FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Wednesday, October 28, 2015

8:30 a.m. to 10:01 a.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

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

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(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

U.S. Pharmacopeial Convention

(USP) Representative

Director of Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

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John J. DiGiovanna, MD

Staff Clinician, DNA Repair Section

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Padma Gulur, MD (via phone)

Professor, Department of Anesthesiology and

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William A. Humphrey, BSPharm, MBA, MS

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PHARMACY COMPOUNDING ADVISORY COMMITTEE INDUSTRY REPRESENTATIVE MEMBERS (Non-Voting)

Ned S. Braunstein, MD

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

William Mixon, RPh, MS, FIACP

Owner-Manager

The Compounding Pharmacy

Hickory, North Carolina

TEMPORARY MEMBERS (Voting)

Lin Chang, MD

(Participation in alanyl L glutamine and domperidone discussions via telephone) October 28th only

Professor of Medicine

Program Director, University of California, Los Angeles (UCLA) GI Fellowship Program

Co-Director, Oppenheimer Family Center for Neurobiology of Stress

David Geffen School of Medicine at UCLA

Los Angeles, California

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

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Perlman School of Medicine

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C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning. I would like first to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you have not already done so. I would also like to identify the FDA press contact for the open session meeting, Ms. Lyndsay Meyer. If you are present, please stand. Right there in the back. Thank you.

Good morning, everyone, for the second day of the PCAC meeting. My name is Jurgen Venitz. I am the chair of the Pharmacy Compounding Advisory Committee. I will now call the committee to order.

We ask those at the table, including FDA staff and committee members, to introduce themselves, starting with the FDA to my left and moving to my right, and finishing up by our members on the phone. So let's start on the left, please.

DR. SUM KO: Hon Sum Ko, Division of Dermatology and Dental Products.

DR. KORVICK: Joyce Korvick, Division of Gastroenterology and Inborn Errors Products.

MR. FLAHIVE: Jim Flahive, Reg Counsel, CDER Compliance.

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

MS. BORMEL: Gail Bormel, acting division director, Division of Prescription Drugs in CDER's Office of Compliance.

DR. VENITZ: Dr. Lo Re, do you want to introduce yourself, please?

DR. LO RE: Yes. My name is Vincent Lo Re from the Division of Infectious Diseases in the Department of Biostatistics and Epidemiology at the University of Pennsylvania.

DR. VENITZ: Thank you. Dr. Chang, would you introduce yourself, please?

DR. CHANG: Lin Chang, faculty member at UCLA, Division of Digestive Diseases.

DR. VENITZ: Thank you. Dr. Gulur, please introduce yourself.

DR. GULUR: This is Dr. Gulur, director of pain care at the University of California.

DR. VENITZ: Thank you.

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

DR. VENITZ: I'm Jurgen Venitz. I'm a clinical pharmacologist and professor at the VCU School of Pharmacy.

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

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

DR. PHAM: Katherine Pham, NICU clinical pharmacy specialist at Children's National Medical Center.

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

MS. DAVIDSON: Gigi Davidson, USP representative to the Pharmacy Compounding Advisory

Committee, and director of pharmacy at the North Carolina State University College of Veterinary Medicine.

DR. DIGIOVANNA: John DiGiovanna. I'm a dermatologist on the staff of the Dermatology Branch, National Cancer Institute, NIH.

DR. WALL: Donna Wall, pharmacist. I represent NABP. And I'm a clinical pharmacist at University Hospital in Indianapolis.

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

MR. MIXON: Good morning. Bill Mixon, The Compounding Pharmacy, Hickory, North Carolina. I'm one of two nonvoting industry members.

DR. BRAUNSTEIN: Ned Braunstein. I'm the head of regulatory affairs at Regeneron Pharmaceuticals. I'm the other nonvoting industry representative.

DR. VENITZ: Thank you, and thank you for coming back for this second day. So let me read the official start of the meeting notes.

For topics such as those being discussed at

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during

breaks or during lunch.

Let us begin, and we are officially beginning with Dr. Hong reading the conflict of interest statement in the record.

Conflict of Interest Statement

DR. HONG: The Food and Drug Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the National Association of Boards of Pharmacy, the United States Pharmacopoeia, and the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

and to the public.

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

Related to the discussions of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These

interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

On October 28, 2015, the committee will discuss four bulk drug substances nominated for inclusion under Section 503A, Bulk Drug Substance List. FDA intends to discuss the following nominated bulk drug substances: alanyl-L-glutamine, glutaraldehyde, glycyrrhizin, and domperidone. Other nominated substances will be discussed at future committee meetings.

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

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

To ensure transparency, we encourage all standing committee members and temporary voting

members to disclose any public statements that they have made concerning the bulk drug substances at issue.

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

Section 102 of the Drug Quality and Security Act amended the Federal Food, Drug, and Cosmetic Act with respect to the advisory committee on compounding to include representatives from the NABP and the USP. Their role is to provide the committee with the points of view of the NABP and the USP.

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

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

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

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

DR. VENITZ: Thank you, Dr. Hong.

As you know, we are asked as a committee to consider three substances to be put on the 503 bulk drug substance list. So what we're going to have is to have three presentations by the FDA, each followed by clarifying questions.

Our first presenter is Dr. Korvick, and she is going to review FDA's summary and recommendation for alanyl-L-glutamine.

FDA Presentation - Joyce Korvick

DR. KORVICK: Good morning. I'm Dr. Korvick. I'm the deputy director for safety for the Division of Gastroenterology and Inborn Errors Products at the FDA.

Good morning, everyone. We're going to discuss alanyl-L-glutamine for this session. This is the review team that worked on the product, my colleagues from the division and a pharmacy quality reviewer from the Office of Pharmacy Quality.

We're looking at the nomination for the alanyl-L-glutamine for intravenous use as a nutritional support in critically ill patients and

to reduce the rate of infectious complications in surgically and critically ill patients. And it's important to draw your attention. This is an intravenous nomination.

This slide shows the physical and chemical characteristics of alanyl-L-glutamine, and you can see it's a diamine. I'm not going to read this whole slide for you.

Possible synthetic routes are important. Multiple methods and routes of manufacture have been reported, including enzymatic processes and E. coli fermentation processes. This dipeptide is produced as a solid and is intended for compounding into a solution dosage for intravenous formulation.

Likely impurities could be other amino acid dipeptides or polypeptides; residual organic solvents and reagents used in manufacture and purification processes; heavy metal or elemental impurities from starting material and agents used in the manufacture process; potential for bioburden including fungus, bacteria, when the product is produced by fermentation; or endotoxins.

In conclusion, alanine is a well-characterized chemical entity. The types and levels of potential impurity of this chemical entity can vary depending on the starting material, the reagent, and the manufacturing process.

The quality cannot be adequately assessed due to the lack of information regarding the manufacturing of alanyl-L-glutamine from the suppliers of this chemical entity. So a key safety concern is the lack of established quality standard for the API intended for compounding into large volume parenteral formulations for repeated intravenous administration to compromised patients with severe underlying illness.

Next, we'll turn to the nonclinical assessment. Pharmacologically, alanyl-L-glutamine is rapidly converted in the body to alanine and glutamine following infusion. Glutamine is not an essential amino acid and is abundant in the blood and intracellular tissue.

Glutamine plays an important role in a number of physiologic functions, including protein

synthesis, immune cell growth, maturation, and function. Glutamine levels decrease in severely ill patients with high catabolic rates and patients with impaired ability to absorb glutamine.

The safety. There were no studies on CNS, cardiovascular, or respiratory function available on review of the clinical data. In nonclinical assessment, we saw one study for acute toxicity for alanyl-L-glutamine in Sprague Dawley rats with single oral doses up to 2000 milligrams per kilogram.

There were two studies that we reviewed for repeat dose toxicity. Again, the first one was a 14-day oral dose-ranging study, and they saw no clear treatment-related adverse events at doses up to 5 percent; a 13-week study, again oral study, in male and female rats, and again there were no clear treatment-related adverse events, suggesting that the highest dose for males studied was around 3000 milligrams, and similar for females, and no observed adverse event level could be calculated because there weren't any adverse events.

Then further nonclinical assessment, for mutagenicity, it was determined not to be mutagenic or clastogenic in the Ames test for the Chinese hamster lung model. However, review of the literature did not reveal any information on animal studies for development and reprotox, carcinogenicity, or toxicokinetics.

Other relevant toxicology studies to share with you, since it's rapidly metabolized to glutamine and alanine, we note here that there was a study, 26 weeks, in rats where they tolerated extremely high dietary levels of alanine.

So the conclusion for the nonclinical assessment was that it was well-tolerated in rats at high dietary levels orally for 13 weeks. And again, no intravenous animal studies were available for this compound.

In our human safety review, we have concerns related to intravenous administration of bulk compounded parenteral products, again regarding potential impurities that I listed earlier.

Adverse event reactions. The safety profile

should be similar to that of glutamine because this is rapidly converted to glutamine. However, in the literature, we note that caution is made when administering this product to patients with liver and kidney disease, and that patients with specific amino acid metabolism defects may be at greater risk for hyperammonemia and CNS toxicity.

So we reviewed the literature. Before that, though, we asked our colleagues in the Office of Safety Evaluation to look at the FAERS database. And we searched these terms listed here, including glutamine.

We came up with three foreign reports of an adverse event for alanyl glutamine, and these probably could not be related directly to the use of alanyl glutamine because these patients had underlying morbidity.

We came up with, for the search on glutamine, 83 unduplicated adverse event reports. Eleven of those cases had no concomitant drugs administered. There were seven unique death cases listed, and the cause of death was three for

cancer, one for stroke, and three were unknown. And two of the seven had a history of cancer. There were two nonfatal cases of these, one hospital admission for an upset stomach and vomiting, and one for sickle cell crisis while taking glutamine.

Since this is derived from dietary supplement sources, we also had CFSAN look at their adverse reporting system, which is different than FAERS. As you can imagine, there are a lot of different things reported, and there are no systematic, standard names for some of these products that you can buy off the shelf.

They reported 49 spontaneous reports, and 33 were documented to have taken the oral product containing glutamine. You can imagine some of these products have names, but they don't always have what's in them.

We noted these 33 cases, and there were no fatalities reported, and there was a wide range of adverse reactions related. However, again, because of the type of data, a direct linkage to cause and

effect with taking these dietary supplements could not be drawn.

Then we turn to the safety data in the literature. We found one recent large study in critically ill patients in intensive care units in multiple countries, a multi-center study, with organ failure receiving mechanical ventilation.

Then in this study, 611 adult patients received 45 grams of glutamine supplements daily. Fifty percent of that dose was provided as alanyl glutamine intravenously, and 50 percent was orally, alanyl glutamine and glycine glutamine.

The adverse reported events, 52 serious in 46 patients, and 4 were considered to be potentially related to study drug. There was no statistically significant difference between adverse events across groups, and the study also noted elevated serum urea levels in patients receiving glutamine.

But an interesting outcome was the measurement of mortality. The authors reported the 28-day mortality, the in-hospital mortality, and

the mortality at six months. And all of these were higher in the alanine glutamine-treated group, alanyl-L-glutamine-treated group, and statistically so for the in-hospital mortality and the mortality at six months.

Because of these results, a recent update in 2015 in Canadian practice guidelines recommended that parenteral supplementation with glutamine not be used based in part on the mortality results from the Heyland trial. That was the trial I just reported.

The data suggests that glutamine supplementation should not be given in high doses or early in acute critical illness in patients with multi-organ failure or unresuscitated shock requiring significant vasopressor support.

In a recent Cochrane review in 2014, they noted that alanyl-L-glutamine or glutamine supplementation had little effect on the risk of mortality or the length of ICU stay with glutamine supplementation. So there are concerns about the safety of bulk substance potential toxicity from

heavy metal contaminants.

Our literature review went further, and you have our backgrounder, which delves into the details very briefly. But we are going to just briefly highlight that we focused on four published literature reviews.

These were systematic reviews and meta-analysis of the literature and the Aspen paper in 2011. As you can imagine, things have progressed since then. There's a Cochrane review in 2014, a review by Wischmeyer et al. in 2014, and then the updated Canadian Practice Guidelines.

I should point out that these publications include multiple clinical trials, generally small in size with varying results. And this is in contrast with the one large multi-center randomized study by Heyland et al.

This just gives you a view of the Cochrane review and the various outcomes that were studied, including infectious complications, length of ICU stay, and mortality.

I just show this to you here because you can

see that the number of patients included in these various studies vary depending on the studies included per the particular analysis because not all studies reported each of these outcomes, and that the quality of evidence for these various outcomes vary from moderate to low.

This is an overall schema representing key findings from the meta-analysis of these studies. I just put this here to show you that there's a variety of outcomes. Mortality, the Cochrane found no impact. For the Wischmeyer review, they had a trend favorable for this supplementation with glutamine. This should say, parenthetically, these studies do have some alanyl-L-glutamine but mostly glutamine. However, the Heyland showed a negative impact.

So you can see that divergence in outcomes for these, either trending, nonsignificant, favorable, or unfavorable across these outcomes.

So as I mentioned before, the majority of these studies in the Cochrane review were small. Three-quarters had sample sizes fewer than a

hundred. The vast majority of these had sample sizes under 50.

Over half of the studies in the Wischmeyer and the Canadian reviews had sample sizes less than a hundred. Again, there are varying outcome results and are of varying quality within the meta-analysis and across the meta-analysis. On the other hand, we have this one large glutamine supplementation study. However, this study may be slightly different than the kind of study -- the patients that were studied in these other reviews. However, it is a large single study, randomized, controlled.

Moving on to other questions in this review, yes, this product is intended to be used in critically ill patients. Are there alternative approved therapies? Although not FDA-approved for intravenous administration, glutamine is a component of an approved product and is the subject of a USP monograph, and therefore can be used in compounding under Section 503A of the FD&C Act.

So again, our conclusion for effectiveness

is that supplementation of parenteral glutamine may improve clinical outcomes when given to appropriate patients as part of complete nutritional support. However, this has not been persuasively established.

The timing of administration, dosage, and specific subset of critically ill patients for whom glutamine supplementation might be beneficial has not been determined and requires further study. Significant benefit/risk evaluation is necessary, given these knowledge gaps; also noting the recent data from the Heyland study, which suggests glutamine supplementation may be associated with increased mortality in critically ill patients.

In light of the above effectiveness considerations and given the safety concerns surrounding potential toxic impurities in the parenteral administration of alanyl-L-glutamine for chronically ill patients, and in conjunction with the increased mortality observed in a large randomized, controlled trial, we do not recommend that alanyl-L-glutamine be placed on the list of

bulk substances that may be used for compounding under Section 503A of the FD&C Act. Thank you.

Clarifying Questions

DR. VENITZ: Thank you.

Are there any clarifying questions? Dr. DiGiovanna?

DR. DIGIOVANNA: Yes. DiGiovanna. So I would get the sense that a major concern here has to do with impurities based upon synthesis. And I guess that's based upon the status quo now. But if that should change in the future, I think that would change the balance. Is that reevaluated or reevaluable at some point if a better synthetic, more pure product were to become easily available?

DR. KORVICK: I think that what is unique about these substances is they're used in large volume on a daily basis, perhaps for a long time. So what might be a single small-volume infusion for an antibiotic, that concentration in there might be negligible, but the cumulative effect.

As I understand it, and my colleagues may be able to help me, I think that it's not clear when

you do this compounding what you're going to pull off the shelf to use to compound. So I think maybe Jane would have a comment on that. I don't know that we can assure, as the same way that we could ensure with an approved product, that we would have that level of quality.

MS. AXELRAD: Yes. I think this is related to what we talked about yesterday in that there aren't data to suggest what should be the standards for it, and there are no monograph standards for it.

I think it's conceivable that there might be at some point a monograph developed in the USP for this if it were on the list. But I also think that Dr. Korvick said that the impurities was one part of it, but I think that she was also citing studies, including a randomized, controlled study, that had nothing to do with the impurities in it, but basically showed that it didn't really help and could hurt.

So I think the impurities -- it's possible that if someone had data, they could identify what

levels of impurities would be okay if you were going to be using it chronically, like Dr. Korvick said, maybe.

DR. KORVICK: I would also like to add that it's important for these various reasons that our division would like to encourage people to come in with applications so that we can provide quality products to this vulnerable population.

I think we've been reaching out to the various groups and nutritional societies, et cetera, to work on these things, and there are a number of these types of products that languish. And that's why people reach for them to compound them.

So we would like to see more applications where we have a quality product that has the standards that we are accustomed to when we give prescription drugs, and that we know what the safe doses and so forth in the recommendations could be. So bringing those under that NDA process would give us a better product for the population at large.

DR. VENITZ: Can I ask you to amplify on the

alternative treatment that you're referring to in slide number 23?

DR. KORVICK: Slide number --

DR. VENITZ: Twenty-three. You are referring to an FDA -- not approved for IV, but a component of an approved product.

DR. KORVICK: We have some products that are multiple amino acid combinations, so you might be able to find that in one of those. Right now, I can't tell you the name of them.

DR. VENITZ: No. That's fine. But that's for oral use only. Right?

DR. KORVICK: What?

DR. VENITZ: That is for oral use only?

DR. KORVICK: My colleagues in OUDLC helped me with this, so I can't answer that question.

MS. AXELRAD: We have to look that up. I think we'd have to look it up and get back to you. Your question is whether the alternative approved therapies -- it says here, although not FDA-approved for intravenous administration, glutamine is a component of an approved product. Right?

DR. VENITZ: Yes. I'd like to know whether there's an approved product --

DR. KORVICK: So this would be oral. I'm reading the slide now. Thank you. It's a little early. I apologize.

DR. VENITZ: So this is oral only. There's no IV product that is approved?

DR. KORVICK: No. Glutamine itself is under USP. There's a monograph for glutamine.

DR. VENITZ: Okay. Thank you.

Yes, Mr. Mixon?

MR. MIXON: Did you come across any clinical information that would make this product more advantageous than just plan L-glutamine for use in patients that are extremely metabolically compromised? My experience with L-glutamine is in clinical nutrition with parenteral TPN therapy. So my question is --

DR. KORVICK: Are you talking about alanyl-L-glutamine?

MR. MIXON: Yes. Is there any reason at all that this would be better than just plain L-

glutamine, which is already approved?

DR. KORVICK: The reason that we understand that it might contribute somebody to the therapy, it's not that it provides more for the patients. But this particular diamine is more stable than glutamine, so it may be more convenient for administration than glutamine. That's what we understand.

MR. MIXON: But we haven't heard from any nominators that this product is needed for parenteral nutrition. Correct?

DR. KORVICK: It is not an essential amino acid, so you can use glutamine. This spans a very short amount of time after you infuse it in the body as alanyl-L-glutamine. Basically, what it does is provide glutamine.

MR. MIXON: Right. Thank you.

DR. VENITZ: Any further clarifying questions?

(No response.)

DR. VENITZ: Then thank you.

Our next presentation is regarding

glutaraldehyde, and we've got Dr. Ko presenting FDA's summary and recommendation.

FDA Presentation – Hon Sum Ko

DR. KO: Good morning. I am Hon Sum Ko from the Division of Dermatology and Dental Products. Today I'm going to discuss glutaraldehyde as a candidate for the 503A list for bulk substances for compounding. This slide shows my colleagues in this review for glutaraldehyde, including Dr. Bain, Dr. Yao, and Dr. Tran.

Glutaraldehyde has been nominated to be put on the list of bulk drug substances to be used for compounding under Section 503A for two proposed uses, for the treatment of warts and as a soaking solution for heart valve repairs.

This presentation will focus on the treatment of warts. The use of glutaraldehyde as a soaking solution for heart valve repairs is in fact the use of the substance as a reagent in the preparation of the heart valve as a medical device. So this will not be addressed under bulk drug substances under 503A.

Glutaraldehyde for the treatment of cutaneous warts has been mainly used as a topical formulation, and frequently as a solution. The mechanism of action is not entirely clear, and the current consensus seems to be through chemical dehydration, causing superficial tissue necrosis.

There may be other mechanisms of action because glutaraldehyde is a keratolytic agent, and it may perhaps have antiviral activity as it also binds DNA and protein.

This slide shows physical and chemical characterization. The substance is a small compound of 110 molecular weight. It's a dialdehyde with a density near that of water, and it's liquid at room temperature. When it boils, it will decompose.

This slide shows the two possible synthetic routes for glutaraldehyde. It may be synthesized from cyclopentene through oxidation, or a combination of acrolein, together with methyl vinyl ether, through an intermediate and then hydrolysis to give this dialdehyde.

So the likely impurities would be starting material and possible air oxidation products from aldehyde to acid, glutaric acid and 5-oxopentanoic acid. So the conclusion, after review for the physical and chemical characteristics, would suggest that this substance is well characterized physically and chemically.

From chemical synthesis and stability perspectives, the compounding of glutaraldehyde as a topical product is reasonable when it is properly stored, protected from heat and air.

Nonclinical assessment. We discussed earlier about mechanism of action, so I'm not going to address any further.

Safety pharmacology in animal studies showed adverse effects potentially on nervous system, cardiovascular, and respiratory systems after systemic exposure. And as to locally, it causes irritation of skin, eyes, and respiratory tract, and it would be exacerbated by repeated exposure.

Developmental and reproductive toxicity as well as carcinogenicity studies have not shown

positive results, and it's a skin sensitizer. The mutagenicity studies, since it is reactive with binding DNA and protein as a cross-linker, in vitro studies show positive results. However, in vitro studies do not clearly indicate that there is mutagenicity.

There have been no reports of in vivo human pharmacokinetic studies for glutaraldehyde. In vitro studies suggest that glutaraldehyde solution can absorb into and bind to the skin tissue. And because a lot is bound already, only a small fraction would pass through the skin and become available systemically.

Human safety data. As we discussed earlier, glutaraldehyde is an irritant, and so irritation to respiratory and dermatological systems through the vapor or direct contact will be able to occur. And so this presents occupational hazard to workers exposed to this substance in the environment.

Again, as mentioned earlier, it is a sensitizer, and so it may cause allergic contact dermatitis. And for clinical use, the primary

concern is about skin ulceration and necrosis, which will be discussed further next slide.

Human safety data in clinical trials. There have been dedicated dermal safety studies for glutaraldehyde for the toxicity and for teratogenicity, and these were negative in results.

There is low sensitization and irritancy potential. However, there have been no randomized, controlled trials specifically to determine the safety of glutaraldehyde, and available data are primarily from open label studies or case reports.

Frequently they may have a brown discoloration that could be transient. Again, irritation, allergic contact dermatitis, skin ulceration, necrosis -- these have all been reported. And skin ulceration and necrosis are more prone with higher concentrations of glutaraldehyde, such as 20 percent or higher.

For efficacy in the treatment of cutaneous warts, there has been a small controlled clinical trial comparing glutaraldehyde, 10 percent solution, to a formulation that is not marketed in

this country. The study was done in the United Kingdom, where they have a salicylic acid/lactic acid paint for plantar warts, and the results were comparable in terms of cure rates. And from the open label studies in the literature, there have been varying degrees of efficacy, between 71 to 100 percent for cure rates.

Historical use. Glutaraldehyde has been compounded for medical use for several conditions, for excessive sweating in the foot, for nail fungus, and also for cutaneous warts. So it is a viable option for the treatment of cutaneous warts, and the use appears to be widespread, with approved formulations in some countries.

To summarize and conclude in terms of the full criteria we use, glutaraldehyde is well characterized in its physical and chemical properties. Its topical use may result in adverse events such as skin discoloration, contact dermatitis, and skin ulceration and necrosis, especially with high concentrations. These risks may be managed by the use of lower strengths, like

10 percent or lower.

There is evidence of efficacy in the treatment of warts, based primarily on open label studies, and its use for cutaneous warts has been widespread for quite some time, like over 14 years.

Therefore, we recommend that glutaraldehyde for topical use be placed on the list of bulk drug substances under 503A of the Food, Drug, and Cosmetic Act for compounding. Thank you.

Clarifying Questions

DR. VENITZ: Thank you, Dr. Ko.

Any clarifying questions? Dr. Carome?

DR. CAROME: Mike Carome. Two questions. Is this intended to be self-administered by the patient at home or is it used in the doctor's office?

DR. KO: This can be self-administered, yes.

DR. CAROME: And in terms of the local reactions that you describe, including skin ulceration and necrosis, do you know how this product compares to other treatments used for warts in terms of those types of adverse events?

DR. KO: For approved treatments, in this country, there is an over-the-counter monograph with some salicylic acid formulations with different excipients. And the use with what is monographed would be unlikely to be associated with those events.

DR. VENITZ: Dr. Davidson?

DR. DIGIOVANNA: This is Dr. DiGiovanna. Let me just address your question. There are many, many treatments for warts, and warts are very common. Glutaraldehyde isn't a commonly-used treatment.

However, the spectrum of warts in individuals is quite enormous, and people who take care of rare diseases, particularly some more recently-identified immunosuppressive disorders that are generally inherited -- Dock8 deficiency is a disorder related to very extensive susceptibility to human papilloma virus, molluscum contagiosum, systemic infections, and lymphomas; as is another disorder, WHIM syndrome, which is related to warts immunodeficiency -- these individuals have horrific

issues with respect to morbidity and mortality from lymphoma, but their lives are disrupted by thousands and thousands of warts.

So those individuals we try to get to a point where you can manage their lives. And so the alternative would be for a treatment where some dermatologist would use very toxic, destructive treatments; for example, for individual lesions, intralesional bleomycin, the chemotherapy, which would cause necrosis.

So you really have to place this into a balance. We're not talking about treating a child with one or two or even 20 or 30 warts. You're really talking about the very difficult situation. So that's the scenario where this drug would be considered.

DR. KO: Right. And I agree entirely with Dr. DiGiovanna. A lot of the treatments, so-called treatments available, are off-label uses. So it would be something available when we have this for compounding.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: Just a comment. Glutaraldehyde solution does have a USP-NF monograph. So I'm not sure why it's on this list, but it is under Glutaral solution.

MS. AXELRAD: Apparently that's a 50 percent solution, and --

MS. DAVIDSON: It's not defined in the monograph as a given percentage. It just has a range of plus or minus 10 percent in the NF monograph.

DR. VAIDA: In a follow-up, I was going to ask also if this is supposed to be administered by patients at home. But you also have for adverse reactions an occupational hazard to workers exposed. So is this an issue with patients giving it at home, also being exposed? Or is it a low strength?

DR. KO: The amount to be used topically probably is not causing that. We have asked the Office of Drug Safety to look into adverse event reporting under the FAERS system, specifically for reports on glutaraldehyde use for warts. And they

really didn't find any. Most of the reports were from industry use or other purposes.

As you know, the substance is also available for other uses. It's a disinfectant cleared by the Center for Devices and Radiological Health. So it is not something that is unknown or not available. But for compounding, this would be something different.

DR. VENITZ: Thank you.

Are there any other questions or comments?

(No response.)

DR. VENITZ: Then thank you, Dr. Ko.

Our last FDA presentation is by Dr. Connelly. She's going to tell us about glycyrrhizin and the FDA's review and recommendation.

FDA Presentation - Sarah Connelly

DR. CONNELLY: Good morning. It is a pleasure to present findings from FDA's collaborative review of glycyrrhizin. Glycyrrhizin by intravenous administration has been nominated for inclusion on the list of bulk substances for

use in compounding under Section 503A for use in the treatment of chronic viral illnesses such as hepatitis C. I will be presenting on behalf of the FDA review team, which also includes Dr. Mark Powley, Dr. William Ince, and Dr. George Lunn.

Glycyrrhizin, also known as glycyrrhizic acid or glycyrrhizinic acid, is extracted from the root of the licorice plant, Glycyrrhiza glabra. Although the National Formulary-grade ammonium glycyrrhizate is well characterized with tests for assay impurities, identity, residue on ignition, optical rotation, and water, the 503A nomination refers to other preparations.

These include USP dietary supplement monographs for powdered licorice and the NF monograph for licorice fluid extract. Together with Chinese traditional medicines, these preparations exhibit low glycyrrhizin assay values and are poorly characterized with regard to impurities. And they may contain other pharmacologically active compounds such as morphine, ephedrine, pseudoephedrine,

methylephedrine, and amygdaline.

These next few slides provide information pertaining to the nonclinical safety of glycyrrhizin. In primary pharmacology studies, antiviral activity has not been adequately demonstrated. Selectivity indices for hepatitis C and other viruses were generally estimated to be less than 10, consistent with a lack of significant antiviral effect.

An identified concern from safety pharmacology is glycyrrhizin's inhibition of 11-beta-hydroxysteroid dehydrogenase in the kidney, which will be discussed in more detail in the human safety slides.

No effects were observed on cardiovascular, respiratory, or gastrointestinal systems of cats given single intraperitoneal doses of glycyrrhetic acid in safety pharmacology studies.

The lethal dose-50 for glycyrrhizinic acid and various salts in acute toxicology studies in mice, guinea pigs, and dogs was in the range of 308 to 12,700 milligrams per kilogram. Intravenous

administration of ammoniated glycyrrhizin in mice resulted in convulsions and hemolysis.

In repeat dose toxicology studies, high oral doses of glycyrrhizinic acid and/or its monoammonium salt in rats and mice led to apparent mineralocorticoid excess, otherwise known as pseudohyperaldosteronism, which I'll also discuss more in the human safety slides. Oral doses of glycyrrhizin crude extract caused myolysis, or muscle breakdown, of heart papillary muscles in rats.

Regarding mutagenicity, developmental and reproductive toxicology, and carcinogenicity studies, the weight of evidence suggests glycyrrhizinic acid and related salts are not genotoxic, are not teratogenic, and in mice administered oral disodium salt of glycyrrhizinic acid for 96 weeks, no carcinogenic effects were observed.

Regarding toxicokinetics, orally administered glycyrrhizinic acid is hydrolyzed in the gastrointestinal tract to form glycyrrhetic

acid, which is then readily absorbed. Intravenous administered glycyrrhizinic acid is metabolized in the liver, excreted via bile, and subsequently metabolized to glycyrrhetic acid in the gastrointestinal tract.

In summary, nonclinical safety conclusions are that nonclinical data appear to support the safety of low-level exposures to glycyrrhizinic acid through oral routes such as diet. However, there is little nonclinical data for intravenous glycyrrhizinic acid administration.

A primary concern is the potential for off-target effects related to inhibition of 11-beta-hydroxysteroid dehydrogenase. Convulsions occurring following intravenous dosing in mice may also be relevant for clinical administration.

These slides provide information pertaining to human safety of glycyrrhizin, where pseudohyperaldosteronism effects have been most commonly observed. These effects are related to glycyrrhizin's inhibition of conversion of cortisol to cortisone in the kidney, as shown in this

figure.

The metabolite glycyrrhetinic acid inhibits 11-beta-hydroxysteroid dehydrogenase, leading to elevated cortisol levels in the kidney, which stimulate the mineralocorticoid receptor with effects such as sodium retention, edema, hypokalemia or low potassium, and hypertension.

A Medline search for licorice revealed more than a hundred case reports describing events related to pseudohyperaldosteronism, including hypokalemia or low potassium, hypertension, edema, myopathies, with some further serious cases of rhabdomyolysis, the arrhythmia Torsades de Pointes, paralysis, posterior reversible encephalopathy syndrome, a syndrome associated with brain swelling on MRI, and cardiac arrest. The glycyrrhizin dose typically was not available on these case reports.

Patients with predisposing sodium-retaining conditions such as ascites and hypertension, which can occur in chronic hepatitis C infection, may be more susceptible to glycyrrhizin's pseudohyperaldosterone effects.

In this slide, data from a clinical trial by Manns et al. identifies patients with chronic hepatitis C that were administered intravenous glycyrrhizin at 200 milligrams either 5 times or 3 times a week for 12 weeks, or were administered placebo.

As shown in this table of the trial's most frequent glycyrrhizin-related adverse events in patients with chronic hepatitis C infection during 12-week treatment, pseudohyperaldosterone effects were observed.

For example, highlighted in red, if it shows up, hypertension events considered possibly or probably related to glycyrrhizin therapy were higher in the glycyrrhizin-containing groups compared with the placebo groups. And highlighted in blue at the bottom of the table, hypokalemia or low potassium was only reported in patients treated with intravenous glycyrrhizin.

This slide discusses efficacy of glycyrrhizin in the treatment of chronic hepatitis C infection. No clinically meaningful antiviral

effect, as measured by hepatitis C virus RNA, has been demonstrated using intravenous glycyrrhizin for the treatment of chronic hepatitis C infection in eight identified clinical trials. Some trials have shown a decrease in alanine aminotransferase or ALT levels, but this was not sustained following treatment cessation.

Several meta-analyses have concluded that there are scientifically insufficient data on glycyrrhizin therapy to evaluate its usefulness. Stickel and Schuppan's 2007 paper states, "The treatment of liver disease with glycyrrhizin, regardless of the etiology, cannot be advocated due to the lack of obvious benefit."

Currently approved oral hepatitis C direct-acting antiviral treatment options in the United States include the fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without ribavirin, the fixed-dose combination ledipasvir/sofosbuvir, and the combination of the individual product sofosbuvir plus simeprevir.

These approved hepatitis C treatment options have demonstrated antiviral efficacy with sustained virological response rates exceeding 90 percent in many populations. Sustained virologic response is defined as a lack of detection of HCV RNA in the blood a certain time period measured in weeks after treatment is completed. And achieving sustained virologic response, or SVR, is considered a virologic cure of chronic hepatitis C infection.

As stated in the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America HCV guidance, across numerous phase 3 programs, less than 1 percent of patients without cirrhosis discontinued treatment early, and AEs, or adverse events, were mild. Most AEs occurred in ribavirin-containing arms.

Discontinue rates were higher for patients with cirrhosis, approximately 2 percent for some trials, but still very low. In addition, these approved hepatitis C oral treatment regimens remove risks of intravenous administration, such as phlebitis and infection.

Four trials of intravenous glycyrrhizin use in the treatment of chronic hepatitis B infection were identified. Two trials were small pilot studies that also included approved treatments for chronic hepatitis B, interferon and lamivudine, confounding the results.

Two trials described an effect on aminotransferases, though did not demonstrate any effect on HBV serologies. Therefore, these studies do not provide convincing evidence for use of intravenous glycyrrhizin in the treatment of chronic hepatitis B.

A review article on the antiviral effects of Glycyrrhiza species describes two studies of glycyrrhizin use in HIV patients, where some patients were stated to have achieved increased CD4 cell counts. Notably, both referenced studies were from Japan and were conducted in the 1980s, before the availability of highly active antiretroviral therapy, and thus do not provide evidence for any beneficial use of intravenous glycyrrhizin in the treatment of HIV.

Use of Glycyrrhiza species, or licorice, dates back to ancient manuscripts from China, India, and Greece, and have been in use for curative and flavoring purposes for more than 4,000 years. Literature suggests that glycyrrhizin has been used for more than three decades to treat chronic hepatitis in Japan. Use of intravenous glycyrrhizin in pharmacy compounding in the United States is unknown based on review of the published literature.

This slide summarizes clinical conclusions regarding glycyrrhizin. Glycyrrhizin is not an antiviral compound, by our definition, and intravenous glycyrrhizin has no demonstrable antiviral effect in clinical studies of patients with chronic hepatitis C infection, in contrast to the significant efficacy of available, approved, all-oral HCV direct-acting antiviral combination therapies. Likewise, data for intravenous glycyrrhizin in the treatment of chronic hepatitis B and HIV have not demonstrated efficacy.

Regarding safety considerations, the

association between glycyrrhizin use and serious pseudohyperaldosteronism-related adverse reactions, such as low potassium and hypertension, is well established, and patients with chronic hepatitis C infection may be more susceptible to glycyrrhizin's pseudohyperaldosterone effects.

We were unable to find evidence of the history or extent of the use of glycyrrhizin in compounded products in the United States either to treat chronic hepatitis C infection or for other uses.

In conclusion, we do not recommend that intravenous glycyrrhizin be included on the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act. Thank you.

DR. VENITZ: Thank you, Dr. Connelly.

Any clarifying questions by committee members?

(No response.)

DR. VENITZ: Any questions by our members or special government employees calling in?

(No response.)

DR. VENITZ: Okay. Then thank you.

DR. CONNELLY: Thank you.

DR. VENITZ: Go ahead.

MS. AXELRAD: I'd like to just -- not for Dr. Connelly, but going back to the previous presentation on glutaraldehyde, I just wanted to respond to Ms. Davidson's question.

In the review in the briefing materials on glutaraldehyde, we have a footnote that says -- footnote 1 on the first page -- "USP monograph exists for glutaral concentrate -- glutaraldehyde in a 50 percent aqueous solution -- a different concentration than that proposed in the nominations.

USP Guidelines state, 'Some drug substances are available as concentrated solutions and are intended to be used as intermediates for final formulations.'" And I'm not going to cite everything that's in here.

But then we talk about the definition of bulk drug substances in 21 CFR 207.3(a)(4), and we

say that that excludes intermediates used in the synthesis of the bulk drug substance. And we say, "Therefore, we are evaluating glutaraldehyde for the list in forms or concentrations other than those provided in the USP monograph."

The monograph also says in it that the labeling for glutaral concentrate has to say that the article is not intended for a direct administration to humans or animals. It's right at the end under Additional Requirements. So I think that's why we felt the need to evaluate it and review it.

MS. DAVIDSON: Okay. Thank you for that clarification. And I think it's important to make that very visible to the public as they try to decide where the boundaries on monographs are because if you read the definition of the glutaral solution, it doesn't talk about concentration at all. So I think, as a point of clarity for users, it would be very helpful to make it clear why this was not considered. Thank you.

MS. AXELRAD: Thank you.

Committee Discussion and Vote

DR. VENITZ: Okay. Now, we don't have any nominator presentations, and it looks like -- and I'm looking at you -- we have no presenters for the open public hearing. So we are basically ready to move towards our favorite activity, and those are the votes, and then take a long break.

So I'm opening the discussion for all the three drug substances of interest before we proceed with a vote. Any additional comments or additional clarifying questions? Any comments? Any general questions, specific questions, related to any of the three compounds? Yes, Dr. Jungman?

MS. JUNGMAN: I think my question is actually for Gigi. With respect to alanyl-L-glutamine, if we want a USP monograph for this, it seems to me that there are a couple of options. Right? We either put it on the list and folks compound it without the guidance of a monograph until USP picks it up, or you don't put it on the list, and eventually USP picks it up and then folks can compound it starting then.

Do you have a sense of how likely either of those scenarios are in terms of what motivates USP to pick up a substance for a monograph?

MS. DAVIDSON: I think it's input from stakeholders, primarily. I would comment that there is a reference standard for L-alanyl-L-glutamine already. So it would be very easy to characterize the substance for a USP monograph instead of a dietary supplement monograph. But again, if stakeholders pressured USP for the drug monograph for L-alanyl-L-glutamine, it would probably have a higher priority.

DR. VENITZ: Yes?

MS. AXELRAD: Just in response to that, obviously if the committee gives us advice that things shouldn't go on the list and we decide that things shouldn't go on the list, and USP goes and does monographs for them all, it will make the entire process sort of a waste of everybody's time.

So we have had discussions with the USP. We hope that if things are on the list, that USP will develop monographs for them because then there will

be standards by which they can be compounded. But we also hope that if we decide that things are not put on the list, that USP will respect that decision and not do monographs for them, because if they do, it basically undercuts the entire process.

MS. DAVIDSON: And just to clarify, I think that my comments were primarily under the context that it would be added to the list and given a high priority based on stakeholders' need for quality standards for that substance once it hits the list.

I doubt that USP would create a monograph for something that wasn't on the list, but I can't speak with 100 percent certainty on that.

DR. VENITZ: Yes?

DR. KORVICK: This is Dr. Korvick. I just want to make a comment. I think we talk about the substance, and it is always a problem. I don't know how deeply the USP delves into the actual manufacturing process that goes on and the actual potential for contaminants.

The other issue that we did bring up is our concern that a lot of these different nutrition

products out there are not approved products. There's a lot of unapproved use out there, and people use all kind of different doses. They use all kind of different starting substances to bring those in and compound them.

Just saying it's easy to describe how to make an amino acid, it's not quite the same. And we again would urge people to think about these kind of products, especially in the nutrition area, and bring them in under the NDA. I think that's really important, and we've been trying to work on that. And so I share some other concerns that Jane does about the USP process.

DR. VENITZ: Thank you.

Any further discussion?

(No response.)

DR. VENITZ: Then I'm assuming there's consensus to move to the votes. Okay. Let's do so. So let me do the usual spiel while you're pulling out the slide.

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 those three products that we just presented, and you will have the opportunity after we go through the official voting process, as we go around the table, to make any additional statements that you wish. And I'm assuming our call-in colleagues are going to email again? Yes? Okay.

So is everybody ready for the vote? Okay. Then the first voting question is related to alanyl-L-glutamine. So you should vote on whether alanyl-L-glutamine should be placed on the list, yes or no.

(Vote taken.)

DR. HONG: Question number 1, we have 1 yes, 10 nos, and zero abstain.

DR. VENITZ: Okay. Then let's go around the table. This time let's start to my right. Dr. Carome.

DR. CAROME: Mike Carome. I voted no. I thought FDA's review paints a compelling reason why this should not be on the list. We're talking about critically ill patients who have a high mortality rate, high morbidity rate. We need to use evidence-based treatments in managing these patients.

The quality of this product cannot be adequately assessed due to a lack of adequate standards. And I think great weight needs to be given to the one large randomized, controlled trial that showed an increase in mortality, which I think is the most important measure to use in trials for such patients.

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

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

MS. DAVIDSON: Gigi Davidson. I voted no, for the same reasons, but additionally for the risk of contaminants that Dr. Korvick mentioned.

MR. HUMPHREY: William Humphrey, and I voted

no, for the same reasons.

DR. PHAM: Katherine Pham. I voted no, for the same concerns regarding the vulnerable patient population, as well as hoping to see that if there's compelling need, it will go through the NDA process.

MS. JUNGMAN: I voted no, for the reasons my colleagues have enumerated.

DR. VAIDA: Allen Vaida. I voted no, for the reasons mentioned.

DR. VENITZ: Jurgen Venitz. I voted no, and I've got nothing to add.

Dr. Gulur? Dr. Gulur?

DR. GULUR: Hello?

DR. VENITZ: Do you want to comment on your vote?

(No response.)

DR. VENITZ: Dr. Chang, do you want to comment on your vote, please?

DR. CHANG: Yes. I voted no, for the same reasons that everyone else mentioned.

DR. VENITZ: Okay. One more time, Dr.

Gulur, do you want to comment on your vote?

DR. GULUR: Hello? Are you able to hear me?

DR. VENITZ: Yes. We can hear you.

DR. GULUR: I voted no, for the same reasons.

DR. VENITZ: Okay. Then we have to correct the record because right now you're listed as a yes vote. So you intend --

DR. GULUR: No. I --

DR. VENITZ: Please go ahead.

DR. GULUR: I vote no.

DR. VENITZ: Okay. So we will correct the record. We have a unanimous vote for no.

Any additions? Any questions?

(No response.)

DR. VENITZ: Okay. Then let's proceed with our next vote.

So we have the same vote, this time regarding glutaraldehyde. You should be voting on whether glutaraldehyde should be placed on the list for topical use, yes or no. Please go ahead and vote once it starts blinking. Okay. Go ahead and

vote.

(Vote taken.)

DR. HONG: Question 2, we have 9 yeses, 1 no, and zero abstain.

DR. VENITZ: Thank you. So now let's start to my left. That means Dr. Gulur, please elaborate on your vote.

DR. GULUR: I voted no because you have [indiscernible].

DR. VENITZ: Can you repeat? Your vote is no? Is that correct?

DR. GULUR: Yes. That is correct.

DR. VENITZ: Do you want --

DR. GULUR: [indiscernible].

DR. VENITZ: Can you repeat? All I know is that your vote is no. Do you want to add anything to your vote?

DR. GULUR: Yes, [indiscernible], for these patients.

DR. VENITZ: Thank you.

I'm Jurgen Venitz. I voted yes. I thought there was sufficient evidence of safety and at

least some efficacy clinically. And the physical characteristics of the drug in question allowed its compounding, especially in light of the fact that there is already a monograph out there.

DR. VAIDA: Allen Vaida. I voted yes because of the restrictions with topical only.

MS. JUNGMAN: Elizabeth Jungman. I also voted yes because of the lack of serious safety concerns and reasonable evidence of effectiveness, given the relative seriousness of the condition.

DR. PHAM: I voted yes, for similar reasons of safety and efficacy, as expressed, and that it has been used as a widespread practice for such an historic period of time.

MR. HUMPHREY: William Humphrey, and I voted yes, for the same reasons.

MS. DAVIDSON: Gigi Davidson. I voted yes because of the evidence for efficacy and the lack of safety issues.

DR. DIGIOVANNA: John DiGiovanna. I voted yes. I just wanted to thank Dr. Ko and his team for their thoughtful review of this area, and just

to say I think this is one of the scenarios where permitting certain substances to be compounded permits the physician to be able to practice medicine for those patients that fall outside of the norm, and to selectively be able to choose therapies, which may be somewhat unusual but effective and longstanding in their specific situations.

DR. WALL: Donna Wall. I voted yes, for the reasons that have been mentioned.

DR. CAROME: Mike Carome. I, too, voted yes, for all the reasons stated, with the understanding, in addition to limiting to topical use, FDA has recommended limiting it to doses of 10 percent or lower concentrations. And I hope that would be part of what the list states.

DR. VENITZ: Okay. Thank you. That concludes our second vote. So now let's proceed to the third and last vote for this morning, please.

So glycyrrhizin is the last compound for us to consider here. The question that we're voting on is should glycyrrhizin be placed on the list,

yes or no. Please go ahead and vote.

(Vote taken.)

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

DR. VENITZ: Okay. Our usual roundtable. Dr. Carome, if you would want to get started, please.

DR. CAROME: I voted no. Both preclinical and clinical studies of this product demonstrate no significant antiviral activity. There is a clear safety risk, and that is hypokalemia from the pseudohyperaldosteronism, and that occurred in one clinical trial at a more than rare rate, approaching 3 to 4 percent; and finding there are several highly active, highly effective, FDA-approved drugs for the viral infections for which it is being considered, which include hepatitis C and HIV.

DR. WALL: Donna Wall. I voted no, for the same reasons. There's just too many other products, I think, that are much more effective than this product. So if you needed to use this

product, I think it should be done under a special study.

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

MS. DAVIDSON: Gigi Davidson. I voted no, for the same reasons, and due to the significant safety signal.

MR. HUMPHREY: William Humphrey. I voted no, for the same reasons, the lack of clinical efficacy and the safety concerns.

DR. PHAM: Katherine Pham. I voted no, for the same reasons.

MS. JUNGMAN: Elizabeth Jungman. No, for the same reasons.

DR. VAIDA: Allen Vaida. I voted no, for the reasons mentioned.

DR. VENITZ: Jurgen Venitz. As much as I like licorice, I voted no, for the same reason already stated.

Let's go to our call-in folks. Dr. Gulur?

DR. GULUR: I voted no, for the same reasons stated, which is the efficacy data was weak and the

safety concerns were significant.

DR. VENITZ: Thank you.

Dr. Lo Re?

DR. LO RE: I voted no, also for the lack of demonstrable antiviral activity, the safety concerns, and the fact that clinically, this would have to be used intravenously.

As Dr. Connelly nicely pointed out, as a field, there's been considerable effort in developing all-oral direct-acting antivirals. And I'd be concerned about the toxicities of phlebitis, infection, while we have in our armamentarium many highly efficacious, well-tolerated, all-oral antivirals.

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

This does conclude our morning session. We will have a long break, without naps, and reconvene at the scheduled time. That is 1:00 p.m. So enjoy yourselves, not too much. We will get back together at 1:00 and follow our schedule as published.

MS. AXELRAD: Can I just say something? I

apologize for the long break. I'm sure maybe you are happy to have a break, but may not be. But we can't move the afternoon session up, much as we would like to, because there are two speakers for the open public hearing session, and it's scheduled at a specific time. And of course, all of our presenters were not planning to come now. Their schedules, we can't gather them up and get them down here early.

So I apologize. But I hope you enjoy the break. And if you need a place to sit or hang out, we can help find a place for you to be if you're not going to go back to somewhere. We can convene at the break and figure out where you all would like to be.

Adjournment

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

So the meeting is not adjourned, but temporarily put on hold until 1:00.

(Whereupon, at 10:01 a.m., the morning session was adjourned.)