that are acceptable for use in compounding?

DR. VENITZ: So "yes" means it will be compounded or you will be able to compound it. Do

we have any questions from the attendants on the phone? Because I think you're going to have to email your vote.

DR. CUSH: We're good.

DR. VENITZ: Okay. Everybody has the little red lights blinking, so go ahead and push your button of your choice.

(Vote taken.)

DR. VENITZ: Dr. Gulur, please vote by phone meaning send your email.

DR. GULUR: I sent the email in. Are you able to hear me?

DR. VENITZ: We haven't gotten it yet. Hold on. Okay. The folks on the phone, you have to mute, otherwise we get feedback, unless you talk. Mute your computer.

DR. GULUR: My computer's muted.

DR. VENITZ: Do we have all the votes? Dr. Gulur, try it again.

DR. GULUR: Okay. Trying again.

DR. VENITZ: Thank you.

DR. GULUR: Did you receive it?

DR. VENITZ: We still haven't gotten it yet.

DR. GULUR: Is there a number I can call?

DR. VENITZ: I think you're being called as we speak.

DR. GULUR: Okay.

DR. VENITZ: Where is Jeopardy music when you need it?

(Laughter.)

(Pause.)

DR. HONG: For question 1, we have 1 yes, 10 nos, and zero abstain.

DR. VENITZ: Okay. Let's start going around the table. Dr. Carome, you go first.

DR. CAROME: I voted no because there are safety concerns and there's a lack of evidence that the drug is clinically effective.

DR. WALL: I voted no because I didn't see a lot with efficacy. I thought about, well, they could use it orally and you can do that over the counter, so I voted no.

DR. DiGIOVANNA: DiGiovanna. I voted no for the same reasons.

MS. DAVIDSON: This is Gigi Davidson. I voted no for same reasons. I would also add that adding it to the list, I had concerns about routes of administration and indications that would be wide open.

MR. HUMPHREY: William Humphrey. I voted no for the same reasons.

DR. PHAM: Katherine Pham. I voted no for the same reasons, more so the lack of efficacy.

MS. JUNGMAN: Elizabeth Jungman. I voted no also because of concerns about the lack of effectiveness data and safety signals.

DR. VAIDA: Allen Vaida. I voted no for many of the reasons that were already cited.

DR. VENITZ: I'm the odd man out. I voted yes. I thought there was sufficient evidence in terms of safety, even though I'm obviously aware of what could happen with respect to INR.

However, we were shown a laundry list of products that are already on the market, so there is a long history of use. I didn't see any problems with physical characteristics and evidence

of effectiveness. I'm not sure how much we are going to get for any of the products we're going to look at in the future. Since I'm outvoted, I would have added the restriction to oral and topical use only.

Okay. Do we have anybody on the phone that needs to tell us how they voted? Dr. Gulur?

DR. GULUR: I voted no for the same reasons that have been stated already, lack of efficacy and safety data.

DR. VENITZ: Okay. Thank you. Then let's start the discussion on the --

DR. CUSH: Hello. One more. Sorry.

DR. VENITZ: I'm sorry.

DR. CUSH: This is Dr. Cush.

DR. VENITZ: Go ahead.

DR. CUSH: Okay. I voted no for a lack of data on efficacy or safety. And I would also state this compound should not be used in other administration, meaning topical or anything other than oral. It really shouldn't be used at all.

DR. VENITZ: Okay. Thank you. Then let's

start our discussion of the second bulk substance, our perspectives of bulk substances. Any discussion, any comments, or everybody is ready for the vote? Mr. Mixon?

MR. MIXON: I want the committee to consider somebody with oral condition that needs curcumin in a lozenge or a troche. That's a perfect use for a compounded medication. Whether it's a dietary supplement or not, it has utility in that fashion to treat this oral condition.

Anyway, you get my point. If we vote to eliminate the ability of compounders to compound with curcumin, then we're going to lose that therapeutic treatment option.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. I was influenced by the large amount of curcumin that is ingested by many people worldwide with a broad safety net. I was less impressed with the spectrum that we were presented of the diseases where it was evaluated for efficacy. There are probably many, many more in the literature where individual

patients are considered to potentially have utility from this.

I think, as Mr. Mixon said, the issue of diseases like leukoplakia that may not be very common but are very awkward and difficult sometimes to manage and very diverse between different individuals, where the treatments may involve disfiguring ablation of precancerous areas or potentially other unapproved uses for drugs -- which very well may be effective, for example isotretinoin, which is widely used for leukoplakia in individuals that have had oral cancer and have persistent leukoplakia -- I think for individuals who are unable to do that, having potentially an option of a compoundable product offers a benefit.

I didn't see any evidence of that. So to restrict its availability by prescription for individual patients, where the safety profile we've seen seems to far exceed those of most other drugs, I would think would convince me that a physician should be able to prescribe this product for

individual patients by prescription.

DR. VENITZ: Any other comments by any of our folks on the phone? Dr. Casak?

DR. CASAK: Yes. In regards to the use of curcumin for oral leukoplakia, actually, I presented that information, and it was a study to prevent cancer in oral leukoplakia. Two patients, as you mentioned, benefited from children, but one of them actually developed cancer.

If we look in the briefing document, actually, some other diseases have been reviewed, and there's a pediatric study -- if I remember that -- it was actually conducted in St. Jude showing that there's no effectiveness for it as a mouthwash drug for the treatment of mouth ulcerations and the cycles [indiscernible] related to chemotherapy.

In regards to a comment made before by Dr. Cush, I would like to point that if this drug indeed was a COX2 inhibitor, then we are going to discuss inclusion of a product that it shows at least or shares a mechanism of action that we know

needs to be strictly controlled and studied in much larger populations with products that we know the concentration and everything, because as we know, COX2 products have serious adverse events.

DR. VENITZ: Thank you.

Anybody on the phone with a comment or a question?

DR. CUSH: Yes, I'd like to make a comment. This is, again, Jack Cush in Dallas. I'd like to state that the closing argument made by the FDA reviewer on why this should not be on the list was that inclusion on the list would result in patients avoiding current standards of care.

That's a very hyperbolic statement for which no evidence was provided. In fact, anyone who knows patients who take over-the-counter products and nutraceuticals often do so with prescription products.

DR. VENITZ: Dr. Cush, I'm just being advised that you are not supposed to vote on curcumin, so I'm not supposed to let you talk any further. I apologize.

DR. CUSH: Why am I not supposed to vote on curcumin?

DR. VENITZ: I'm just the bearer of bad news.

DR. CUSH: Well, that's a mistake since -- all right. Thank you very much.

DR. VENITZ: Any other comments? Yes, Dr. Jungman?

MS. JUNGMAN: So this is probably just a question for FDA. I was concerned about the ASHP public commenter's concerns about the difficulty of compounding the substance for IV formulation given its poor solubility. I'd just be interested in maybe further discussion of how this would actually be compounded and how we could ensure that it was done safely.

DR. LEE: Can I say something? Yes, I'm from FDA. I'm glad you bring this up from the quality perspective because let me just bring up several points for you guys to consider.

First of all, curcumin is a quite a general term. It actually refers to a pure substance all

the way to the mixture. By looking at this, you may need to think about in terms of the context of compounding.

First of all, let's say you can get a mixture, first of all, how do you compound, like how do you know, and how do you actually figure out the doses needed for the patient? Because this is a mixture. For a pure compound, it's very easy.

Then I think also, like mentioned, that this is a poorly soluble drug. If the drug, you cannot absorb in your body, it's pretty much useless. I think from the formulation perspective, it's a little bit more complicated in that sense.

If you formulate it into injectable products, which is going to be a suspension -- let's say if you don't put any solubilizing agent there, then the particle size, particular matter, it becomes a safety concern.

Also, because this general term ranges from pure compound to the mixture, because curcumin does not really distinguish one from the other, how do you -- the stability profile, like the degradation

pathway will be totally different from the pure components and also the mixture. These are the things that, I think, you may want at least to consider from the quality perspective.

DR. CASAK: There is a published article about parenteral solution that they somehow overcame those problems -- I can't remember if it's was liposomal or nano. There are several published small phase 1 studies with parenteral curcumin, but those were not included in this review because we are not talking about those particular products.

DR. FOJO: Hello? This is Dr. Fojo. Can you hear me?

MS. JUNGMAN: Do you mind if just respond to that or just follow up on that? I'm a little bit confused about the mention in this article that we're not considering this -- we would be considering this for any formulation, including IV formulation. Am I wrong about that?

Can you help me draw that distinction? Is FDA comfortable that this could be compounded for IV use safely?

DR. CASAK: No, not curcumin, no.

MS. JUNGMAN: Okay. Then I misunderstood you. Thank you.

DR. FOJO: Hello? This is Dr. Fojo?

DR. GULUR: Dr. Fojo, I can hear you.

DR. FOJO: I had asked this before, and then I'm asking it again. Are we voting on the three indications that were raised by the FDA or on a general application or use of curcumin?

Because as I said, there was a lot of potential indications and quotes, but we've not considered the data for that or thought about it carefully. It seems to me that some of the conversation that's going on here is saying that we should add other considerations.

If that's going to be the case, then, in my opinion, we need to go back and look at those other considerations, and what is the evidence and what is the risk/benefit. I think we're talking about the three indications that were proposed here, and that's what I'm voting on.

Also, I would mention that the comment was

just made by someone who unfortunately is not going to vote and is not too happy with that. But if you start to say, well, patients will take this, but they'll also take other medications, in fact, that's not a don't worry about it; patients will be taking other medications. To me, that's, whoa, beware. They're going to be taking this with other medications.

Then you need to know what are the drug interactions that might occur here because you might take two therapies that might be well tolerated individually, but when they're now combined and that has not been studied properly, then you do have the risk of some unanticipated toxicities occurring.

I don't think to say that, well, don't worry, they'll take this plus the indicated medication, the established medications is something I would feel very comfortable with.

DR. VENITZ: Dr. Pham?

DR. PHAM: I think that the struggle here is that with the COX inhibition, it would have been

probably nice to still see a lot more of that included in that information. I was just looking for anything once that was brought up. And there was even a 2012 pilot study that I was trying to see if that was part of our briefing documents. It was a pilot study of 45 patients that looked at safety and efficacy.

Again, kind of going back to what we discussed earlier, you might not see a lot of robust studies and a lot of clear evidence showing efficacy in these things. And going back to whether or not safety information has been fully inclusive, again, there's this safety and efficacy pilot study that I don't know that it got presented just based on looking at the briefing document, briefly, but the malignancies that developed, I think, in the safety information presented, I struggle with kind of figuring out where that goes in the context, too, because I feel like those were all high-risk patients of developing malignancy to begin with.

I think I did need to actually see a lot

more of the studies related to rheumatoid arthritis or that indication to really fully assess the safety concerns.

DR. VENITZ: Yes, Dr. Axelrad?

MS. AXELRAD: I think it bears repeating what I said this morning just to make sure that people who haven't been at other meetings are clear, that if we vote to put this on the list, then it can be used for anything. It's not just for the indications or uses that we evaluated.

The reason that we only evaluated these uses is that there really was no other support submitted. There was mention of a number of different uses for this drug but no other articles or support for those. So we didn't start looking in the literature for new sources of information with regard to that. If we had had something to go on, we might've evaluated it for another use.

We do have the docket, so if it is not put on the list and if people want to re-nominate the substance for arthritis or some other use and supply support for it, then it could be considered

for that. Also, even if it is not put on the list, it's still available as a dietary supplement.

DR. VENITZ: Last comment, Dr. Carome?

DR. CAROME: But just to be clear, I understand we're not voting for any particular uses, but the only uses for which we had a presentation on and evidence to consider were those proposed by the nominators.

MS. AXELRAD: That's correct.

DR. VENITZ: Mr. Mixon first, and then Dr. Braunstein next.

MR. MIXON: If I were to get a prescription from, say, a dentist or an oral surgeon for this drug, the first thing I would do is, if I didn't have a dose, he or she would probably consult with me about how could this patient use this drug, what do you recommend, what's a dosage form that might work; we'd go to the literature and get the best information we can to make a decision on how to compound the drug in whatever particular dose. And that comment was in response to what somebody said earlier about, well, how do we use it, and how do

you know, and all that.

Also, I would recommend that the committee approve this drug for oral/topical use only and eliminate the IV form of it.

Lastly, one of the conclusions from the FDA presenter was the use of curcumin may delay effective treatment of the serious condition for which curcumin was nominated. Well, that's absolutely not true because if it's by prescription, then the healthcare provider who is treating this patient is in the loop. So that's completely ridiculous to say that. Thank you.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: Yes. This is for Jane. It's an operational legalistic kind of question. If for some reason the committee does not vote to put the drug on the list, with respect to the four lists -- and then it's nominated under a different indication than was reviewed today, would it still be considered under list 1 of the four 503A lists you discussed earlier, so that it could still be compounded while it's still being evaluated?

In other words -- it's getting a little complicated right now. I think we could use a little bit of clarity around that.

MS. AXELRAD: Let me explain the process. Curcumin right now is on list 1. I believe that regardless of how the committee votes, whether they vote yes to put it on the list or no, not to put it on the list, that it will remain on list 1 until we go through the entire process with regard to that substance, which means rulemaking. After today, you'll vote however you vote. We'll go back and consider how you voted. We'll decide whether we want to propose to put it on the list or not. And we'll put out a proposed rule that we'll either propose to put it on the list, or we'll say that we've evaluated it and we propose not to put it on the list.

Then there'll be a comment process so people could comment. As part of that rulemaking, for example, they could give us evidence that says, gee, you should have considered this for

osteoarthritis, or rheumatoid arthritis, or some other use. Then as part of the rulemaking, we would evaluate that.

In all likelihood, we would bring that back to the committee before we went with the final rule and our final decision on whether to put it on the list or not. But it will probably remain on list 1 all during that time unless somebody comes up with some really significant safety concern associated with the substance, which we haven't yet seen.

Does that clarify it?

DR. VENITZ: Okay. I think we are ready for the vote unless somebody is violently opposed to that. I don't have to read the whole -- okay, go ahead.

MR. HUMPHREY: If we decide not to put this on the list, does it prohibit Bill from making a troche?

MS. AXELRAD: At the moment, not. But if ultimately after we take into account your recommendation and we decide that we are not going to propose it for the list, then we will issue a

proposed rule that says we're going to put these 10 substances on the list and we're not going to put these 8 substances on the list or however it comes out.

If curcumin is one of the ones that we're not going to put on the list, people can comment on that. If they think that we are making a mistake and it ought to go on the list, they'll give us more information, and then we'll reconsider it. And we'll probably come back to the advisory committee if there was that kind of a conflict between what we were proposing and what we heard.

Ultimately, it will either go on the list that's in the regulation as something that can be compounded or it will go on list 4 that says it can't be compounded. If it goes on list 4 at the end of the day, people cannot compound with it. But if it goes on the list, then they can. But not now.

In the interim, as long as it remains on list 1, people can continue to compound it while we go through that entire process of a proposed rule

and a final rule.

DR. VENITZ: Okay. Mr. Mixon?

MR. MIXON: Jane, if it doesn't get included on this list of bulk substances that we can compound with, could we compound with the over-the-counter supplement?

MS. AXELRAD: Let's not talk about over-the-counter because I can't talk about that. But if it's just a dietary supplement, if somebody takes curcumin and wants to combine it with another dietary supplement, they can do that. It's not what we would consider a compounded drug as long as they're not making drug claims about it.

MR. MIXON: Well, if I compounded upon prescription a troche from an over-the-counter supplement, is that in violation of the law?

MS. AXELRAD: I can't -- there are over-the-counter drugs and there are dietary supplements. And you're really getting to the point beyond my expertise in this. I think the CFSAN person is here.

But I'm just saying, if it's a dietary

supplement that you can buy at a health food store or whatever and you compound that into a different form or you make it with another dietary supplement, as long as you're not combining it with a drug and you're not making drug claims about it, it's not a compounded product, and we're not overseeing it.

MR. MIXON: No. I'm talking about under 503A pursuant to a valid prescription for an individually identified patient -- this is a list of bulk substances, so if curcumin is not on the list of bulk substances that we can compound with, the way I see it, there's nothing precluding us from walking out and getting a bottle curcumin capsules off the counter and using those to make a troche. And that's essentially what we're being forced to do as compounders. I mean, we're having to do workarounds.

MS. AXELRAD: You're not taking a compounded -- I'm sorry. You're not taking a bulk substance that's called curcumin.

MR. MIXON: Right.

MS. AXELRAD: And you're making it into something.

MR. MIXON: I mean, this is all hypothetical. I have never once had a prescription for MSM or compounded curcumin. But I'm just saying what if a dentist wanted to treat leukoplakia with curcumin; they wanted it made in to a troche where it makes perfect sense because you're treating a condition of the mouth, if curcumin is on the list of substances or not on the list of substances that I can compound with, then my only option to take care of that patient is to compound it from a dietary supplement, which is a far worse condition. It's going to make a worse preparation than if I were able to do it from the bulk powder.

The position that this committee is putting compounders in if we vote not to include it, I mean, it still doesn't preclude, in my mind -- tell me if I'm wrong. I'm trying to get clarification, but I think it's an important distinction, too. If we can still compound with it using a dietary

supplement, then what's the use in not having it approved in its pure form?

The unintended consequences could be that a compounder tries to, God forbid, make an injection out of a capsule of a dietary supplement -- I would hope that would never occur, but I'm amazed every day -- I'm sure you are, too -- as to what people try to do.

Do you see my point? Do you see where I'm trying to -- I'm not trying to be argumentative. I'm trying to understand.

MS. AXELRAD: I want to try and address what you're asking. First of all, a troche is not ingestion. So a dietary supplement, in order to retain its dietary supplement character, it has to be for ingestion. There were some examples given this morning of things that were and things that were not.

They have to be a tablet, a capsule, a powder, a soft gel, a gel cap, or a liquid form. Those are considered for ingestion. But they can't be sublingual, injectable, topical, or nasal, for

example. Those are just examples.

I'm sure that you could come up with a dosage form that I don't know what the answer is, so we'd have to go back to the drawing board and figure it out.

If you are buying a powder, curcumin power from somewhere and you are making it up into a tablet or a capsule for ingestion, then that's a dietary supplement; it will retain its dietary supplement character, and we aren't really touching that here. Whether you put it on the list or you don't put it on the list will not affect your ability to do that.

Similarly, if you want to take a dietary supplement from the health food store and crush it up and make a liquid to swallow, we're not touching that here because you're not changing its character from a dietary supplement. And we're not dealing with that. We're dealing with compounding of drugs.

That's about all I can say about that. It's only if you're doing something with it that is

making it a drug, like you're offering it for sale on your website to treat leukoplakia, for example, and/or you're mixing it with a drug, so you're either making a drug claim about it, or you're mixing it up with a drug, or you're offering a topical or a nasal form of it, which would mean it's not for ingestion.

Then if you do any of those things, then you've crossed into the world of compounding, and unless it's on the list, you couldn't do it. But if you stay out of that world, its presence or absence on the list is not going to be affected by that.

MR. MIXON: Well, taking a capsule and making a suspension is compounding. Taking a capsule, emptying it, and taking the ingredients and making a --

DR. VENITZ: We have a vote. I think that is some discussion that might have to be continued at a later point in time. We're already 15 minutes late, ladies and gentlemen.

The vote is in front of you. Should

curcumin be placed on the list? Yes means it should be placed on the 503A list; no, it should not be. Go ahead and vote please.

(Vote taken.)

DR. HONG: For question 2, we have 4 yeses, 6 nos, and 1 abstain.

DR. VENITZ: Let's go around the table. I guess I'm the left-most person, so I'm going to go ahead. I voted no. I thought there were issues in various -- Dr. Gulur, you go first. You're left more than I am.

DR. GULUR: I voted no. I did not find the argument for the safety or efficacy convincing. In addition to Dr. DiGiovanna's point, it is widely available for oral ingestion and as a dietary supplement, so that will continue if we don't place it -- but for compounding, to turn it into a drug, would want more information.

DR. VENITZ: Okay. Thank you.

Dr. Fojo?

DR. FOJO: I voted no, and I agree with everything that was just said. As I mentioned

several times, I think with regards to the discussion that we had, it's a clear no. It seems to me that if it was another indication that was thought to be possibly valuable, then that should be voted on in the future. For this indication, a clear no.

DR. VENITZ: Thank you. I voted no as well. I would add to what my predecessors said that there is concern on my behalf about the stability, the potential difficulty to compounding property of this, the low bioavailability and high variability, in addition to the issues that were raised.

DR. VAIDA: Allen Vaida. I voted no for some of those same reasons, and it would be available for any route.

MS. JUNGMAN: Elizabeth Jungman. I voted no. I was concerned about the heterogeneity, and the poor solubility, and the limited nature of the safety data. So I wasn't persuaded that the evidence supported drug claims.

DR. PHAM: Katherine Pham. I abstained although I do agree with my colleagues who voted,

their logic towards the no. I still didn't feel like I had all the comprehensive evidence to make the decision, and neither the yes or no really matched how I felt about the product, but do hope that if there are people who will re-nominate this to the open dockets, that they would consider presenting the comprehensive evidence.

MR. HUMPHREY: William Humphrey. I voted yes. I am really troubled about the oncology indications because I don't think there's enough clinical evidence to support that. But the things we didn't hear about today, rheumatoid arthritis and stuff, I think there's a lot of literature about that.

MS. DAVIDSON: Gigi Davidson. I was going to vote no going into this discussion, but I changed my mind to yes because I was convinced of some perception of efficacy for the leukoplakia and lack of alternatives.

The biggest reason I voted yes was at the end of the discussion when it was suggested that I could go out and buy a dietary supplement that is

not regulated and of unknown standard and unknown quality, that concerns me. And I would prefer that something be on the list and in the regulated and controlled environment that Dr. Wall refers to, and that hopefully there might be a USP monograph for curcumin of a higher quality and standard that would not be optional.

I would expect that down the road, FDA would expect some sort of certificate of analysis for substances that are purchased on this list, that are on this list.

DR. DiGIOVANNA: John DiGiovanna. I voted yes. I think its worldwide use is broad, and I think the safety measures are extensive. I was also concerned about this idea that if something is not on the list and can't be compounded, that a dietary substance of less quality, that can be used for preparation to get around compounding, allows the public to be exposed potentially to a less quality preparation. That's it.

DR. WALL: Donna Wall. I voted yes. I thought there was some efficacy use. Quite

honestly, when I was looking at it also, that it said it had a lot of effects on the P450 system, I would rather have an agent like this being dispensed by a pharmacy with appropriate patient oversight as to their medications and look for drug interactions than somebody saying go out and buy it on the marketplace.

DR. CAROME: Mike Carome. I voted no for all the reasons others who voted no stated.

DR. VENITZ: Thank you. We are down two, so now we are proceeding with another three ahead of us. Our next presentation is by FDA, where they're going to present their recommendation regarding germanium sesquioxide.

MS. AXELRAD: Dr. Venitz, before he starts, could I just say one thing?

DR. VENITZ: Please go ahead.

MS. AXELRAD: I thank everybody for their votes and their thoughts on this. I do want to address two things. One is the suggestion that if something is on a compounding list, it will have standards and a certificate of analysis, whereas a

dietary supplement is going to be done according to lesser standards.

As you said, there are USP monographs for dietary supplements. USP could do a monograph for the substance if it were put on the list, for a substance that is put on the list. But because there really are no data on safety or efficacy, I think it would be difficult to identify what the right standards were for identity, strength, quality, or purity since there are no data from an approved drug, for example, like there is for most of the drugs to set that.

I would also note that there are GMP standards applicable to dietary supplements, but drugs that are compounded under 503A, the pharmacies are exempt from good manufacturing practice requirements.

A dietary supplement would be manufactured under some GMPs but a drug compounded under 503A would not be. I thought it was sort of important to point that out going forward.

DR. VENITZ: Okay. Thank you. We have

Dr. Balasubramaniam. He's going to give the next three presentations. Go ahead.

**FDA Presentation - Sanjeeve Balasubramaniam**

DR. BALASUBRAMANIAM: Hi. My name is Sanjeev Bala. I'm a medical oncologist in the Division of Oncology Products I. I'm in the Office of Hematology Oncology Products. This is the review team that worked on germanium sesquioxide and the other two substances we're going to talk about later this afternoon.

The nomination for germanium sesquioxide was for "treatment of patients with cancer and chronic illnesses." This review will focus on the indication for cancer. The nomination was for compounding of germanium sesquioxide for intravenous infusion at a dose of 100 milligrams per milliliter.

As a background, germanium sesquioxide is sometimes seen in dietary supplements. These are considered adulterated due to safety concerns and cannot be legally sold in the United States. There is currently an active import alert for all

germanium compounds except for those used as semiconductors.

This is under FDA Import Alert number 54-07, which quotes, "Germanium sesquioxide is a non-essential trace element that has caused nephrotoxicity and death when used chronically by humans even at the recommended levels of use." Toxic germanium compounds are also involved in the synthesis of germanium sesquioxide and these can contaminate the end product.

This substance has several synonyms that can be found in various chemical databases. It's stable when stored in a tightly closed container and unstable when exposed to high humidity.

The synthetic pathway was initially described in the 1960s by Mirinov and colleagues using acrylonitrile and trichlorogermane starting materials. This is also the current method that's cited in the Merck Index.

Similar methods have been developed using these similar starting materials as well as inorganic germanium compounds. These inorganic

germanium salts can contaminate the germanium sesquioxide, the final product, with dangerous levels of inorganic germanium, which accumulate in the body and cause toxicity.

The starting materials, acrylonitrile and acrylic acid are converted into acrylamide during the hydrolysis steps of synthesis, and these contain structural alerts for genotoxicity. The reaction intermediate trichlorogermane can form complex structures in the body and has unknown safety.

In conclusion, from a chemistry standpoint, germanium sesquioxide is well-characterized, but due to the demonstrated toxicity of likely impurities, it's not recommended for inclusion on the list of bulk substances under 503A of the FD&C Act.

The nonclinical assessment of germanium sesquioxide was evaluated using a limited database. In a paper from 2004, there were some quotes of germanium sesquioxide being able to induce interferon-gamma and enhanced NK-cell activity

in vitro and in vivo in animal models. However, we feel that animal models uncommonly accurately predict the efficacy in humans.

Safety pharmacology was also limited. There was evidence that intraperitoneal administration of water-soluble germanium sesquioxide resulted in dose-related reductions in mean arterial pressure in rats. Intraperitoneal administration at higher doses did not show any changes in pain sensation.

You can see the list of median lethal doses here were quite high based on studies in mice and rats. It did induce some behavioral changes including somnolence and muscle contraction or spasticity in mice.

Chronic toxicity studies demonstrated small decreases in body weight in male rats, slight decreases in the generation of blood products, and some impact on kidney function.

There were no mutagenicity studies available for evaluation as well as reproductive and developmental toxicity studies other than a reported teratogenicity in chick embryos. There's

no toxic kinetic data available for analysis and these were not found to be carcinogenic in mice or rats.

From a nonclinical standpoint, germanium sesquioxide does not appear to be mutagenic or carcinogenic but their inadequate and nonclinical data otherwise characterize the safety profile of this single substance at high doses. However, because inorganic forms of germanium are nephrotoxic and potentially can contaminate organic germanium compounds, the safety can't be asserted.

Developmental and reproductive toxicity studies were observed in studies with other germanium compounds.

From a clinical standpoint, there were very few data from which to draw conclusions. The trials available for evaluation, including citations provided in the nomination, were for another form of organic germanium called spirogermanium, which was studied in clinical trials including at the National Institutes of Health in the early 1980s. In these studies,

significant life-threatening safety concerns arose during clinical trials.

There are no clinical trials assessing the safety of germanium sesquioxide, and there are no pharmacokinetic data available for evaluation.

From a safety standpoint, the limited information available about this substance gives rise to significant concern about its use in compounding, as well as the concern that the substance could be contaminated with other highly toxic inorganic intermediaries with germanium salts. Prolonged intake of germanium products has been associated with at least 31 cases of renal failure, some of which led to death.

Again, there are limited clinical efficacy data from which we can extract information with respect to cancer diagnosis and for treatment of cancer. There's one case report in the peer-reviewed literature, dating from 2000, in which a patient who had already undergone treatment with chemotherapy and radiosurgery began self-administration with a high dose of oral

germanium sesquioxide that parenthetically she bought at her health food store and purportedly had a complete response, to be noted that this was after she had had definitive therapy for this rare form of lung cancer.

Subsequently, a trial in ClinicalTrials.gov opened in 2005 to assess the efficacy of oral organic germanium in cancer fatigue but there have been no results reported and attempts to contact that sponsor went unanswered.

The nomination of this product is for a serious and life-threatening disease. Because of that, there's no evidence available in the literature that would indicate that germanium sesquioxide is effective for the treatment of cancer. There are, however, numerous FDA-approved products that have been demonstrated to be effective in the treatment of cancer.

In general, we have evaluated germanium sesquioxide based on the four qualities that this panel is to be evaluating this substance: its physicochemical characteristics, its safety,

effectiveness, and evidence of historical use. Although it's physically and chemically well-characterized, it can include impurities that are toxic. There is lack of evidence of efficacy of germanium sesquioxide in oncology.

Based on our evaluation of the four criteria identified above, we do not recommend that germanium sesquioxide be included on the list of bulk drug substances that can be used in compounding in accordance with Section 503A of the FD&C Act.

**Clarifying Questions**

DR. VENITZ: Thank you. Are there any clarifying questions by the committee? I have a question. Since there is an import ban, how could you legally produce this in the United States?

DR. BALASUBRAMANIAM: Based on an internet search, there are producers within the United States that presumably would be able to escape the restrictions of an import ban.

DR. VENITZ: Okay. Thank you.

Yes, Dr. Wall?

DR. WALL: Under the rat studies, we're talking about the dose. They had major adverse events of muscle contractility or spasticity. Did you notice -- well, one, did you pick up as to maybe what was the cause of that? And two, was there any bleed over of this into any of the human populations that you looked at?

DR. BALASUBRAMANIAM: There were no human data available for any of these analyses, so there's no bleed over of that kind of information. These were generic toxicity studies that didn't go into very much detail other than the reactions that we listed at the doses that you saw, which were very high doses.

DR. VENITZ: Any other questions?

(No response.)

DR. VENITZ: Okay. Then I think you are next again.

**FDA Presentation - Sanjeev Balasubramaniam**

DR. BALASUBRAMANIAM: Okay. My name is Sanjeev Bala --

(Laughter.)

DR. BALASUBRAMANIAM: -- from the Division of Oncology Products I. This is the review team, which should look familiar. We're going to be discussing rubidium chloride for the treatment of numerous types of cancer as an injection in strengths from 0.54 micrograms per milliliter to 282 micrograms per milliliter to be administered by slow intravenous infusion.

Historical background is important for this particular nomination because it's based on the work of one individual from the 1960s.

Keith Brewer is a physicist who, based on his own investigations, determined that the Hopi Indians of Arizona have a low rate of cancer as compared with other Americans, so 1 in 1000 versus 1 in 4 Americans. Of course, that's methodologically flawed.

He found that rubidium chloride was found at higher concentrations in the soil around Hopi reservations. Based on that, he asserted that this led to their development of cancer.

The proposed mechanism -- again, his

proposal -- was that rubidium cations, which are positively charged ions of rubidium, compete with potassium in cellular channels and cause the tumor microenvironment to become more alkaline.

He performed experiments with patients in the 1960s and '70s, occasionally substituting cesium and other positively charged heavy metal, and occasionally in combination with the compound laetrile in what he called high pH therapy and published this in the single-reported 1984.

I'd like to quote from his trial. He reported, "In addition to the loss of pains, the physical results are a rapid shrinkage of the tumor masses. The material comprising the tumors is secreted as uric acid in the urine. The uric acid content of the urine increases many fold. About 50 percent of the patients were pronounced terminal and were not able to work. Of these, a majority have gone back to work."

The current documented use of rubidium chloride is limited to the use of a radioactive isotope of rubidium for radionuclide imaging.

Rubidium 82 has a half-life of 75 seconds that releases positrons and is thus used in cardiac positron emission tomography and sold under the brand name, CardioGen-82. There are no other current uses of rubidium chloride found in the medical literature, including international pharmacopeias.

The nominated compounded is intended for application in a serious and life-threatening disease, cancer. It's physicochemically well-characterized. The synthetic pathway can be seen here from rubidium hydroxide and hydrochloric acid. Per the MSD, material safety data sheet from Acros Organics, it's stable under normal temperatures and pressures. However, one of its reactive metabolites is hydroscopic and can react exothermically with water.

Rubidium compounds are only slightly toxic on an acute toxicological basis but pose an acute health hazard when ingested in large quantities. According to TOXNET, rubidium hydroxide is designated as more toxic than other salts of this

metal and is designated as a pneumotoxin, hepatotoxin, and dermatotoxin. The minimum toxic concentration is listed as 5.75 milligrams per cubic meter, which is recommended as the maximum permissible concentration for occupational exposure.

Rubidium is an alkaline metal belonging to the same periodic series as sodium, potassium, lithium and cesium. In Brewer's own studies, in mouse tumor models, shrinkage of tumor masses were shown after two weeks in mice fed a diet containing cesium and rubidium at 1.11 milligrams per day. These studies have not been replicated using rubidium chloride in relevant models.

Rubidium chloride has shown some toxicity in preclinical studies in which it showed decreased locomotion in rearing in an exploratory box test in rodents. It had an impact on the long-term behavior of rats suggesting a neurological toxicity. The median lethal dose was quite high in mice at 233 milligrams per kilogram. Chronic toxicity revealed that it caused a general

impairment in growth, overall condition, reproductive performance, and survival time.

There were limited other nonclinical data from which to draw conclusions. Based on the effect on rats, we felt that the data are otherwise inadequate to determine whether it would be safe to use in compounding.

Clinical studies, again, are based on the report of Brewer. There were no other data from which to assess the safety of rubidium chloride for the treatment of cancer. The case series that he reported in 1984, patients who were exposed to this high pH therapy using either cesium or rubidium were reported to have experienced nausea and diarrhea. Further details that we would normally use in the assessment of anticancer agents were not available from these data.

An OSE search of the FAERS database did not return any results for rubidium chloride except when used as an imaging agent.

In conclusion, although rubidium chloride was first discussed by Brewer in the '60s, there

are insufficient data since that time to assess the historical use of rubidium chloride in compounding. His claims, however, were never supported by further evidence. There are insufficient data to attest to the safety or efficacy of rubidium chloride for the treatment of cancer, and there are numerous FDA-approved products that have been demonstrated to be effective in the treatment of cancer.

Our final recommendation, because of insufficient data to assess its historical use in compounding, the lack of data on safety or efficacy, and because of the availability of approved medicines to treat cancer, we recommend that rubidium chloride not be placed on the list of bulk substances that can be used for compounding under 503A of the FD&C Act.

**Clarifying Questions**

DR. VENITZ: Thank you. Any clarifying questions by the committee members?

(No response.)

DR. VENITZ: Any members on the phone, do

you have any questions?

DR. CUSH: No.

DR. VENITZ: Okay. Thank you. Moving right along. Go ahead.

**FDA Presentation - Sanjeev Balasubramaniam**

DR. BALASUBRAMANIAM: Thank you. Number 3, deoxy-D-glucose for the treatment of cancer. Here's the review team.

Its nominated for use is chemotherapy, which we interpreted to mean for the treatment of cancer. It was also nominated for the treatment of viral infections such as herpes simplex virus, which will be discussed in a separate presentation to follow.

Deoxy-D-glucose is a rare and naturally-occurring monosaccharide that can be represented in multiple chemical forms. It's very soluble in water, and it's synthesized from other monosaccharides.

The likely impurities from its synthesis include D-glucal and 3, 4, 6-tri-O-acetyl-D-glucal, which have reactive double bonds and therefore may react with normal cellular molecules. D-glucal

also replaces glucose 1-phospate in phosphorylase-catalyzed glucosyl transfer reactions. It's physicochemically well-characterized by spectroscopic and physicochemical means.

The mechanism of action of 2-deoxy-D-glucose is by the inhibition of the function of glucose in normal cells. It shares the same glucose transporters and enzymes as all human cells use and forms, in that synthetic pathway, 2-DG-6-phosphate, which is not further metabolized.

This inhibits the phosphohexoseisomerase enzyme as well as glucose-6-phosphate dehydrogenase. As a result, the output from glycolysis, which is the breakdown of sugar by normal human cells, is reduced, so ATP production is decreased and also inhibits the production of NADPH by blocking activity of the pentose phosphate pathway. In other words, 2-DG blocks energy production from glucose in human cells.

The hypothetical mechanism of action when used in the treatment of cancer is based on this

process. Normal human cells and cancer cells use glucose to generate metabolic energy, which is called ATP, and is building blocks to sustain growth. 2-DG purportedly depletes cells of energy by inhibiting glucose metabolism in vitro.

It's been shown in vitro and in vivo that it inhibits aerobic glycolysis in cancer cells, decreases cell proliferation, and increases cell apoptosis, which is cell death. The hypothesis is that this could then be used for the treatment of cancer.

However, normal cells work the same way and undergo the same type of injury when exposed to 2-DG. Furthermore, cancer cells are now known to be much more adaptable than this hypothesis would suppose; in other words, more resistant to this type of treatment.

The safety pharmacology includes treatment of animals with intravenous 2-DG at multiple doses, and it showed a decrease in mean arterial blood pressure in rats. It also had neurologic effects.

The acute toxicity showed a median lethal

dose that was quite high. Repeat-dose toxicity or chronic toxicity showed that with via dietary supplementation, body weight and food intake in rats declined, and there were cardiotoxic effects seen on two rat strains as well as increased mortality with median survival decreasing by 45 percent.

There are no mutagenicity information available for analysis. There were developmental and reproductive toxicities seen with the intravenous or intraperitoneal use of 2-DG where it significantly reduced sperm counts in mice and caused resorption of fetuses and malformation of fetuses in rats.

As well as in rats, 2-DG was found to be carcinogenic in which it promoted the development of pheochromocytoma in both benign and malignant forms in rats given a diet with 0.2 or 0.4 percent 2-DG.

In conclusion, dietary supplementation with 2-DG showed cardiactoxicity and decreased median survival in rats. It caused developmental and

reproductive toxicities and carcinogenicity in rats. Therefore, the toxicity profile, especially with chronic oral exposure of 2-DG in animal studies, weighs against its inclusion on the 503A bulk substances list.

From a clinical standpoint, there are limited trials from which to draw conclusions. Its activity appears to be similar to the inhibition of glycolysis mechanism that was described where reactions are similar to the development of severe hypoglycemia which includes flushing, diaphoresis, headache, somnolence, and tachycardia.

The hypoglycemic effect has been noted to routinely be dose-limiting in clinical experience. OSE search of the FAERS database did not result in any findings regarding 2-DG.

There are two clinical trials we can report on that have safety information including the one from Landau that I just mentioned. There's a phase 1 dose escalation trial reported in 2012 in which 2-DG was used alone and in combination with docetaxel, which is a standard approved

chemotherapy for advanced solid tumors using an oral formulation at three different dosing schedules.

Adverse reactions were described as mild, transient, and consistent with severe hyperglycemia. However, these toxicities precluded dose escalation beyond 63 milligrams per kilogram when given with docetaxel, and these doses were not considered to be efficacious.

There are numerous anticancer agents that have been granted marketing approval by FDA after demonstration of safety and efficacy in well-controlled trials.

Based on these two trials, use of 2-DG for the treatment of cancer appears to be beyond the reach of tolerable dosing in both intravenous and oral dosing regiments. The high doses required for a single-agent use based on limited clinical evidence have led to unacceptable toxicity.

Based on the information available, it appears that the agent has been intermittently in use since the 1950s. Medical conditions treated

under these for cancer indications report 2-DG use as a single-agent or in combination with chemotherapy. In both cases, there were no tumor responses reported. It's also been used as an antiviral especially for the treatment of herpes simplex virus.

The trials that we were able to evaluate, one was from 1958. Eight patients with cancer were treated with intravenous 2-DG and there were no responses but they were mild transient toxicities consistent with the mechanism of action.

In 2012, the study reported the use of oral 2-DG with and without docetaxel, but because of toxicity, pharmacodynamically meaningful doses were not attainable.

A study published by a group in India in 2009 reported that they were combining 2-DG with external beam radiotherapy for the treatment of glioblastoma. The trial data were not published in detail. They did claim a survival increase based on historical controls. But on reading the paper, the historical controls actually had a better

survival, so it's not clear how they made those conclusions.

This compound is intended for the treatment of cancer, a serious and life-threatening disease. There are numerous anticancer agents that have been granted marketing approval by FDA after demonstration of efficacy in well-controlled trials. Based on the data 2-DG does not appear to be effective for the treatment of cancer.

Our overall conclusion suggests that there are insufficient data to attest to the safety or efficacy of 2-DG in the treatment of cancer. Toxicity has been commonly reported to be reached before clinical efficacy. There are a number of safe and effective FDA-approved agents available. The possible uses for 2-DG oncology, which only includes life-threatening illnesses are not advisable given the availability of these approved products.

Further investigation with 2-DG, if undertaken, should be monitored through the IND process. There's insufficient information on the

extent of the use of 2-DG in compounding to evaluate the significance of its historical use.

Therefore, we do not recommend that 2-DG be placed on the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act.

DR. VENITZ: Thank you. Any questions about the oncology use before we get to the antiviral use?

(No response.)

DR. VENITZ: Thank you, Dr. Balasubramaniam.

Our next presenter is Dr. Murray, and he's going to talk about the antiviral use of 2-DG.

**FDA Presentation - Jeffrey Murray**

DR. MURRAY: Hello. I'm Jeff Murray from the antiviral division. This is 2-DG for the topical use for the treatment of herpes simplex virus.

The CMC in animal safety pharmacology assessments were made in the previous presentation. A brief overview of herpes simplex virus infections, serious infections such as neonatal

herpes and herpes encephalitis, require systemic treatments, so we're not talking about that today.

The most common infections are initial and recurrent herpes simplex lesions of the skin and oral mucosa, namely genital herpes and herpes labialis, also called cold sores. Also other areas of the skin can be affected.

There are two herpes simplex virus types, 1 and 2. Both are susceptible to approved drugs, which I will outline. HSV-1 predominates in the oral region and HSV-2 in the genital region, but genital or oral herpes can be caused by either virus.

Herpes outbreaks are self-limiting, lasting days usually, but can be painful, temporarily disfiguring, and stigmatizing. Some people have frequent recurrences, and herpes can be transmitted either during or between outbreaks.

Just pictures of herpes labialis, cold sores on the left usually caused by HSV-1 and typical lesions of genital herpes, usually caused by HSV-2.

There are many products approved in the U.S.

for the treatment of genital and oral herpes, including creams, ointments, tablets, and oral formulations for both herpes simplex cold sores or genital herpes. There's also an over-the-counter cream, docosomal or Abreva. Some of the treatments are single-day treatments for oral herpes, but usually multiple days are required for genital herpes infections.

The 2-DG efficacy data sources that we looked at to address the activity of 2-DG against herpes include published cell culture data in animal models. There was one published clinical trial of topical 2-DG for the treatment of genital herpes simplex infections, and there was a few case series of patients with HSV treated with 2-DG as reported in letters to the editors, mainly.

The nonclinical activity data, there were some cell culture data that showed suppression of herpes simplex 1 and 2 in cell lines but only at very high concentrations, micromolar and molar concentrations. Cytotoxicity or cell death was not assessed, so whether the drug had antiviral

activity or only a cytotoxic effect is not clear.

Animal models of 2-DG produced mixed results with positive results in a few studies and no beneficial effects in others. Overall, more studies showed no beneficial effect of 2-DG in the treatment of herpes infections.

There was one clinical trial of 2-DG reported in JAMA in 1979 by Blough and Giuntoli. It was said to be a randomized controlled trial of 2-DG as a 0.19 percent cream versus placebo in women with genital herpes lesions, initial and recurrent. Cream was administered 4 times a day. The vehicle included miconazole and antifungal. Thirty-six women received 2-DG and 15 received placebo.

The authors claimed a significantly shorter duration of herpes lesions up to a 10-day difference in initial herpes and around 5 to 6 days in recurrent, and a reduction in the number of recurrences.

Shortly after that, in the same journal, herpes experts wrote a letter to the editor,

Dr. Corey in 1980, questioning the trial conduct and results. The trial did not appear to be randomized. More than twice as many received 2-DG than placebo because randomization to placebo was limited due to unexplained ethical issues, according to the original article.

Also, Dr. Corey stated that the possible toxicity of the placebo could have explained the difference in treatment effect because the rate of healing on placebo was uncharacteristically long, twice as long as historical rates, suggesting that placebo may have actually slowed the healing. Follow up for recurrences was not well-documented in the article.

Following this, in 1983, there was a case series of 2-DG reported with no apparent beneficial effects. There was another letter to the editor in 1982 by McCray, published a case series of 22 patients who received 2-DG for herpes infections, no infect [indiscernible]. And this author also reported a placebo-controlled trial in 17 patients receiving 2-DG as a 0.19 percent cream

again versus placebo with no beneficial effect.

There was no mention of 2-DG-related adverse events in the Blough trial. It is unclear whether there were no adverse events or whether the article just failed to report them. There's really no pharmacokinetic data to assess the extent of systemic absorption of 2-DG.

The historical use of 2-DG in compounding, the data are insufficient really to quantify the frequency of past or present use. It appears to have been used topically for the treatment of genital herpes in the 1970s around the time of the Blough publication in JAMA, but enthusiasm for 2-DG appeared to decline according to a lot of the review articles that I read that were published in the 1980s with the approval of acyclovir ointment in 1982, oral acyclovir in 1985, and many subsequent other HSV antiviral drug approvals.

According to some internet searches, 2-DG has been used for a variety of other conditions not nominated, including warts, diabetic neuropathy, and dental rinses for oral ulcers.

Our conclusions are that the data are insufficient to fully evaluate the safety or efficacy of 2-DG for the treatment of HSV. Results of nonclinical trial data are mixed. Most animal models show no beneficial effect. The only published clinical trial was a poor quality and largely discredited by HSV experts.

Efficacy was not seen in subsequent clinical reports and there are multiple and safe and effective FDA-approved products, both oral and topical, that are available of the treatment of oral and genital herpes.

There is insufficient information on the extent of the use of 2-DG in compounding to evaluate the significance of its historical use. So we do not recommend that 2-DG be placed on the list of bulk substances that may be used for compounding under Section 503A of the FD&C Act for the treatment of herpes simplex infections.

DR. VENITZ: Okay. Thank you, Dr. Murray. I suggest we defer clarifying questions until we hear our nominators speak and get ready to vote

because that allows us to go back on schedule. We are scheduled to reconvene -- so we're going to take a break now, and we're going to reconvene at 3:30.

(Whereupon, at 3:22 p.m., a recess was taken.)

DR. VENITZ: Okay. Before we get started with our public hearing, I want to welcome an ad hoc member, Dr. Vincent Lo Re. He should be on the phone; is that correct?

(No response.)

DR. VENITZ: Is technology raising its ugly head again? Dr. Lo Re?

DR. LO RE: Yes, I'm on the phone.

DR. VENITZ: Okay. Do you want to give us a brief introduction of who you are so everybody knows who's joining?

DR. LO RE: Sure. I'm an assistant professor in the Division of Infectious Diseases and the Department of Biostatistics in Epidemiology at the University of Pennsylvania. I have a particular area of interest in liver disease, acute

and chronic liver injury.

DR. VENITZ: Thank you very much for joining us, Dr. Lo Re.

Let me, again, read for the record the official OPH statement.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a product and, if known, its direct competitors.

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

at the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

With that said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Let's now proceed with our -- I apologize.

I'm off schedule. We have nominators now. Before we start with the nominators, are there any clarifying questions?

(No response.)

DR. VENITZ: Okay. Then can I ask the first nominator, Dr. A.J. Day from PCCA, to talk about 2-D-glucose?

**Nominator Presentation - A.J. Day**

DR. DAY: Hello again. My name is A.J. Day with PCCA -- and yes, it rhymes -- from Houston, Texas. As a disclosure, we do provide the deoxy-D-glucose for use in pharmaceutical compounding.

The analysis presented by FDA was very thorough, very well done. The cancer analysis relied largely on animal data. The studies in rats noted that there were cardiac and/or respiratory changes seen in IV doses at 250, 500, 1000, and 2000 milligrams per kilogram in mice. Oral doses of 500, 1000, and 2000 milligrams per kilogram led to a decrease in respiratory frequency. Then there was a conflicting study where in 2012, they showed

intraperitoneal doses up to 1000 milligrams per kilogram per day for 14 days had no apparent and detrimental neurological effects.

We have the animal data here. We also show that there was a study from 2010 where they did up to 0.4 percent of the diet being deoxy-D-glucose reduced median survival and maximum lifespan in these animals.

The actual article also noted that the lower dose showed no observable cardiomyopathic changes by histopathology. So that study by Minor and colleagues, when they noted the reduced lifespan in these animals, and they did the autopsies and dissections, they actually noticed that there were physiological changes in the structure of the heart at those high doses, and that was not observed at the lowest dose of the 0.04 percent group. So that data was not included from the analysis, but it is directly from the study.

Continuing the cancer analysis, looking over at the human data, the article by Singh and colleagues used oral dosing. Only the highest

doses there at 300 milligrams per kilogram led to hypoglycemia. No other serious adverse effects were noted.

The Dwarakanath article from 2009 used IV dosing, and they do acknowledge that for clinical efficacy as monotherapy, you have to have high dosing, long duration of therapy, and that combination leads to unacceptable toxicity.

This was also confirmed in a later study. There was also a pharmacokinetic evaluation of deoxy-D-glucose that showed linear kinetics with dose and did not lead to accumulation, indicating a central compartment model.

The cancer analysis shows that, yes, it is physicochemically well-characterized, small molecular weight. However, based on the two trials, the treatment of cancer with this substance appears to beyond the reach of tolerable dosing for both IV and oral regiments.

However, there are lower doses that are being explored in combination therapy with chemo and radiation, and the toxicity profile there

appears to be manageable.

There is another review article here that they said that 2-deoxy-D-glucose exhibited a synergistic anticancer effect when combined with other therapeutic agents or radiotherapy.

Leading to our discussion prior to lunch, where we're looking at a lot of data as monotherapy, considering how it's used in the real world or what the direction of clinical trials are or clinical utilization, it is typically done as combination therapy. But we have to assess what we're given.

Now, there's another review article that was not included in the analysis here, but it essentially confirms the line of thinking where based on our current understanding as explained previously in this article, 2-deoxy-D-glucose as monotherapy is expected to be efficacious only in select tumor types that are sensitive to this agent in normoxic conditions.

Retrospectively, lack of efficacy in earlier studies is not surprising, and therefore, clinical

use of 2-deoxy-D-glucose was more recently visited. We're confirming that monotherapy, high dosing, and long therapy durations are the limiting factors for the utilization in cancer therapy.

Now, if we move over to the second component of the nomination, herpes simplex virus, the analysis from FDA says that while there are some in vitro data suggesting DDG could have some antiviral activity, the overall data do not demonstrate what that activity is in the treatment of experimental cutaneous orogenital infections in the animal models. The lack of evaluation for cytotoxicity is brought up again.

In the Blough article, they do mention analyzing the patients or at least testing for cytotoxic effect. It does have some flaws in that trial. I did not focus too much on the Blough trial nor the letters to the editor because the letters to the editor were not actual published trials. They do not publish any results. They simply were writing back and forth. If you read those, it got a little bit into the schoolyard, and

they were taking blows at each other's clinical chops. I tried to avoid some of that and stick with where is the data.

There is limited clinical trial data. This is to be expected. As Dr. Venitz mentioned earlier, what is the level of evidence that is expected of this committee when approving a substance to be placed on one of these lists? Because if it is the standard phase 3 clinical trial, nothing we're going to talk about is going to meet that level. The funding just isn't there without a drug sponsor who is seeking for patents and market exclusivity.

Let's look at what are some of the suggested alternatives to DDG. We know what the standards of care are when we're treating herpes simplex. We have on the left side of the screen the oral therapies that are approved, and on the right side of the screen for genital HSV approved therapies.

We know what the concentrations are and the dosing frequency. Docosanol, it's not directly virucidal. The approved labeling for this

medication says that it appears to interfere with one or more of the common pathways for viral entry. The specific mechanism is not well-characterized, but they do look at it as not being directly virucidal.

Acyclovir and valacyclovir, well, valacyclovir is rapidly converted to acyclovir. It selectively binds to the thymidine kinase enzyme to inhibit viral DNA synthesis. Through that process, then it becomes phosphorylated, further phosphorylated, and it essentially is going to incorporate into and terminate the viral DNA chain.

It is effective only against actively replicating viruses, not into latent virus, which we know does stay cutaneously. Viral resistance can result, and skipping ahead, it's not just in the immunocompromised patient but also in immunocompetent patients with genital herpes.

Now, penciclovir and famcyclovir, again, penciclovir is the active antiviral compound produced by biotransformation of famcyclovir, so we can group these two together with their mechanisms

of action.

Resistance -- and this is straight from the mechanism of action elicited from the manufacturer. Resistance of HSV and VZV to penciclovir can result from mutations in the viral TK. It's the same mechanism. It's affecting that same thymidine kinase enzyme. It's going through the same mechanism to inhibit the DNA polymerase reaction.

When you have those mutations in viral TK, it may lead to complete loss of viral TK activity. That's the most common type of resistance. It's the complete loss of a viral TK activity, which means that these medications are not effective for those patients. And that's the most common type of resistance. Again, this is in immunocompromised and immunocompetent patients.

We know that when we're treating difficult viruses, which most viruses are characterized as difficult -- but let's look at HIV. We know that we need to approach it from multiple angles. The mechanism by which we attack the virus is complex. Our understanding of the virus' ability to mutate

and to evade some of our defenses such as here, it's not an easy thing to grasp.

I don't feel that there is a lot of data that's really specifically looked at the way that we're going to be able to synergistically support the use of some of our standards of therapy.

What about the mechanism of action of DDG? The multiplication of a number of enveloped RNA and DNA viruses is inhibited by 2-DDG. This is straight from the analysis from FDA. The compound exhibits antiviral activity against those enveloped viruses that require antiglycoproteins for viral assembly for some critical replicative functions.

Now, this quote is from another article, which it's an in vitro article that looks specifically at the mechanism of action. And I'm not sure why it was not included in the FDA's analysis here. But their goal throughout this paper was to look at how is this working in an antiviral fashion.

What they determined was that its effect on the protein that utilizes glucose was not really

that beneficial when they looked at the mechanism. What they actually found from the mechanism -- because they did note that there was still a 10-fold difference in infectivity with the cultures that were treated with deoxy-D-glucose. So they determined that the major contributing factor to why the virus has grown in the presence of DDG and it lacked infectivity appears to be the result of a defect in penetration.

Going back to the mechanism of docosanol, it hasn't been completely defined, clearly defined. However, they are able to pinpoint that its mechanism is more to do with its actual penetration versus what you see with the standards of therapy with acyclovir, famcyclovir, and so on as affecting the thymidine kinase and then the DNA polymerase.

We're losing this synergistically. In the applications that we see, we are combining deoxy-D-glucose. I have never seen it used as monotherapy. It is typically done as a combination usually with acyclovir, 2 to 5 percent, and it's used in topical applications at about 0.19,

0.2 percent concentration. In various rare conditions have I seen a request for it to have an increased concentration of up to 2 percent.

Now, let's look at the typical situation that might pose an issue similar to a risk elicited from one of the studies. If we look at the second main bullet point there, 0.1 to 0.25 percent for mouth rinses. This would be the closest we have to systemic exposure from deoxy-D-glucose from what we see in the real world in compounding.

Assuming the patient uses 10 mL of that mouth rinse and it's a 0.25 -- it's at the top of the range on the concentration. That's 2.5 milligrams per milliliter as an oral rinse; that's a swish and spit, they're not ingesting it. Then they're exposed to 25 milligrams of deoxy-D-glucose for let's say up to 30 seconds. The lowest human oral dose published was 200 milligrams per kilogram, which produced hypoglycemia.

Given the context for what we're actually seeing -- there's not an argument about its utility

in the world of cancer; there's not a lot of clinical data; there's no clinical trials about its use in the treatment of herpes and related viruses. But we do have data about its mechanism of action. It's the same type of data through which we elicit the mechanism of action for acyclovir. It's in vitro data. We also know how it's been used in the compounding world, at which I would propose that it has very small to no significant risk of systemic side effect.

One of the components to keep in mind as we consider how might deoxy-D-glucose be utilized, how might we prevent the lack of effect, lack of benefit that some patients have been experiencing such as in those letters to the editor, if you look at those letters, they talk about the various vehicles that they've used to deliver the medication. That is crucially important.

We know that in any kind of medication system, it's not just the active ingredient that's involved, but it's how we deliver it into the system, what are the pharmacokinetics, what are the

pharmaceutics involved.

We know that deoxy-D-glucose, as mentioned, is very soluble in water. When we're using a vehicle that forms a barrier on the skin -- and in one of those letters to the editor that was supposedly to refute the Blough article, they used lanolin as the vehicle.

Well, now you're forming a barrier on the skin. Number 1, the incorporation of a water soluble ingredient into lanolin is not an easy thing. The active ingredient not only is not going to be well-incorporated into your delivery system, but it's not going to be able to penetrate the virus within the dermis because of the delivery system to begin with.

Hydroalcholic gels were used in another one of those studies. Those are not necessarily ideal for nonlipophilic molecules. You get a minimal disruption of the lipid bilayers by the disruptive nature of the alcohol, but that's also a very volatile substance, and you don't have a lot of alcohol there that's going to stay, so it's going

to leave the surface rapidly. You don't have its benefit of enhancing penetration.

So choosing an appropriate vehicle that does enhance the penetration is important, and there are two very common ones that have been utilized for decades in the compounding world, and those are listed on your slide as well. But it's not just the specifics of the active ingredient, but how we deliver that to make sure that it's appropriate for the patient. Again, it is an adjunctive therapy, not monotherapy. Thank you.

**Clarifying Questions**

DR. VENITZ: Thank you, Dr. Day.

Any clarifying questions? Yes, Dr. Vaida?

DR. VAIDA: At the end of the day, are you saying you're not recommending it really for chemotherapy but you are for antiviral?

DR. DAY: Correct. I would not --

DR. VAIDA: Although your submission says antiviral, chemotherapy, and antifungal.

DR. DAY: When the submission process was requested, there was not clarity on what this

entire engagement process would look like. It was really, send us the data to support how it may be used in compounding.

In large part, we were looking at, well, what's the published data that's available, and we have to list all of those things for which there is literature. That was, in large part, the thinking. There's no precedent to go off of for what this committee would look like, for what our process -- what our allowance is to speak in front of the committee or to defend a view.

So the scope on which a lot of these substances were nominated, including the stuff from this morning, is not necessarily the scope in which we use it in the real world. It's more based off of where we've seen published literature.

In the real world, what we see in compounding, taking it back to clinical experience, would be topical use. And I would include the oral mucosa as topical because we're not advocating for it to be ingested.

DR. VENITZ: Any other questions?

(No response.)

Okay. Thank you again, Dr. Day.

Our next nominator presentation is by Dr. Moon. He is with the National Community Pharmacists Association.

**Nominator Presentation - Richard Moon**

DR. MOON: Good afternoon. The view is a little different from up here. Greetings. I'm Richard Moon, a compounding pharmacist and a member of the National Community Pharmacists Association or NCPA.

On behalf of NCPA and the 23,000 pharmacies they represent, we, again, appreciate the opportunity to lend comments to the Pharmacy Compounding Advisory Committee over these two days. Again, thank you.

My colleague, Cheri Garvin, had this statement the last time you guys met. She said, "We are here for many researchers and scientists today, but I'd like to talk with you about our patients on the front lines. As compounding pharmacists, we often see patients who have been

through traditional therapies with no results. We see those with unique needs, and solving problems is what we do best. While we would love to be able to complete double-blind, placebo-controlled studies in all of our therapies, that's just not realistic."

I'd like to outline what having these substances that we're talking about -- and in this case, DDG -- available to the clinicians can mean to their patients.

Deoxy-D-glucose is just that. It's glucose with a substitution. The substitution in the structure allows the interference with the virus' normal replicating process. Out of all of the substances being debated for the positive list, the FDA recommendation not to include this substance kind of strikes us as odd.

We can't even call it a bulk substance. It's a sugar. It's a sugar with an incredibly safe profile. We have dermatologists and podiatrists, as well as many other prescribers that use DDG as an adjunct for a variety of viral treatments that

would include a range of simple warts to shingles.

Most of my experience in our practice has been with topical, including, as A.J. said, the oral mucosa. We took a brief survey of some our members to see what they would report their uses as. We have prescribers that will write individual prescriptions for deoxy-D-glucose preparations that are included with other active agents for individual patients. And those would include topical creams, the liposomal gels that A.J. mentioned, solutions for warts, combination with pain ingredients used topically to treat shingles in the appropriate basis, oral mucosal bandages for thrush, et cetera, again in different combination of types of basis to affect how they act on the tissue.

We have not seen DDG used as a standalone agent in these therapies but as an additional therapeutic agent with a different mechanism of action to complement existing agents. If a child can reduce the time course of a molluscum outbreak using DDG, then it's a great tool to have. If a

patient can reduce their pain during a shingles episode by just one day, it's a must tool to have.

If you know anyone who's experienced any of the pain or shingles with the stigma of various types of warts, then I believe that you would agree that there's no harm in having a safe viable option for those patients.

There are other indications and research being done on DDG as well and probably because of the indications thing that we're all talking about today, they didn't make this list. But again, I would remind folks that it's a safe topical good tool for clinicians to use. And NCPA would like to urge the committee to consider DDG for inclusion under the list. Thank you.

**Clarifying Questions**

DR. VENITZ: Thank you, Dr. Moon.

Any clarifying questions by the committee? Dr. Wall?

DR. WALL: Did I hear you say that there are ongoing studies with this drug? And if there are, can you comment on what those studies are?

DR. MOON: The Journal of Epilepsy was investigating DDG for seizures. That just kind of jumped out at me. There are a number of things that A.J. had actually included on his presentation. It's a pretty ubiquitous item, and probably because it is so safe. That's my belief.

I couldn't give you a list of indications of things that they're actually researching. But the epilepsy journal kind of jumped out at me, and it was something I didn't know before I did research for this presentation.

DR. VENITZ: But you are advocating only for its topical use, right?

DR. MOON: Pardon?

DR. VENITZ: Your advocacy is only for topical use, not for systemic. Topical, local.

DR. MOON: My experience and what I would advocate is for topical use. When you do look at the data that is out there that the FDA presented -- and it's pretty easy to find -- as far as the investigation in the cancer use that you were actually showed, you had to give way high of a

dose to get any effect, and there was still no proven effect for side effects.

So yes, we see it in topical. Again, the oral mucosa or any mucosal tissue really is, we would consider, topical.

DR. VENITZ: Okay. Thank you.

DR. MOON: Thank you.

DR. VENITZ: Any final questions?

(No response.)

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

All right. We have --

MS. AXELRAD: Dr. Venitz?

DR. VENITZ: Yes?

MS. AXELRAD: We didn't ask any clarifying questions if anybody had any for the FDA presenters.

DR. VENITZ: That's what I was getting ready to say. We are now making up because we have until 4:15 when the open public hearing, so we are now making up for other clarifying questions that I asked you to defer for the FDA presentations.

So any questions, comments, please?

(No response.)

DR. VENITZ: It looks like everybody is ready for the vote then, or votes.

UNIDENTIFIED SPEAKER: [Inaudible - off mic.]

DR. VENITZ: I know. But do we have to wait with the votes until after the public hearing and take a break between now and the public hearing if nobody wants to ask questions, or can we just do the votes now and then have the public hearing?

MS. AXELRAD: You have to do the public hearing.

DR. VENITZ: Okay. All right. Either you ask questions or you take a break.

DR. FOJO: I have a question.

DR. VENITZ: Go ahead please.

DR. FOJO: So is it going to be for 2-deoxy-D-glucose two separate votes, one for -- because we had it in our packages as two different entries, the viral indication and the cancer indication?

DR. VENITZ: The vote is not by indication

or by use; it's by compound.

DR. FOJO: Okay. All right.

DR. VENITZ: What we're talking about right now is the 2-deoxy but we had other compounds before that were discussed by FDA.

DR. FOJO: Right. No, no, I was talking about the 2-deoxy because the cancer and the viral were in the separate entries. They'd obviously been reviewed by different FDA experts.

DR. VENITZ: Right. But the vote is just with -- the 2-deoxy-D-glucose should be on the To Be Compounded list or not.

DR. FOJO: Right. Thank you.

**Open Public Hearing**

DR. VENITZ: Okay. I've learned something. I think I can move the open public hearing up, which I didn't know. I thought that was a cut-in-stone kind of a thing. We do move up the open public hearing. Rather than 4:15, we're going to start now. I did read in the record twice, so I would ask our presenter to please step up to the microphone.

MR. MILLER: Thank you, Mr. Chairman, ladies and gentlemen of the committee, colleagues at FDA. My name is David Miller. I'm the executive vice president of the International Academy of Compounding Pharmacists. I'm coming today to actually follow up on a letter that we submitted as a professional organization to the open docket pertaining to a discussion that was held before the PCAC at its June 17th and 18th meeting.

Before proceeding, I did want to make sure that you understood that I have no disclosures to report. I receive no financial incentives to participate in this particular meeting or present our academy's position and inquiry related to our concerns.

Before I go any further, also I just wanted to mention to frame my discussions for the evening, I know that most of you have heard the joke, when is a door not a door? And if you don't know the answer, I will save that to the end of my presentation.

The reason why I characterize my

statements -- and I know that you should have a copy in front of you of IACP's submission to the docket that was dated on the 3rd of September and submitted, I believe, officially into the docket on the 8th September.

During the June 17th and 18th presentation before the committee, there was a discussion about what constitutes an applicable USP NF monograph, and we've had discussions today about that very, very issue.

It is something that's concerning to our organization because as we were preparing our nominations to this committee for review of bulk drugs, there was an understanding that if a medication had a monograph that appeared within the USP NF, that that was sufficient to justify not submitting it for review by this committee.

In fact, if you go back to the 2nd of July of 2014, instructions provided to the public for a nomination to the 503A bulk substance list specifically outlined the following.

First, a definition of what constituted a

bulk drug substance and an active ingredient. I want to share that with you because it does indeed impact on our concerns. Specifically, a bulk drug substance and an active ingredient is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the body of man or other animals.

Further on, in follow-up to the original posting from the agency at the beginning of December of 2013 and subsequently reissued on the 2nd of July for the second round of submissions to the committee, FDA and the agency specifically asked and instructed nominators that we did not have to and should not be nominating drugs that had a monograph that appeared in the USP NF.

Please note that in that background material, there was no mention of the word "applicable" nor was there any differentiation between what constitutes a dietary supplement monograph and a drug monograph.

Now, our concern is really threefold. First and foremost, we were instructed, as the public, that it was not necessary to submit a nominated drug if it had a USP NF monograph. It's our understanding as healthcare practitioners and as compounding pharmacists that anything that is defined as a monograph and appears within the USP is indeed a monograph. In fact, several of the drugs that we have been discussing here today have dietary supplement monographs.

The first thing that IACP is asking of both the agency and of the PCAC is to clearly define and communicate to the healthcare practitioner community and to stakeholders what exactly is meant by an applicable USP monograph. We've heard a distinctly different set of definitions today than what has been published in the docket and what has been published in the record.

As you recall this morning, the excellent summary on what a dietary supplement is emphasized structure function versus disease treatment. I just read to you from the very FDA backgrounder

that mentions the word "structure" and "function" as being a component of an active ingredient for consideration by this committee. That's our first request.

The second request is we believe if indeed the agency and this committee see these as distinctly different, dietary supplements versus bulk ingredient, API USP monographs, then we need to have the ability to have another opportunity to submit those into the docket for consideration by the committee.

I know that yesterday we have had a new docket opened, and this morning, we heard that we have the ability to add additional nominations to that. It is very important, however, before we begin that process, as a stakeholder community, we have a clear definition as to when a USP monograph applies and when a USP monograph does not apply.

I know it's late. To show you exactly what I'm talking about, I went to Safeway at lunch. This is my bulk ingredient by the way. USP monograph, dietary supplement, published for

ascorbic acid for ingestion, both tablet and it's also available as a liquid. You can buy it over the counter, clearly defines, "Not an FDA-approved drug."

If I was to compound ascorbic acid, as a pharmacist, I can purchase the bulk ingredient. This particular bulk ingredient does have a USP drug monograph but only as an injectable. As a clinical pharmacist, as a compounding pharmacist, I receive a prescription where I need to compound this oral form of ascorbic acid using a dietary supplement monograph in the USP. But what we heard today and we have been instructed in the backgrounders for the submission to the 503A are markedly different.

That's where we're asking for clarification between the agency, this committee, and USP, so the compounding pharmacists know exactly what they're supposed to be doing.

We left this meeting last time asking the question, I just heard that a USP monograph is not a USP monograph. And as I started my presentation,

my question to you was, do you know when a door is not a door? Gigi?

MS. DAVIDSON: I don't know, David. When is a door not a door?

MR. MILLER: When it's ajar. I know that you are -- oh, I know, I know, I know. It's bad and it's late, but these semantics and these words are important to us because the compounding community, physicians and prescribers and pharmacists, want to make sure that every drug that we use gets into the review process in front of this committee. And right now, we believe because of the differences in interpretation between USP monographs for dietary supplements and USP monographs that appear in the NF, even though we consider them to all be part of USP, we are now under the understanding that they are not.

That needs to be clarified. I thank you. And if I can answer any questions for the members of the committee, I'd be delighted to do so.

DR. VENITZ: Thank you. Any questions by committee members?

(No response.)

DR. VENITZ: Okay. Thank you again.

MR. MILLER: Thank you.

DR. VENITZ: I think we may have a second speaker from this morning that now his or her last opportunity to speak up.

(No response.)

DR. VENITZ: Okay. Whoever it is, they missed the final opportunity, and we are getting back to our regular order of business.

Do we want to follow up on the open public hearing, Dr. Axelrad, about applicable USP monographs? Is there something that you want to follow up on or are we going to discuss that perhaps at a future meeting?

MS. AXELRAD: I would just reiterate, I think I defined fairly specifically this morning what we consider an applicable USP monograph and why. I would note, as I noted this morning, because of the fact that we're actually talking about them here and we did at the last meeting, that people did nominate substances for which there

were dietary supplement monographs in the USP. We believe people understood that they were supposed -- that the dietary supplement monographs and the USP were not something that would allow you to compound.

I note that IACP themselves nominated at least three of the dietary supplements that we've talked about for the bulk drug substances list. They felt that they would need to nominate them and have them be considered.

That being said, we can look and see whether we think that there is a need to clarify to the community to make sure that when people look at whether they should put something in the new dockets that have been established, that they would understand the fact that there is a USP dietary supplement monograph isn't sufficient to allow them to compound without it being on the list.

So we can look and see if there's a way of putting something on our website or something like that, so that people would understand that if they want to compound with a dietary supplement, they

should nominate it.

DR. VENITZ: I think that would be helpful especially now with the fact that you're basically reopening nominations now with the guidance that came out.

Any further discussion before we get back -- okay, Dr. Davidson?

MS. DAVIDSON: Just one more comment on the difference between USP drug monographs and dietary supplement monographs. I would encourage everyone to consult the chapters on elemental impurities. Look at chapter 232 and look at chapter 2232; 232 applies to drugs, 2232 applies to dietary supplements.

There's a 10-fold difference in toxicity, acceptable level with heavy metals and other impurities in dietary supplements as compared to drugs.

My question still remains, if we put these items on the list, how is a compounder to know the quality of that bulk drug substance that they're purchasing? If they use a dietary supplement

monograph, there are 10-fold higher than the equivalent level of impurities for a drug, but that's the only standard we have for some of these substances.

So again, if we put the substances on the list so that they can compound with them but don't require any standards whatsoever for use of those chemicals -- because in chapter 795, a certificate of analysis is a "should," it's not a "shall." So how do compounders know the quality of what they're starting with?

MS. AXELRAD: I don't think that issue is unique to a dietary supplement. For any of the substances that are nominated for this list, none of them are, by definition, components of FDA-approved drugs, because if they were, they wouldn't need to be nominated for the list. So it's likely that there are no USP or NF standards for them.

They are required under 503A, all bulk drug substances are required to be made in an FDA-registered facility and accompanied by a

certificate of analysis that tells you what's in there. I think the question is, how do you know what should be in there and what level of impurities?

Again, I think that the way this process worked a little bit in the past, a decade or so ago, is that after that we recommended that substances actually go on the list, that the USP decided that they would do monographs for them. So they worked with somebody to provide some kind of data upon which they could do a drug monograph. It's sort of a circular thing.

Once we recommended that something go on the list, they did a monograph, and then it didn't need to be on the list. We talked about this at the first meeting. But it's a process, so we think that that is the appropriate way to do it. Once a decision is made to put it on the list, if the USP wants it go and develop a standard for it and that they can get data upon which to base their standards, that that is appropriate for them to do so.

MS. DAVIDSON: I just wanted to follow up. I believe that there are data, and that would be treating the monograph as a drug monograph instead of dietary supplement monograph. There are immediately applicable chapters in USP that would make it very clear to the compounder what's expected for that substance.

I offer up, for example, the C of A for 2-deoxy-D-glucose. The nominators supply there's a half mg per kg of arsenic in that substance. How does that compare to a dietary supplement monograph or a drug monograph? How is a compounder supposed to know, is that too much arsenic, is that okay? We really have to get some standards wrapped around this.

**Committee Discussion and Vote**

DR. VENITZ: Okay. Let's return to our final order of business and that is getting ready to vote. Are there any final clarifying questions before I call for the vote?

(No response.)

Okay. We have three voting questions to act

on, and with everybody's permission, I'm just going to read them and then we vote.

The first question is regarding germanium sesquioxide, should that compound be put on the bulk list or not? If it should, you vote yes -- or if you think it should, vote yes. If you think it should not, as FDA recommends, vote no.

Any of the attendants by phone, make sense?

DR. FOJO: Yes.

DR. VENITZ: Okay. Then please go ahead and vote.

(Vote taken.)

DR. HONG: Question number 3, we have zero yeses, 11 nos, and zero abstain.

DR. VENITZ: Can we go around the room staring with Dr. Carome?

DR. CAROME: Mike Carome. I voted no. There are safety concerns, including concerns about kidney toxicity from inorganic germanium. There's a lack of evidence that the drug is efficacious for cancer treatment, and there are certainly a number of FDA-approved treatments for cancer, a variety of

drugs, radiation therapy and other non-FDA-approved treatments that don't involve an FDA-regulated product.

DR. WALL: Donna Wall. I agree with what was said.

DR. DiGIOVANNA: John DiGiovanna. For the same reasons, I voted no.

MS. DAVIDSON: Gigi Davidson. I voted no for the same reasons.

MR. HUMPHREY: William Humphrey. I voted no for the same reasons.

DR. PHAM: Katherine Pham. I voted no for safety concerns.

MS. JUNGMAN: Elizabeth Jungman. No, for the reasons that have been mentioned.

DR. VAIDA: Allen Vaida. I voted no for some of the same reasons.

DR. VENITZ: Jurgen Venitz. I voted no for the same reason.

Dr. Fojo and Dr. Gulur?

DR. FOJO: This is Dr. Fojo. I voted no and for the reasons that have been stated, concern

about safety, definite efficacy, not convincing in any way.

DR. VENITZ: Thank you. Dr. Gulur?

DR. GULUR: This is Dr. Gulur. I voted no for all the reasons stated.

DR. VENITZ: Thank you. We're down one, two more to go. The next voting question relates to rubidium chloride. The questions you have to vote on is should rubidium chloride be placed on that list? Yes, it should; no, it should not, which is what FDA recommends. Please go ahead and vote.

(Vote taken.)

DR. HONG: Question number 4, we have zero yeses, 11 nos, and zero abstain.

DR. VENITZ: Let's go around the table starting with Dr. Gulur, please.

DR. GULUR: This is Dr. Gulur. I voted no for a lack of any convincing data to add it to the list.

DR. VENITZ: Dr. Fojo?

DR. FOJO: I voted no, again, as was just stated, lack of convincing data. I did not think

it should be added to the list.

DR. VENITZ: Jurgen Venitz. I voted no. Safety and efficacy data, as limited as they were, did not support.

DR. VAIDA: Allen Vaida. I voted no for the same reasons as the FDA brought up.

MS. JUNGMAN: Elizabeth Jungman. I voted no for similar reasons.

DR. PHAM: Katherine Pham. I voted no for reasons already stated.

MR. HUMPHREY: William Humphrey. I voted no for the lack of efficacy data.

MS. DAVIDSON: Gigi Davidson. I voted no because of the lack of efficacy in the safety signal.

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

DR. WALL: Donna Wall. I voted no for the same reasons.

DR. CAROME: Mike Carome. I voted no for the reasons stated.

DR. VENITZ: Okay. Thank you. That moves

us to our last voting question for today. Here we are talking about the deoxy-D-glucose. The question that you're voting on, should deoxy-D-glucose be placed on the list? If yes, vote yes. If not, as FDA recommends, vote no. This includes all voting in attendance, including Dr. Lo Re. Please vote on question number 5.

(Vote taken.)

DR. HONG: Question number 5, we have 3 yeses, 9 nos, and zero abstain.

DR. VENITZ: Let's go around the table starting with Dr. Carome.

DR. CAROME: Mike Carome. I voted no. There are safety concerns related to systemic intravenous use. There is a lack of data that the drug is effective for any use. For viral disease, there's a lack of data that it has antiviral activity. And there are many FDA-approved treatment options for both malignancies and herpes simplex virus and other infections.

DR. WALL: Donna Wall. I voted yes. I think that for the herpes or for the viral, I think

that there is some efficacy that maybe should be further explored. No absolutely for the oncology. I think it should only be the topical or the oral ingestion on this product.

DR. DiGIOVANNA: John DiGiovanna. I voted no. I found no evidence of efficacy.

MS. DAVIDSON: Gigi Davidson. I voted yes and would restrict that only to a topical application for the antiviral uses. I feel like there is some compelling testimony to the benefit it adds to patients with shingles.

MR. HUMPHREY: William Humphrey. I voted no for the same reasons as Dr. DiGiovanna and Dr. Carome.

DR. PHAM: Katherine Pham. I voted yes for similar reasons stated by Dr. Wall regarding restriction, just to the topical for the evidence that was given regarding HSV and the detailed considerations of formulation delivery by Dr. Day in his presentation.

MS. JUNGMAN: Elizabeth Jungman. I voted no because of the sufficient alternatives, the weak

evidence of effectiveness and concern about use in indications other than HSV.

DR. VAIDA: Allen Vaida. I voted no because it could be used for any indication, the variety of strengths from 0.2 to 10 percent and that there are other products on the market.

DR. VENITZ: This is Jurgen Venitz. I voted no. Systemically, obviously toxicity rules. As far as the topical indication, I concur with FDA's recommendation that it should be pursued using the IND route, but it was not convincing.

Dr. Fojo?

DR. FOJO: I voted no. Certainly, there was no efficacy data for the cancer indication. I wasn't convinced by the viral indication. I was just going to say one thing at the end. The FDA, on several occasions said, oh, we shouldn't approve it because there's approved drugs that are good or better, even for this indication -- for a given indication.

I think it has to do with the drug itself. It doesn't matter -- I mean, the implication there,

if you take it further, is that, well, if there wasn't something, maybe we would approve it. The thing is there are good things here for viral illnesses, but even if there weren't, this shouldn't be approved.

DR. VENITZ: Thank you. Dr. Gulur?

DR. GULUR: I vote no for all the reasons stated, lack of safety, efficacy, and really this particular drug especially, there was no convincing data to move forward with.

DR. VENITZ: Thank you. Dr. Lo Re?

DR. LO RE: I voted no also for the reasons of lack of data on efficacy, concerns about systemic toxicity.

**Adjournment**

DR. VENITZ: Okay. Thank you, everyone. I think this concludes our meeting for today unless I'm missing something. So thank you all for hanging in as long as you did. We reconvene tomorrow morning at 8:30. Thank you.

(Whereupon, at 4:24 p.m., the afternoon session was adjourned.)