FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE

(PCAC)

Tuesday, March 8, 2016

Afternoon Session

1:03 p.m. to 4:06 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

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Office of Executive Programs, CDER, FDA

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(Participation in March 8th PM session and March 9th session)

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William Mixon, RPh, MS, FIACP

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TEMPORARY MEMBERS (Voting)

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(Participation in quinacrine, boswellia, D-ribose, and chondroitin discussions)

Professor of Internal Medicine and Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Jeffrey A. Cohen, MD, FACP

(Participation in acetyl-L-carnitine discussion via telephone)

Professor and Chair, Neurology
Geisel School of Medicine at Dartmouth
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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:03 p.m.)

DR. GULUR: Welcome back, everyone. Before we begin, I will introduce two voting special government employees who will be in specific portions of this afternoon's topic. They are, Dr. Lenore Buckley, who was with us for the first session. She will participate in the D-ribose and chondroitin topic. And we have Dr. Jeffrey Cohen, who is professor and chair, neurology, at Dartmouth. He will participate in the acetyl-L-carnitine topic by phone.

Dr. Braunstein, if you could introduce yourself.

DR. BRAUNSTEIN: I'm Ned Braunstein. I'm the industry representative. I work for Regeneron Pharmaceuticals.

DR. GULUR: Thank you.

We will now proceed with FDA presentations. We will start with aloe vera. Dr. Kettl?

DR. CAROME: Were there handouts for the afternoon session for slide sets?

DR. GULUR: We'll be getting copies for everyone.

FDA Presentation - David Kettl

DR. KETTL: Good afternoon. My name is Dave Kettl. I'm a clinical team leader in the Division of Dermatology and Dental Products in the Office of New Drugs here at CDER. My presentation today will be related to the submission of aloe vera freeze dried 200 to 1.

I am presenting a summary of the review that was conducted by a large number of people on the review team. The lead reviewers are summarized on this slide and relate to multiple disciplines across chemistry, botanicals, the clinical pharmacology, non-clinical, as well as the clinical use of this product.

Aloe vera freeze dried 200 to 1 was nominated for treatment of burns, cuts, ulcers, and diabetic wounds. The nomination states that the substance will be used to prepare topical creams and gels at concentration of 0.1 to 10 percent. The nomination itself does not specify the basic

characteristics of cuts, burns, and wounds for which the nominated product is intended.

There's no discussion of the size, location, duration of the wound, infection status, all of which are critical elements for determination of efficacy and safety of the proposed product. The nomination did not include a substantial amount of detail, but it is our understanding that the 200 to 1 ratio indicates 200 grams of aloe vera of botanical raw material, which would yield 1 gram of the freeze dried product.

This is some background about aloe vera plant material itself. Again, the concept to consider is related to the issue of whether the general aspects of aloe vera plants, of which there are between 400 and 500 cultivars known, how it relates to the nominated product. Some of our information as presented will deal with aloe vera in general because that's essentially all we could find related to this product.

The aloe vera, as you probably know, is a succulent plant species within the aloe genus.

Different references have between 360 and 500 different species. The whole leaf and extracts are commonly used as herbal and traditional medicines, as oral laxatives, or topical agents for burns and wounds. There are commercially available products derived from aloe vera, but they are regulated variably as food, dietary supplements, or cosmetic products on the U.S. market. There's also a USP-NF drug monograph for aloe that will be discussed later.

The nomination itself does not provide a definition of aloe vera freeze dried 200 to 1. Again, as I stated, our understanding, though somewhat speculative, is that the name suggests that the extract or dry powder derived from the leaf or other parts of the aloe vera raw material yields a concentration of 200 to 1 where 200 grams of the raw material would yield 1 gram of the freeze dried extract. No solvents are specified in the nomination.

The majority of aloe vera products are complex mixtures of various substances. The aloe

vera gel contains mainly polysaccharides, a group of poorly characterized and relatively large molecules. The polysaccharides may be qualified as a as whole class but not individually at the molecular level. Differentiation of polysaccharides from aloe and various other botanicals remains challenging.

The aloe latex, or whole leaf extract, contains anthraquinone glycosides, aloin A and aloin B, which are purported to have laxative effects. They also contain other classes of not well characterized molecules.

The agency needs to understand precisely what the nominated substance is and what components it includes. The various compounds that may or may not be contained in the nominated substance would ultimately of course determine its safety profile. It's difficult to definitively make a safety determination without knowing the exact constituents of the nominated product.

As I stated, there's a USP monograph for aloe, USP38NF22. It defines aloe as the dried

latex of the leaves of the aloe vera plant with that specific genus and species known in commerce as aloe vera. There are various other qualifications and other species included in the monograph name and determination.

The identification and assay in the monograph is based on the amount of aloin, which is present. And aloin is only found in the latex or outer leaf rind of the aloe leaf. The polysaccharides, which is the major portion of the aloe leaf, is not tested.

The monograph describes a particular type of aloe. We don't know how the nominated substance compares to the monograph description, but the nominator has indicated that their freeze dried substance is not covered by an applicable monograph.

The USP monograph, in our determination, is not sufficient to ensure the quality of the nominated substance, aloe vera freeze dried 200 to 1. The chemical characterization of only a small portion, e.g., the anthraquinones by

themselves, of a complex aloe vera mixture is not sufficient to ensure quality and consistency of the product.

Aloe vera freeze dried 200 to 1, which we presume is derived from the gel rather than the latex skin of the aloe leaf, likely contains no aloin or only trace amounts of anthraquinone. Even if the nominated substance were consistent with the USP monograph, we might still have concerns about how well characterized each was for use of actual compounding.

Aloe vera gel, latex, and extracts contain multiple classes of molecules, polysaccharides and anthraquinones being the predominant ones, but they have complex physical/chemical characteristics, which are poorly characterized.

Available analytical methods could not adequately characterize and differentiate one aloe vera product from another. For example, there's contaminants from other botanicals, such as other aloe species, and these would be difficult to detect.

The nominated substance, aloe vera freeze dried 200 to 1, is complex and not well defined. The USP aloe vera monograph only assayed the anthraquinone, e.g., aloin portion, but not other components, including the major components, which I stated are polysaccharides.

In conclusion, the product quality conclusion is that the agency does not consider aloe vera gel freeze dried 200 to 1 as well characterized and cannot be adequately controlled for compounding drug use from a quality perspective.

A well characterized preparation derived from aloe is one that would identify and control for the various components, such as the anthraquinone, aloin, and polysaccharides. The nominated substance may be derived from the gel, but we are unsure of that, and we do not consider the nominated substance to be adequately well characterized.

From a non-clinical perspective, aloe vera has been evaluated in various aspects of

non-clinical testing. In terms of pharmacology, the aloe vera products have been reported to possess a wide range of pharmacologic activities, however most claims are not supported by robust data from well controlled studies. The studies are either inconsistent or contradictory regarding wound healing benefits, which might be due to differences in test material and animal models, which were used.

In assessments of repeat dose toxicity, repeat oral doses administered via drinking water or diet to mice or rats caused diarrhea, decrease in weight gain, reduction in RBC count, and sperm damage. And in general, there's a lack of non-clinical data to evaluate the chronic dermal toxicity of aloe vera, particularly for a topical product.

The mutagenicity assessments included a negative Ames test for aloe vera gel, aloe vera whole leaf extract, and aloe vera charcoal filtered whole leaf extract. There were some anthraquinones, e.g., emodin and aloe emodin,

extracted from aloe vera, which exhibited genotoxicity in in vitro genotoxicity assays.

In developmental toxicology, aloe vera has abortifacient activity when taken orally, and aloe vera extract induced skeletal malformations in an oral embryo fetal toxicity study in rats.

In a one-year photocarcinogenicity study in hairless mice, aloe gel, aloe emodin, and aloe whole leaf extract, and decolorized leaf extract, had a weak enhancing effect on photocarcinogenic activity of simulated solar light.

In a two-year drinking water carcinogenicity study of mice and rats, aloe vera whole leaf extract is an intestinal irritant in both rats and mice and a carcinogen of the large intestine in rats. But there's a lack of non-clinical data to evaluate the dermal carcinogenicity potential of aloe vera.

Moving from non-clinical to human safety data, our search indicated that there's very limited safety data from clinical trials for either aloe vera, and essentially no human safety data to

adequately characterize the safety of the nominated substance.

For aloe products in general, there are reports of contact dermatitis and local dermal reactions. Note also that the proposed use includes use on non-healthy skin, either abraded skin, burned skin, or diabetic ulcers, and this would affect the safety profile of the product.

There was no pharmacokinetic information available for aloe vera or the nominated product. Searches were conducted through the FAERS and CAERS adverse event reporting system, which specifically found no reports for the nominated product. Aloe vera gel contaminated with other aloe vera components, e.g., anthraquinones, remains a potential safety concern for topical applications on open wounds.

Regarding oral use of aloe vera extracts and laxatives, in 2002, the FDA required that all OTC aloe-containing laxative products be removed from the U.S. market or reformulated because the companies that manufactured them did not provide

the necessary safety data, which included mutagenicity, genotoxicity, and carcinogenicity information.

In addition, in the treatment of burns, cuts and wounds, there are alternative approved products that may be safe or safer than the nominated product. There's a lack of long-term dermal safety data and pharmacokinetic data, which are necessary for full safety evaluation of topical products.

The safety profile of aloe vera shows the anthraquinone derivatives in aloe latex may be unsafe, especially when used at high doses for repeated use, for example concerns again about potential carcinogenicity. There's limited information specifically on the safety of the nominated 200 to 1 freeze dried aloe product for topical use.

The efficacy information related to the specific nominated product again is extremely limited. As we broadened our examination of general aloe vera products, there is a 2012 Cochrane review, which was conducted on the use of

aloe vera products, which included several different forms of aloe vera, for treating acute and chronic wounds.

It was a comprehensive review of surgical wounds, burns, lacerations, and other skin injuries resulting from trauma. A chronic wound was defined as any one of the following: skin ulcers, infected wounds, surgical wounds healing by secondary intention, pressure ulcers, arterial and venous ulcers. These studies also included treatment of hemorrhoids and skin biopsy lesions, which healed secondarily.

Of 178 possibly relevant studies that were identified in the Cochrane review, only 7 were randomized, controlled studies, and therefore deemed adequate for review. The exam in the literature included various formulations of aloe vera and included gels, creams, dressing, and mucilage. Apparently, none were for compounded products that specifically included the aloe vera dried 200 to 1 nominated product.

The total number of subjects in these trials

was 347 in the 7 Cochrane review studies. All but two of them were studies that were conducted in the 1990s, and the biggest aloe vera arm was 50 subjects. Most of them were in the 10 to 20 range.

The conclusion of the review was that there's currently an absence of high quality clinical trial evidence to support the use of aloe vera topical agents, or aloe vera dressings, as treatment for acute and chronic wounds.

A separate review by another author in 2006 looked at 371 subjects across four different clinical trials and also concluded that there is a paucity to draw a specific conclusion regarding the effect of aloe vera for burn wound healing.

The agency notes, however, the historical use of aloe vera. There probably is reports of at least 4,000 or 5,000 years of anecdotal reports. But again, these include various forms of aloe vera, and they are used in herbal medicine as a general tonic and as a food, which is sold in grocery stores.

The medicinal uses vary according to the

prescriber, but include uses for abdominal pain, swelling, burns, skin diseases, urinary disorders, fever, gastritis, constipation, headache, bloodshot eyes, convulsions, hemorrhoids, and treatment of parasites. But again, there's insufficient information regarding the historical use for any of these indications for use of the nominated product in pharmacy compounding.

In summary, the nominated product is not well characterized in its physical and chemical properties, especially the major components, which are polysaccharides. As an endogenous compound, topical use was associated with minor and infrequent side effects, which included local irritation and redness, and occasional allergic reactions. But there's insufficient and conflicting information from controlled clinical trials regarding the efficacy of the aloe vera topical products in the topical treatment of cuts, burns, and wounds. Furthermore, what information there is does not appear to have used the nominated 200 to 1 freeze dried aloe vera.

Various forms of the botanical raw material from the plant aloe vera have been used for centuries, if not millennia, but there is insufficient information regarding historical use in pharmacy compounding.

In conclusion, the agency does not recommend that aloe vera freeze dried 200 to 1 for topical use be placed on the list of bulk substances that can be used for compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act.

DR. GULUR: Thank you. At this time, we will accept clarifying questions from the committee.

(No response.)

DR. GULUR: Thank you. Since there are no questions, we will now proceed with the nominator presentation. We have one presentation on aloe vera from Ms. Kieffer from Fagron.

Nominator Presentation - Kimberly Kieffer

MS. KIEFFER: Good afternoon again. So FDA had some major concerns about the characterization of aloe vera, and I won't be able to characterize

all of the components, but I want to at least elucidate here what exactly this aloe vera freeze dried 200 to 1 is.

What it is, is a material that we use as the industry standard for topical products. It's used in cosmetics, dental care, baby care, et cetera. And this is what we use in compounding because it's shelf stable, and it's fairly concentrated, so it's easy to work with.

FDA did review the components of the aloe plant, but I wanted to go over them again. The whole plant of the aloe does contain some fairly toxic substances. It contains this list of organic compounds called anthraquinones. There are 12 in all in the aloe plant, and they're contained in the sap of the aloe.

So think of the aloe as an outer leaf, which is the rind, and then a sap that forms underneath the rind, and then underneath there is a gel, or the fillet, and that's where the polysaccharides and enzymes and other components live.

So when we're talking about a whole leaf

extract, a whole leaf extract is the entire plant powdered and broken down into a powdery form that can be used. That would contain all of the components, all of the anthraquinone components, particularly the aloin, which is the anthraquinone component of highest concentration. It comprises about I think 14 or so percent of the anthraquinone compounds.

The aloe USP monograph is specifically dealing with the whole leaf plant. So in this case, they're taking the plant, powdering it, and then assaying it. And they're looking for a concentration of aloin at about 16 percent, so that's fairly high.

There's also decolorized whole leaf extract of aloe vera, and this is very similar. These extracts can also be done using alcohol or other solvents. They're not always necessarily just freeze dried.

In the case of the decolorized material, they filter using activated charcoal to clarify the liquid. That's typically done to remove bitterness

and color from the material. This extract will also contain some residual latex and gel components. And in these we find that we're looking at an aloin content that might be less than 10 parts per million, which is considerably less than the whole leaf plant; although I have seen some studies where that can actually be a little bit higher.

Now, the aloe latex, we talked about this earlier. This is the sap that forms underneath the rind and is secondary to the outer leaf, and that lies in between that and the fillet or the gel component. This is where the anthraquinones live primarily, and the anthraquinones are irritants. Some of them are irritants. If you look deep into the literature, you can find that some of them actually have anti-inflammatory and other properties.

So in terms of aloe vera gel, that's the inner part of the leaf, this is where we prepare the freeze dried aloe powder from. This is simply just the gel inside minus the latex and the outer

rind. This is dried and powdered through vacuum filtration or vacuum drying. I will show you just a little flow chart of how that works.

I got this information from our manufacturer and got their flow chart information. In this case, they begin with fresh aloe leaves, and then they hand remove the outer parts of the plant to remove all of the latex and the outer leaves. And they grind and use an enzymatic treatment process and then filter. And they use cellulase as the enzymatic treatment, but they use it primarily just to break up the pulp so that it's easier to filter.

Then it goes through a low temperature vacuum evaporation process, which vastly concentrates the liquid into a liquidy, more dense mass, and then that is spray dried using maltodextrin as the carrier. This makes the product shelf stable.

Then it takes us needing to use 10 percent of this gel material that we take out of plants and can condense it down into something like 0.1. So when we're talking about usage ranges for aloe vera

topically, in this product in particular, we're looking at concentrations typically at 0.1 to 0.5 percent. I rarely have -- in fact, in all of the years I've been assisting with compounding have I seen anything up in -- for this product, in the 10 percent range. It wouldn't be necessary.

One more addition. The typical aloin concentrations in this product are less than 1 part per million, and that is assayed on the C of A, and that's coming from the manufacturer and then again upon independent verification.

So we looked at some toxicology information that FDA presented, and if you read in all of those studies, almost all of them reached back to a whole plant extract being used. In the NTP report, where they took a mouse model and fed them an aloe extract for two years, we did see carcinogenic activity. And they also used a decolorized whole leaf plant, and in that one we also saw intestinal irritants. But again, that was with the whole leaf extract of the plant. And they even quantified the concentrations of anthraquinones in those studies,

and they were higher, much higher than what we're seeing in our aloe vera gel.

But conversely, in a Central European Journal of Immunology report that was published, they fed mice just the inner leaf of the gel that contained low to no concentrations of anthraquinones. And in that study, they found an anti-tumor effect when exposed to a carcinogen.

In another CEJI publication, aloe vera gel fed to mice showed a stimulation of cell mediated immunity and antibody production. So instead of seeing carcinogenic activity, we're actually seeing a protective effect.

Also in the cosmetic ingredient review expert panel final report on aloe vera and its safety for topical use in cosmetics, we found that levels of under 50 parts per million are determined safe. And if you haven't looked at this study, it's exhaustive. It's about 100 pages, and it examines all of the products that are readily available on the market that use aloe vera products and when and where they are toxic and not toxic.

And their review concluded that it was in fact safe for topical use.

FDA mentioned that we have options for wound care. We do have a few options. Like I said, I've been in this industry for quite some time and wound care is always a struggle and a challenge for many doctors and patients.

These are good options. Collagenase is used pretty widely. Regenerex is used less widely, obviously, because there are limitations to how long and for how much of it can be used. We're not proposing that aloe vera would be the monotherapy. In fact, generally speaking, what we see with our clients is that they're using it as adjunct. They're adding it to topical antibiotics, or proliferatives, or other agents to assist in the wound healing process.

I wanted to just look at a couple of positive studies because when our physicians are looking for ways in which to treat their patients, their patients that are not responding to traditional therapies, this is what they're looking

at. And when they're thinking, oh, I heard about aloe vera, I maybe want to try that, I heard that it's somehow successful in burns or wound healing, because like we said, it's been used for thousands of years, they're looking to the literature and they're finding this kind of data.

This was done on rats. And in this case, they compared the effects of an aloe vera gel with a saline control and an aqueous cream placebo. They also tested it against silver sulfadiazine cream at 1 and .5 percent, which would be a more standard therapy. But they also tried a, silver sulfadiazine and aloe vera combination and a silver sulfadiazine and nystatin combination. And what they found was that in the silver sulfadiazine group, they actually had a retardation of wound contraction. When they added the aloe vera in both the nystatin case and the aloe vera case, when they added those to silver sulfadiazine, they saw a reversal of this trend.

So this is showing that there's something else happening. They're assisting the silver

sulfadiazine in whatever it's doing and then adding an additional component. The nystatin is an anti-fungal, and aloe vera has also been shown to have anti-fungal activity.

In another study on rats, we found that -- and in this case, they actually specified that they used lyophilized freeze dried gel, and that's going to be consistent with the aloe vera freeze dried powder that we're speaking about today.

In this case, they measured the effects of the aloe vera gel on collagen, hexosamine, total protein, DNA content, rates of wound contraction, epithelialization, and tensile strength to measure the effect it was having on the treated and the untreated wounds.

The results indicated that wounds treated with aloe vera, in the diabetic wounds in this case, or the diabetic rats in this case, showed that it had enhanced effect on all of the processes of wound healing.

So back to the FDA approved drugs. Yes,

they have a specific goal in mind, but they don't necessarily handle all of the aspects of wound healing. And that's again, is what we find that physicians are looking for in terms of treating their patients with complex wounds.

This was another one. This was a human study since we talked about mice. Of course, this is a small group of patients, but they were treated with either aloe vera or Vaseline. And what we found in the Vaseline treated case that they healed almost 8 or 7 days slower than those treated with the aloe vera gel, and only minor adverse events were observed.

Here's another study. Again, a small group of 50 patients with partial thickness burns were divided into two random groups. The aloe vera gel was used from unrefined gel taken from the inner leaf, so they did not use a concentrate.

The aloe vera gel was compared with 1 percent silver sulfadiazine, and the results were that in the aloe gel group, they healed remarkably quicker than the 1 percent silver sulfadiazine

group. And then the aloe vera group also reported that they were relieved of pain earlier. These aren't necessarily conclusive findings, but they are findings that would support that physician giving this a shot.

To conclude, what I have found in my research of aloe vera, is that aloe vera modulates inflammation and increases rates of wound contractions and epithelialization. It decreases scar tissue, which is important because when these wounds are healing poorly, they tend to create aberrant healing processes and overstimulation of collagen production, which can lead to keloid scars, or hypertrophic scarring, which is also a problem that will then have to be managed.

It increases the organization of regenerated scar tissue, increases level of collagens and glycosaminoglycans, and there is low to no occurrence of serious adverse effects topically or orally. And you can look at these full term references to read more about that.

So for this reason, I feel that this

substance is relatively safe. And it has been used in compounding for a long period of time, like I said, as an adjunct therapy. But I would hate to see it go away as something that a physician might want to try.

Clarifying Questions from the Committee

DR. GULUR: We will now entertain clarifying questions for the nominator from the committee. Dr. Jungman?

MS. JUNGMAN: You referred a few times to the industry standard for this, and I was wondering whether that is documented anywhere and if you have any sense of how broadly it's followed.

MS. KIEFFER: It is documented in the clinical or the final review that the cosmetic review board did. So what we're seeing in terms of what we use, this 0.1 to 0.5 percent, this is typically what's used in commercial and cosmetic products.

MS. JUNGMAN: And then just to follow up, did that consider use on wounds at all?

MS. KIEFFER: No.

DR. GULUR: Thank you. We will now proceed with FDA presentations for D-ribose.

FDA Presentation - Shari Targum

DR. TARGUM: Good afternoon, ladies and gentlemen, members of the advisory committee. My name is Shari Targum. I am a clinical team leader in the Division of Cardiovascular and Renal Products, and I will be giving the presentation on D-ribose in heart disease. I would like to start by acknowledging my colleagues who reviewed D-ribose for the division.

D-ribose has been nominated for use in the treatment of heart disease and chronic fatigue syndrome. This presentation will focus on the treatment of heart disease, and Dr. Maynard will give the next presentation on chronic fatigue syndrome. D-ribose has been studied as an adjunct metabolic agent and not as an alternative to approved therapies for cardiovascular disease.

As far as historical use, there is evidence of academic investigator studies in humans as far back as 1946 and use as a dietary ingredient as

early as 1999. However, we were unable to find evidence of pharmacy compounding for drug use.

This slide shows the chemical structure of D-ribose, a monosaccharide with an aldehyde ribose group at one end. D-ribose is a naturally occurring compound and a component of some biomolecules, such as ATP. D-ribose is commercially available and has been used as a food additive.

There are several ways that one can synthesize D-ribose. The most likely route is fermentation based synthesis, and D-ribose appears to be well characterized physically and chemically.

This slide summarizes 3 non-clinical studies. In the first, 3 doses of oral D-ribose, along with control, were administered to rats for 13 weeks, with a reported dose related increase in water consumption, decrease in body weight, and increase in cecal weights.

In the second study, a 28-day study of rabbits given intravenous D-ribose, there was an increase in neutrophil percentage and a decrease in

glucose levels in males, and no values were provided.

Han administered 2 doses of intraperitoneal D-ribose to mice for 30 days and compared to a glucose control, the mice exhibited impairment of spatial learning and memory ability.

Proceeding to human safety data, there are limited human safety data and no long-term information. From publications, there have been reports of hypoglycemia, hyperperistalsis, loose stool, diarrhea, gastrointestinal discomfort, nausea, uric acid elevations, elevations in liver enzymes, and increased serum uric acid.

I'm going to highlight two safety concerns. Asymptomatic mild hypoglycemia was reported in a crossover study of 19 healthy subjects. In the publications, there were no reports of the signs and symptoms of hypoglycemia, however, the controlled efficacy studies were small and either excluded diabetics or did not report glucose effects. D-ribose may not register on a glucometer, creating potential challenges for

optimal insulin management in diabetics.

There are no publications evaluating long-term exposure to D-ribose. Advanced glycation end products are formed by the non-enzymatic glycation of free amino acids by reducing saccharides such as D-glucose and D-ribose and are associated with vascular and neurologic complications.

AGEs are said to induce inflammation in intracellular reactive oxygen species. According to Harrison's Principles of Internal Medicine, AGEs, quote, "bind to a cell surface receptor leading to cross linking of proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and altered extracellular matrix composition."

According to Han, D-ribose is highly active in the production of AGEs, and D-ribose injection in mice impaired spatial learning and memory. Many diabetics develop progressive cognitive impairment, and high levels of urinary D-ribose have been measured in diabetic patients.

One proposed mechanism for diabetic cognitive impairment has been the accumulation of AGEs as the result of high D-ribose concentrations. However, as I mentioned, there are no clinical data concerning the short- or long-term cognitive effects of D-ribose.

The next two slides show the placebo controlled studies in heart disease. In 1992, Pliml studied the effect of placebo or oral D-ribose in 20 men with stable coronary disease and found a statistically significant greater treadmill time to 1 millimeter ST depression with D-ribose compared to placebo, but the electrocardiogram readers were unblinded and there was no difference in the time to angina. Except for the Pliml study, the other efficacy publications in these slides were co-authored by St. Cyr, who was an employee of Bioenergy.

In a randomized, double-blind crossover study, Omran gave a 3-week course of either D-ribose or a placebo to 15 patients with coronary disease and congestive heart failure. While there

were quality of life and functional improvements in both groups that the authors noted were statistically significant with D-ribose, the study did not compare between group differences. So the comparison was between baseline and post-treatment for D-ribose.

Sawada conducted a randomized, double-blind crossover study in 26 patients with ischemic cardiomyopathy and gave D-ribose or a placebo during dobutamine stress testing. The authors found no effect on stress induced ischemia.

In an uncontrolled study, Vijay studied 16 heart failure patients with cardiopulmonary testing and found an improvement in ventilatory parameters compared to baseline, but there was no comparator group.

Perkowski administered preoperative oral D-ribose to 40 patients for off-pump coronary artery vascularization and reported an improvement in mean cardiac index but no other changes were reported. And again, there was no comparator.

As this slide demonstrates, there are many

available therapies for angina and congestive heart failure, including pharmacologic therapies for angina and also non-pharmacologic options.

In conclusion, D-ribose is well characterized physically and chemically. There is no convincing evidence of a meaningful clinical benefit. There are many safe and effective FDA approved therapies available for angina and congestive heart failure.

There is limited safety information, including reports of glucose lowering, hypoglycemia, diarrhea, hyperperistalsis, loose stool, gastrointestinal discomfort, and nausea. And although used since 1999 as a dietary ingredient, there is insufficient information regarding the historical use of pharmacy compounding for drug use.

Non-clinical data indicate that D-ribose causes non-enzymatic protein glycation leading to the formation of advanced glycation end products, or AGEs. In one mouse study, D-ribose administration led to impaired spatial learning and

memory ability.

There are no direct human data that address whether D-ribose affects cognitive ability and memory, although the presence of both cognitive impairment and high urinary levels of D-ribose in diabetic patients raise that possibility.

We do not recommend that D-ribose be included in the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. Thank you very much.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will now entertain clarifying questions from the committee. Dr. Wall?

DR. WALL: I have a question about the hypoglycemia. You were talking in that study about asymptomatic mild hypoglycemia. Was that a certain percentage that dropped? Was it a couple of points? What defined out asymptomatic mild hypoglycemia?

DR. TARGUM: Yes, that's a good question. I

looked at the publication, and I did not see values.

DR. WALL: So what led them to say it was anything you could pick up that said it was -- what led them to that conclusion?

DR. TARGUM: Yes, it's a report.

DR. WALL: Okay. And then also the last comment, and I was curious, the D-ribose may not register on a glucometer. Can you tell me what were they -- were they saying that the -- I don't understand the comment, let's just put it that way.

DR. TARGUM: That comment did not come from the publications. That comment was just -- in looking at D-ribose, we looked very carefully at whether the hypoglycemia could have been related to glucometers. But we think it's more than that. There was an animal study where glucose lowering was reported. There was at least one study where a lowering of glucose was reported. So we think that the phenomenon is more than just a glucometer issue.

DR. WALL: Okay, so you were thinking that

the ribose had a direct interaction with the glucometer, which caused a question, but you've now said, no, there's really some level of change in the glucose within the blood; you just don't know what it is.

(Dr. Targum nods in affirmation.)

DR. WALL: Okay.

DR. GULUR: Dr. Braunstein?

DR. BRAUNSTEIN: Yes. I just have a question. It's again about this hypoglycemia. I think what you're referring to is hypoglucosemia. Right? Because there's ribose in the blood at that time, or at least it would seem to be.

What tissues can utilize ribose as an alternative sugar source? How does the body -- can the body utilize ribose as an alternative sugar source? Because if you're just substituting ribose for glucose, it seems that may be perhaps why it's asymptomatic, it's not such a big deal.

DR. TARGUM: I'm going to let my colleague from the Division of Metabolic And Endocrine Products address that question.

DR. CHONG: William Chong, Division of Metabolism and Endocrine Products. So I'll first address Dr. Wall's comments about the glucometer question. Based on my review of the published literature, there are some very old studies, that probably did not utilize glucometers, and they measured glucose level changes that ranged anywhere from 10 to 40 milligrams per deciliter. Most of these were in normal human volunteers. How this applies to diabetics is not really clear.

In regards to Dr. Braunstein's question about the utilization of ribose, I'm not entirely clear where and what tissues can utilize ribose as a metabolic fuel, but that is the hypothesis about -- to explain why there is a decreasing glucose, that perhaps the ribose is being utilized and there is a decreased need for glucose in the bloodstream for those tissues, but not aware of that being a definitively understood concept.

DR. GULUR: Thank you.

We will now proceed with nominator presentations. We have one presentation on

D-ribose from Ms. Kieffer from Fagron.

My apologies, we do have another presenter from the FDA.

FDA Presentation - Janet Maynard

DR. MAYNARD: Good afternoon. My name is Janet Maynard, and I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products. I will be discussing D-ribose for chronic fatigue syndrome. The review team for D-ribose for chronic fatigue syndrome is listed on this slide.

By way of overview, D-ribose was nominated for use in heart disease and chronic fatigue syndrome. This presentation will focus on the use in chronic fatigue syndrome. The term chronic fatigue syndrome will be used because this was the term used in the nomination.

FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for chronic fatigue syndrome, which is also referred as myalgic encephalomyelitis and systemic exertion intolerance

disease.

In the literature, one study was identified that assessed the use of D-ribose for chronic fatigue syndrome. This was an open-label, uncontrolled pilot study performed to evaluate the use of D-ribose in 41 patients with fibromyalgia and chronic fatigue syndrome.

Patients received 5 grams of D-ribose orally 3 times per day until the 280 gram container was empty. Five patients were excluded from the analyses due to non-compliance, thus 36 patients were included in the analyses. The average age was 48 years; 75 percent had a previous diagnosis of fibromyalgia, and 58 percent had a previous diagnosis of chronic fatigue syndrome. The average duration of therapy was 28 days.

In terms of safety results from the study, 5 patients did not complete the study, 3 discontinued due to adverse events, including hyper-anxious feeling, lightheadedness, and increased appetite; 2 patients did not begin the study.

Of the remaining 36 patients who completed

the study, one patient experienced transient nausea and the other felt mild anxiety. You have heard a description of the other safety considerations, including hypoglycemia, by the Division of Cardiovascular and Renal Products.

The authors reported significant improvements in energy level, sleep patterns, mental clarity, pain threshold, and patient states of well-being when comparing questionnaires and enrollment and at the completion of the study in all patients.

When evaluating the efficacy results by underlying diagnosis, the 9 patients with chronic fatigue syndrome noted improvement on the measured parameters outlined in this table. Of the 35 patients completing the assessment of overall subjective feelings, 23 or 66 percent experienced improvement during the course of the study being somewhat better to much better while taking D-ribose.

Of note, limited conclusions are possible from the available data. Only a single study was

identified, and it is open-label. Thus, it did not have a comparator group. Further, the number of patients with chronic fatigue syndrome was small, and the clinical interpretation of the numerical changes is unclear.

This review focused on the intended use for chronic fatigue syndrome, which is a serious disease. No treatments have been approved by FDA for chronic fatigue syndrome. While the efficacy of D-ribose for chronic fatigue syndrome is unclear, it is used by some patients for treatment of symptoms associated with chronic fatigue syndrome.

As discussed by DCRP, D-ribose appears physically and chemically well characterized. I'll refer you to DCRP's presentation regarding historical use in compounding. Limited safety data from one uncontrolled study suggests D-ribose is generally well tolerated in chronic fatigue syndrome. Other safety considerations have been reviewed by DCRP.

While the efficacy of D-ribose for chronic

fatigue syndrome is unclear, it is used by some patients for treatment of symptoms associated with chronic fatigue syndrome. While this lack of evidence of efficacy would be dispositive for a new drug application, which is required to include substantial evidence of efficacy, efficacy is only 1 of 4 criteria for bulk drug substances, and as noted in the proposed rule from January 1999, a single criteria would not be dispositive on its own.

Further, an important consideration weighing on the division's recommendation is the context of use. There is significant unmet medical need for chronic fatigue syndrome as there are no approved agents indicated for the treatment of chronic fatigue syndrome, a serious disease.

Given these considerations, we recommend that D-ribose be placed on the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act for the proposed indication of chronic fatigue syndrome.

DR. GULUR: Thank you. We have one more

presentation from the FDA.

FDA Presentation - Susan Johnson

DR. JOHNSON: One more D-ribose presentation. As we've discussed this morning, I'm Sue Johnson. I am presenting for Dr. Ganley who is ill today. We talked about the reason that ODE IV is involved in this determination similarly to this morning's discussion. The review divisions that participated in this review are highlighted in red, and again in green ODE IV.

The divisions have reviewed the information and arrived at a recommendation based on their benefit/risk assessment. And again, as sometimes occurs, they have reached different recommendations based on different uses of D-ribose. The review division memos and their presentations today have provided their rationale, and we want to thank them for carefully reviewing the data and thoughtfully deriving their recommendations.

Because there's not one uniform recommendation, ODE IV was tasked with reviewing the memorandum, and we have concurrence from the

OND director that you heard from earlier, Dr. John Jenkins.

There are numerous websites that advocate the use of D-ribose for a variety of conditions. And in addition, there are various use patents that have been submitted to the patent and trademark office for consideration. D-ribose was nominated for inclusion on the 503A bulk drug substances list for heart disease and myalgic encephalomyelitis chronic fatigue syndrome, which I will refer to as ME/CFS.

D-ribose has been marketed as a dietary supplement. It's sold as a powder or capsule, either alone or in combination with other dietary ingredients. It can be purchased today without a prescription on the internet or in stores. We are not aware of any history of compounding of D-ribose.

As a food additive, FDA received notice for D-ribose from Bioenergy Incorporated on February 8, 2008. Bioenergy informed FDA that D-ribose is generally recognized as safe, or GRAS, provided

it's used in conjunction with an additional carbohydrate energy source.

On November 10, 2008, FDA sent a letter to Bioenergy acknowledging that Bioenergy had concluded that D-ribose is GRAS, that FDA had not made its own determination regarding GRAS, at the time, FDA had no questions regarding Bioenergy's conclusion, and that Bioenergy had and has the continuing responsibility to ensure that food ingredients that they market are safe.

To summarize the interpretation of the data from the review divisions that you've heard, the randomized studies of D-ribose in patients with heart disease and a single study in patients with ME/CFS do not provide evidence of effectiveness. D-ribose is associated with dose related asymptomatic hypoglycemia, and D-ribose can bind with proteins to form advanced glycation end products, AGEs.

Looking again at the study that you have heard about for ME/CFS, the single study was conducted in patients that had ME/CFS and

fibromyalgia. The subjects were enrolled through the Vitality 101 website, which was the website run by the study investigator.

Potential participants were asked to respond to an email newsletter that they had signed up for on the website. It's not clear from the study publication how subjects were screened for fibromyalgia or ME/CFS, and it is not clear whether this was a self-certification. Subjects were told through the website of the potential benefits of therapy and possible risks.

Those agreeing to participate were sent questionnaires in the mail and a 280 gram container of D-ribose, brand name Corvalen. They were instructed to ingest 5 grams 3 times a day until the container was finished. The study was not blinded, not controlled, and 9 subjects were reported to have ME/CFS.

The questionnaire was completed by patients and returned to the investigator. The questionnaire was comprised of a visual analog scale with numbering 1 through 10 responses to

questions related to energy, sleep, mental clarity, pain, and sense of wellbeing.

Thirty-six of the 41 patients completed the questionnaire and no significant benefit was shown in the ME/CFS subjects. We conclude that this study is not adequate to establish benefit in patients with ME/CFS. It did not enroll a sufficient number of subjects with the disease. It was unblinded and uncontrolled, and enrolled a population who may have been influenced by information on the investigator's website.

One of the safety concerns that OND has is about the potential association between D-ribose ingestion, particularly for the treatment of a chronic condition, and the product of advanced glycation end products, or AGEs. In this schematic, glucose is used as the example, but the schematic represents the metabolism of any reducing sugar, including D-ribose. Protein glycation can lead to the formation of protein/protein cross links.

Shown here are the sequence of reactions

that are shown with glucose that generate the Amadori product on the surface of the protein marked in green. Subsequently, there is formation of a protein/protein cross link via an amino group on the surface of a second or the red protein.

The net result is the formation of a covalent cross link between two proteins or other macro molecules. This macro molecule can undergo further glycation and cross link to yet another macro molecule or protein. These cross linked aggregates are formed over an extended period of time and are called advanced glycation end products, or AGEs.

The significance of advanced glycation endpoints we have learned in significant amounts from diabetics who are particularly susceptible to the formation of glycation endpoints. The glycation of hemoglobin forming A1c, hemoglobin A1c, is used in the assessment of diabetic treatment.

The progressive cross linking of long-lived proteins like collagen in vascular endothelial

cells leads to the progressive loss of elasticity and thickening of the basement membrane in blood vessels, promoting plaque formation. In the eye, the accumulation of aggregated proteins causes opacity of the lens and eventually presents itself in the form of cataracts.

So where does ribose fit into this issue with AGEs? There are numerous articles in the published literature that support the belief that D-ribose glycation occurs more readily than glucose glycation. Ribose protein glycation occurs in animals administered D-ribose and has been demonstrated in vitro in human bone. In diabetics, glucose macro molecule glycation leads to injury in tissues like cataracts, nephropathy, vascular tissue, and this is a process that occurs over years.

So the question is, with chronic use of D-ribose, what's the consequence of ribose glycation?

To provide some perspective on the amount of ribose ingested in the study, patients used 15

grams per day. And the American Heart Association recommends that added sugar intake, that is sugar in addition to that that occurs naturally in the diet, should range from between 25 and 37 and a half grams per day. So the amount of D-ribose ingested in the study was substantial.

The Office of New Drugs does not recommend D-ribose for the 503A bulks drug list because there is no history of compounding as a drug. There is no evidence to support the effectiveness for the conditions nominated.

These two criteria alone are sufficient to recommend that it not be on the 503A list, but in addition, there are potential safety concerns with the use of high amounts, like that used in the study and for extended periods of time in chronic conditions like ME/CFS or heart disease.

D-ribose is a dietary supplement. If it is not added to the 503A list, it will remain available as a dietary supplement if patients with ME/CFS or heart disease choose to use it. Again, the effectiveness of D-ribose has not been

adequately demonstrated in ME/CFS, and I should point out that there is also a concern about using it for extended periods of time in heart disease.

ME/CFS is a serious chronic, complex, systematic disease that can profoundly affect patients over time. Over the past several years, there have been efforts by the FDA, NIH, HHS, and the Institute of Medicine to enhance the understanding of the disease.

However, conducting open-label uncontrolled studies with D-ribose or other treatments in patients with this disease does not answer important effectiveness questions. And listed here are resources for information on ME/CFS. Thank you.

DR. GULUR: Thank you. At this time we will take clarifying questions from the committee.

(No response.)

DR. GULUR: As there are no clarifying questions, we will move on to the nominator presentations. We have one presentation from Ms. Kieffer from Fagron.

Nominator Presentation - Kimberly Kieffer

MS. KIEFFER: Hello again. So ribose is an aldapentose, monosaccharide, but is also the key backbone of RNA. It's essential to the formation of ATP. So what we're searching for in these patients is a way to give them additional energy source. ATP is a main energy source for cellular function/dysfunction of which can be implicated in neuromuscular disease and many others. And I've provided here the pathway.

D-ribose is naturally occurring in milk, eggs, meat, nuts and vegetables. It is also endogenously produced. It is available as a food additive and dietary supplement. I've listed here a number of companies that are providing this material through online sources, Whole Foods, drug stores, et cetera.

Currently there is GRAS notification from Bioenergy that we discussed earlier. Of course the FDA always accepts with or without questions but needs to make their own determination, however this GRAS statement gives a lot of information about the

safety and efficacy, and also quite a bit of information on the dose limitations. What they are actually proposing in their GRAS statement is that they be allowed to add D-ribose to food products up to 17 grams. D-ribose is also the subject of a USP dietary monograph.

So we looked at some clinical assessments, and, yes, there are low concentrations of cohorts. We don't have a ton of really great substantial data, but we do see that it is having effect in some patients. For coronary artery disease, we're seeing showed improvement in the tolerance of ischemia. We're also seeing significant improvement of quality of life, and almost all of the studies that we've looked at report significant improvement of quality of life. Of course there are also studies that don't report significant improvements. And I won't go over the fibromyalgia study because I think we exhausted that one.

So in terms of safety, FDA notes no significant concerns regarding animal safety data. Few to no serious adverse effects have been

reported in clinical trials, and the oral toxicity study that was done in GRAS concluded no observed adverse events levels.

In terms of the AGEs, D-ribose induced advanced glycation products, there are studies. I've read them all. And they do suggest that ribose does hyper-induce the formation of AGEs much more rapidly than glucose, but AGEs are part of natural aging.

AGEs are implicated in the progression of diabetic diseases, retinopathy, neuropathy, heart disease, even neurotoxicity. Ribose has been shown in mouse studies and in vitro to induce AGEs more rapidly than glucose. It is known that in states of hypoglycemia, diabetic patients are also rapidly producing AGEs.

However, it is not conclusive based on the data that we have what the dose or exposure levels are to produce this effect, or specific risk. Ribose is part of our food source and is endogenously produced, and so far in studies, we've only demonstrated -- the animal studies only

demonstrated that excess dosing was responsible for the AGEs.

Also, I wanted to speak to the asymptomatic hypoglycemia. In most of the studies that we read, that we looked at in this, and I looked at several and FDA provided many others for us to look at, and also in the case of the Bioenergy statement, the hypoglycemia was asymptomatic and concluded statistically insignificant. It was also concluded that it was transient.

Again, what does this mean in terms of a diabetic patient? That's unforeseen. These are things that the physician that would want to try these particular therapies would need to evaluate certainly.

To conclude, simply, the material is well tolerated in clinical trials. Clinical data does suggest that there is a quality of life improvement. We're looking for an energy source for these people that have these chronic conditions.

Ribose is available as a dietary supplement

from many vendors without quality standards or monitoring. So again, this material is available to compounders as a USP product. This is a much higher standard than can be verified in some of the materials that can be gained online.

If this material is not available for compounding, physicians and patients will go to Amazon and buy this material. Compounding can provide formulations with specific USP monograph material in the particular dosage form that the physician is wanting. And the physician and compounder, or one, are at liberty to care for the success of the patient.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will now take clarifying questions for the nominator.

Dr. Braunstein?

DR. BRAUNSTEIN: What are the advantages, though, of providing this in a pharmaceutical form as opposed to -- just for clarification -- as opposed to as a food additive, going to Whole Foods and buying some D-ribose? Because I understand the

studies were done with the food additive. Is that right?

MS. KIEFFER: Right. It's considered a medical food, what the CSF study was done on. The difference is, is that a compounding pharmacy is specifically equipped to prepare drug dosage forms specific to the patient's needs. They have analytical equipment to prepare a dose of 35 milligrams or 300 milligrams. Also, they have a lot of control in place, and SOPs in place, to make sure the best product is getting to the patient.

In addition, USP monographing sets a standard for what parameters the chemical must be consistent with. There are chemicals coming from all over the world. There are a lot coming from China. There are a lot coming from India, et cetera. Very few of them are prepared here.

Some of them are prepared in FDA inspected facilities, but some of them are not. Compounders are bound to use USP monograph material when available. So, in that case, they have a better product going forward. They have material that's

been verified for quality and purity.

DR. BRAUNSTEIN: Yes, but I understand, but there's no USP pharmaceutical monograph for this product, otherwise there wouldn't be a need --

MS. KIEFFER: Yes, there is. There is a dietary monograph.

DR. BRAUNSTEIN: There's a dietary monograph?

MS. KIEFFER: Yes, but a dietary monograph is better than no monograph. That means the USP sat down and decided what would be appropriate for this particular chemical, and it will be measured against that.

DR. GULUR: Dr. Davidson, would you like to comment?

MS. DAVIDSON: I'm not aware of a dietary supplement monograph for ribose. Is that maybe something that's not yet official? I'm not finding it anywhere in the USP database.

MS. KIEFFER: Really? I believe there is one. I can verify that.

MS. DAVIDSON: Okay.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Thank you.

Thank you everyone. We will now have our afternoon break. Committee members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. Please return to your seats by 2:30. Thank you.

(Whereupon, at 2:16 p.m., a recess was taken.)

DR. GULUR: Welcome back, everyone. If everyone could please take their seats, we will now continue with the FDA presentations. Dr. Muniz?

Commander Muniz, if you would like to do the presentation on chondroitin.

FDA Presentation - Javier Muniz

CDR MUNIZ: Hello. Good afternoon, everyone. I'm here to talk to you about chondroitin sulfate. My name is Commander Javier Muniz. I am a medical reviewer with the Division of Anesthesia, Analgesia, and Addiction Products,

and I'm going to be presenting to you on behalf of our team.

I want to personally thank the members of my team and their contributions to this project, Dr. BeLinda Hayes and Dr. Daniel Mellon from the pharmacology/toxicology point of view; Dr. John Feeney, my clinical team lead supervisor; and Dr. Normal Schmuff and his team from chemistry.

Chondroitin sulfate has been nominated for the topical use of the treatment of joint pain associated with osteoarthritis. Before we get into the presentation, I want to point out something you're going to notice over and over throughout the presentation, is that there's very little data that we could find on topical chondroitin use, so we expanded our search into the medical literature and so on, and we expanded into oral chondroitin.

The reason we did that was because we thought that that could give us some insights into the potential analgesic properties that the moiety may have and give us some insights about potentially the safety profile of chondroitin

sulfate.

What is chondroitin sulfate? So chondroitin sulfate is a glycosaminoglycan, and it's a long chain of alternating sugars. These chains could be over 100 units long. And this could be sulfated throughout various positions here in the molecule, and we're going to talk a little bit about that later.

Normally in the body, it is found attached to proteins, and we call those proteoglycans. Chondroitin sulfate is thought to be one of the main components of cartilage, and we think it gives the compression resistant.

So this is remarkably stable under neutral conditions at a low temperature, but degradation and desulfation occurs at elevated temperatures. We see a breakdown of these long polysaccharide linkages under acidic circumstances, such as in the stomach and under basic conditions.

Commercially, we get chondroitin sulfate from animal tissue. Most of the chondroitin sulfate in the United States comes from bovine

sources, but it can also be porcine, avian, seafood. There are two major components of chondroitin sulfate, and one is chondroitin sulfate A, or chondroitin 4 sulfate, and the other one is chondroitin sulfate C, or chondroitin 6 sulfate.

So depending on the species, we may see that these ratios of A and C may be different. And it's usually a white powder, and it's available as a sodium salt, and it's soluble in water. Because we get chondroitin sulfate from animal tissues, there could be some concerns about contamination and so on, for example bovine spongiform encephalopathy. The way we deal with that is through a BSE importer letter, so we just don't get the product from places where BSE is endemic.

We've already mentioned briefly the pharmacology here. I want to talk to you about the nonclinical data, and again we're going to try to get what we can for the topical chondroitin sulfate, and then we're going to expand into the oral use.

How does this work? Well, the bottom line

is we don't know. Several people have proposed ideas about how this could happen, how could this be of help? And some of the ideas you can see in here. Some people think it may protect the chondrocytes or the cells that make up the cartilage. Some people think it may be kind of the building blocks for cartilage, so maybe it helps build them up. Some people have proposed that it stops the cartilage and some of this connective tissue from breaking down, or that it may have some anti-inflammatory properties.

From pharmacokinetics, there is no topical chondroitin data. We expect very minimal, if any, absorption. This is, remember, a very large molecule, highly charged, so its penetration through the skin is expected to be very low.

So from the oral administration, we expect very low bioavailability. Remember, we talked about the molecule becoming unstable under acidic circumstances. So it's likely that any absorption, or most of the absorption is of metabolic byproducts of chondroitin sulfate.

When it comes to safety pharmacology, again we have no topical studies, extremely limited data with a parenteral route of administration. There's no evidence of adverse effects on cardiovascular, gastrointestinal, renal systems, but we don't have any data on central nervous systems or the respiratory system. And toxicology, we don't have any oral or topical studies.

It is thought that this is not genotoxic at least in vitro. There are some developmental and reproductive studies. There's a very old single study in which they use subcutaneous injections of chondroitin sulfate in mice, and the following adverse events, effects were seen: cleft palate, flex or curled tails, and growth inhibition of the fetus.

However, it is important to note that these were not observed or any other adverse effects were reported using oral administration in rats or mice. Unfortunately, the actual study reports are not available, and it has very limited utility when discussing what's ahead here in the topical use of

chondroitin sulfate. For carcinogenicity, we don't have any studies either from dermal or oral.

Our non-clinical conclusion is that the clinical safety profile has not been adequately characterized, and we'll see in a minute some of the things we can do to help with that. But there's no evidence of adverse effects based on this limited data we have.

Some of the things we would like to see to better characterize the safety profile of chondroitin sulfate are chronic toxicology studies in two species, the same with carcinogenicity. We need some more reproductive and developmental toxicology. And with topical use, sometimes when we see things such as hypersensitivity reactions, photosensitivity, so we need some studies also to adequately characterize the safety profile of chondroitin sulfate when used topically.

So I'm going to switch here gears, and on the next few slides, I'm going to be discussing the clinical safety profile of chondroitin sulfate. And again, you'll see that we have very limited, if

any, information from topical use, and we just have to expand to gain some insights into some of the oral use.

What we did here is we looked through the literature, and then we also took a look at the FAERS and the CAERS databases, which are some of the voluntary mechanisms we have for people to report adverse events to the FDA. So let me discuss here a little bit of what we have.

For topical chondroitin use, we have a single study, and this was done by Cohen in 2003. And that's topical chondroitin as part of a combination product. This product had chondroitin, glucosamine, camphor, peppermint oil. The study tells us that it was well tolerated for 2 months, it was a small study with 30 patients, and they were being treated for osteoarthritis knee pain.

We have a lot more experience with oral chondroitin. Notable adverse events in the literature are allergic reactions, elevated liver enzymes, and drug/drug interactions. We saw a number of cases of elevated INR. INR is

international normalized ratio. It gives us an idea of the coagulability of the blood. And it was observed with concomitant use of warfarin, which is a blood thinner.

So in the FAERS and CAERS databases, again, very minimal experience with the topical chondroitin. There was only one case of one rash, and unfortunately was confounded by multiple factors, so we can't really draw any conclusions from that. We did see also other cases of elevated INR with concomitant use of warfarin.

Now, I am going to talk about the GAIT trial. This is the Glucosamine/Chondroitin and Arthritis Intervention Trial. It's a trial we're going to be talking about later when we discuss clinical efficacy. But this was a large trial conducted by NIH. And they used an arm of chondroitin sulfate and another one of a combination of chondroitin sulfate and glucosamine, and it was for a 6-month period. They also did an extension of that study, known as the GAIT 2, for 2 years.

So roughly, 300 patients were assigned to the chondroitin only and another 300 to chondroitin and glucosamine. And what we learned from that study is that there were no serious adverse events noted that could be directly attributed to chondroitin monotherapy.

Chondroitin sulfate is an approved product in multiple countries throughout the world. One of the things we did is we found, for example, Droglican is approved in the European Union and is manufactured by Bioiberica in Spain. And we looked into a summary of product characteristics, which is sort of the equivalent or similar to our package inserts or labels, and we looked at some of the undesirable effects.

You can see here from the gastrointestinal disorders, we see nausea, hypersensitivity, edema, fluid retention being very rare, and under special warnings and precautions, it states that patients with impaired glucose tolerance should be monitored. And in very rare occasions in such patients cases of edema and water retention have

been reported.

There's no dose response information for oral or topical chondroitin use. In the clinical safety conclusions, again, I want to highlight that we have minimal experience reported with topical chondroitin. We have one case reported in the FAERS database of a rash with topical chondroitin, but it had multiple confounding factors.

We do have a lot more experience with oral chondroitin, as it has been summarized here. There may be interactions with warfarin and a risk for bleeding associated with the use of oral chondroitin based on these cases of drug/drug interactions in both the FAERS and in the medical literature.

None of the warfarin interaction cases were specifically linked to the topical use of chondroitin.

So, let's reach now to clinical efficacy. Again, the only one study that we just discussed, the Cohen study from 2003, this was a randomized, placebo-control, parallel-group trial with roughly

60 patients, and people were treated for 2 months. Patients were instructed to apply this cream liberally into the joint and repeat as necessary. On average, people were using the creams about 3 times a day.

The study tells us that there were improved pain scores observed at 8 weeks. It's important again to highlight that this was a combination product. The study was not designed to evaluate the single components here, so it's hard to draw any conclusions. Also, the author tells us that there were some concerns about the blinding. Apparently, there were some texture differences between the placebo and the active cream.

Again, the GAIT study, this was a randomized, placebo-controlled, active controlled trial investigating the efficacy of oral glucosamine and oral chondroitin sulfate, and it enrolled 1500 patients for a 6-month period. It had a full factorial design, and they had a placebo arm, 1200 milligrams a day of oral chondroitin, 1500 milligrams of glucosamine, a combination of

both the 1200 and the 1500 milligrams of chondroitin and glucosamine, and a positive control of 200 milligrams of celecoxib or Celebrex daily.

You can see here on the overall results that chondroitin, all the combination was not statistically significant. The measure here was the response rate, so they just didn't differentiate from placebo while celecoxib did.

The second part of this slide here, the subgroup, this is an often quoted, often mentioned, post hoc analysis that was conducted in which they looked at patients that had over 300 points on the WOMAC pain subscale. And in this one, chondroitin or celecoxib were not statistically significant from placebo, but the combination product was.

Here's a list of some of the studies that we looked at, and you can find them in your background document. They range in size and duration of treatment and so on, but we think that the GAIT study is definitely the most significant of these studies, the one that we can look at and find the most information.

We could not find information on the historical use of chondroitin in pharmacy compounding, either topically or orally, although oral chondroitin use has been discussed for at least 3 to 4 decades in the medical literature. It has been used to treat multiple conditions, including joint pain associated with osteoarthritis, interstitial cystitis, and overactive bladder. It has also been used in products for the treatment of dry eyes, corneal inflammation, and for cataract surgical procedures.

In conclusion, chondroitin sulfate is specified in mixtures that can be characterized with various analytical techniques, and it's stable both as a solid and an aqueous solution, so it is well characterized. However, there are insufficient data to support the safety or efficacy of topical chondroitin in the treatment of joint pain associated with osteoarthritis, which is a serious condition. We also know that we have a number of safe and effective FDA approved agents that are available for the treatment of joint pain

associated with osteoarthritis.

Further clinical investigation with topical chondroitin should be monitored through the IND process. There is insufficient information on the extent of use of topical chondroitin in compounding to evaluate the significance of its historical use.

Finally, our recommendation is the following. We do not recommend that chondroitin sulfate for topical use be placed on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. So that's my presentation. Thank you.

DR. GULUR: At this time, we will take clarifying questions from the committee.

(No response.)

DR. GULUR: Since there are no clarifying questions, thank you Commander.

CDR MUNIZ: Thank you.

DR. GULUR: We do not have any nominator presentations for chondroitin, so we will now continue with FDA presentations for

acetyl-L-carnitine. Dr. Bergmann?

FDA Presentation - Kenneth Bergmann

DR. BERGMANN: Good afternoon. I'm Ken Bergmann from the Division of Neurology Products, and I'm presenting on behalf of the review team. I thank my colleagues, Dr. Carbone, Dr. Podskalny of DNP, and also Dr. Zhang from OPQ, and what I'm reporting represents the work of the combined group.

The nominated uses that we're going to consider for acetyl-L-carnitine, which I'm going to call ALC from now on, are peripheral neuropathy, cirrhosis of the liver, and specifically hepatic encephalopathy and Alzheimer's disease. We know a fair amount about ALC, and the reason is, as you'll see, is that a close relative of this, L-carnitine, is an approved drug. And part of the knowledge comes from the NDA holder for L-carnitine has actually done studies with ALC as well. I just want to emphasize that everything in the briefing materials is in the public domain.

In terms of chemistry, this is a well

characterized molecule that does decompose at its melting point. It's very soluble, but under aqueous solutions, there is a hydrolysis that can occur, so degradation may happen.

With regard to the chemistry, there are a number of synthetic routes, and likely impurities are not thought to be particularly toxic, to our knowledge. And the conclusion of Dr. Zhang, the OPQ reviewer, is that ALC is stable as a solid under ordinary conditions. It may have some stability issues when formulated as a solution.

With regard to non-clinical safety pharmacology, it's synthesized in a number of organs in the human by acetylation of carnitine. It has a key role in mitochondrial energy homeostasis and in phospholipid and acetylcholine synthesis.

For the non-biologists in the audience, mitochondria are the energy generators in mammalian cells. So they have key functions that are vital to life. Safety pharmacology investigations using intraperitoneal administration showed mild

increases in behavior in rats. There were no reports of cardiac or respiratory effects. In acute toxicity studies, lethal doses were associated with convulsions and death.

There were no adverse effects associated with intraperitoneal administration up to 300 milligrams per kilogram. And in the repeat dose toxicities, which were up to 4 months in some species, there were no clear toxic effects.

However, there are gaps in the knowledge that are important. Dietary administration over three reproductive cycles did not appear to have clear effects in offspring of rats, but there's no real mutagenicity, carcinogenicity, or toxicokinetics data.

In conclusion, the available non-clinical information is limited, but didn't reveal any significant toxicity associated with ALC in animals.

With regard to clinical pharmacology, L-carnitine, the parent molecule, but ALC is also a prodrug in the sense that it can be metabolized to

L-carnitine. Under chronic conditions, dietary bioavailability is quite good.

Bioavailability is quite variable depending on length of administration and dose that's given, and we'll come back to that in a moment. The way it gets into a cell is a very sterospecific transport that can increase the concentration inside the cell, and specifically the mitochondria.

All of the L-carnitine related compounds, and we'll see this as a pool of compounds, exists in a concentration based dynamic intracellular balance. It's mostly excreted in the urine, and the remaining carnitine that is in the large intestine is broken down by GI bacteria. And after a single IV dose, it's rapidly excreted over 12 to 24 hours.

Now this is a cartoon of the carnitine pool, and I'd just all your attention to the area inside the red square. This is inside the mitochondria, and what's important about this is to see that carnitine and acetyl-carnitine are in a balance. And I would use the analogy this is akin to filling

up a bathtub where you can only go so far, and then the overflow drain takes over, so the system remains in balance. And this is true whether you begin pushing with L-carnitine or acetyl-L-carnitine.

In terms of our sources of information for clinical safety, we have the L-carnitine label itself. As you can see, it would be very hard to distinguish the toxic effects of ALC from L-carnitine itself. We have CDER's Office of Surveillance and Epidemiology, the FDA Adverse Event Reporting System. What's important to note about this is that ALC would only appear in this database if it were co-administered with a prescription drug. And it's important to note that this is a voluntary reporting by patients and healthcare providers for serious adverse events.

The Center for Food Safety and Nutrition, CFSAN, also has similar adverse event reporting system. These reports contain scant information about the individual baseline medical condition, how much was taken, seriousness, and recovery, and

so forth. It's fairly bare bones. Then finally, we have information from clinical trials that include safety reporting.

Going through these with regard to the L-carnitine label, L-carnitine is approved for the indication of very specific inborn errors of metabolism where carnitine is affected, or secondarily affected, by other inborn errors of metabolism, a very small specific population of children really where in some cases the genetic defect exists in just one family.

There are no reports of L-carnitine overdose. There's no real contraindications or warnings, but it's not been fully evaluated in patients with renal insufficiency, which is important because that's how it's excreted. Chronic administration of high doses can result in potentially toxic metabolites. That's at least theoretical.

With regard to drug interaction, it does appear to affect the INR in patients taking warfarin, and that's been described more than once.

The effect on human pregnancy and unborn fetus is not known. It is likely to be excreted in milk.

Common adverse events are transient, nausea, vomiting and dizziness. Less frequent is body odor and gastritis. Now, body odor is important in this regard because it's described as a peculiar body order, occurs in some chemicals, but what's important about it is it makes clinical trials extremely difficult to evaluate in a blinded fashion. It takes a special kind of design to avoid that.

Seizures have been reported to occur in patients, both with and without pre-existing seizure activity. And in patients with pre-existing activity, there is an increased frequency and or severity reported.

In terms of the FAERS system, there were 13 cases that were reported. Again, these were in association with other drugs. Five of the cases were for treatment of peripheral neuropathy, 8 were not reported, and attribution to ALC could not be determined, or it was unlikely given the case

details or the presence of a more likely etiology. And in every case, there was at least one additional suspect product.

In the CFSAN event system, a very broad search was performed looking at any form of carnitine. And ALC was only the solitary ingredient in 8 of the 68 events identified. I will say that there are 39 products on the market that contain ALC, last look at the food supplement database.

Products in the other reports containing ALC were formulated with a variety of all kinds of things, vitamins, minerals, trace metals, and other proprietary ingredients. The most common things that were seen in 31 patients that seemed to represent reasonable cases were convulsions in 5, GI distress, and allergic complaints, such as rash, swelling of the face, and symptoms that suggest hypersensitivity .

Clinical trials that included safety reporting for ALC, important to note that there were no new or previously undescribed adverse

events seen when compared to L-carnitine. And the most common adverse events collected in a non-systematic fashion from case reports and trials are listed here.

With regard to clinical efficacy, first peripheral neuropathy. It was studied for both prevention and treatment of peripheral neuropathy related to cancer chemotherapy, and diabetes mellitus, and HIV treatment.

Small clinical trials tended to show improvement in nerve conduction velocity, which is a measure of successful treatment of a peripheral nerve condition. It's basically measuring how fast a signal can go down a nerve. Also, some studies looked at patient reported pain. There were no measures however of the clinical meaningfulness of the outcome.

In a larger multicenter trial where ALC was given 2 grams per day for a year, there was a small benefit in this blinded trial in nerve conduction velocity, though it was still very much within the abnormal range, and no clinical benefit was

ascribed to the change in conduction.

There are other randomized multicenter trials, which I won't go into except to say that they were performed with well defined methodologies and rigorous controls, and they did not demonstrate efficacy. And these were in the various conditions related to chemotherapy listed here.

Another condition that was looked at was cirrhosis of the liver. And liver disease causes a generalized brain dysfunction known as hepatic encephalopathy. This results in part from the inability of the liver to detoxify ammonia in the body, which is produced by the normal degradation of dietary proteins.

The diagnosis of hepatic encephalopathy is made by measuring this arterial ammonia and with supportive evidence from the EEG brainwave test and psychometric testing, paper and pencil tests of mental function.

Jiang and his colleagues did a systematic review of therapeutic efficacy in hepatic encephalopathy of 33 trials. Six of the trials

were blinded and randomized, but they had considerable irregularities in design. These six trials were all by a single investigator, and it was apparent on review that the same population was reported upon in different ways in these trials. But looking across this, the serum ammonia was reduced on average about 26 milligrams per deciliter, but this was not again a clinically meaningful result.

Finally, Alzheimer's disease. We had benefit of a Cochrane collaboration review. These are academically oriented systematic meta-analyses of available data. And Hudson and Tabet looked at 33 randomized placebo-controlled trials, and 16 of the trials were assessed as appropriately designed.

Sixteen of these were multicenter trials, and some of these were conducted by the NDA holder for L-carnitine. These authors were able to get reports, detailed reports, from the NDA holder.

The test dose of acetyl-L-carnitine was 2 to 3 grams daily, which is roughly the same dose as L-carnitine in inherited metabolic disorders.

Treatment from 12 to 52 weeks and up to 1400 patients participated in these trials. And all trials assessed the potential cognitive effect of ALC on patients with mild to moderate dementia, and in addition, most considered the severity, functional ability, clinical global impression -- in other words, outcomes that we would consider in fairly rigorous Alzheimer's disease efficacy trials.

The assessment of the Cochrane collaboration stands by itself, that there was no evidence suggesting a statistically significant result. And there was no recommendation for routine use in clinical practice. Now, they did note that at one particular time point, these studies did seem to show -- or at least in particular, one study did seem to show that there was a benefit, however in methodology analysis of trials you have to take into account repeated testing for significance.

When you have a p-value of 0.05, it means 1 in 20 times you test, it's going to be a false positive. So it's not uncommon in multiple

testings within a trial to have a particular significant result that by and large doesn't hold up across trials.

Of interest, one trial in Alzheimer's disease, the post hoc analysis suggested that early patients may benefit. A subsequent multicenter trial was performed in younger onset Alzheimer's patients and did not reveal any efficacy, unfortunately.

The European Commission also asked the European Food Safety Authority to review ALC, and they concluded that there wasn't sufficient evidence to suggest consumption of L-carnitine and a contribution to -- excuse me, acetyl-L-carnitine and contribution to normal cognitive function.

The extent of ALC use in pharmacy compounding is unknown. It's been available since at least 1964. It's been widely available as a dietary ingredient in supplements for at least three decades. By 1983, it was understood as being a naturally occurring endogenous chemical substance in people as a result of L-carnitine metabolism,

and the original L-carnitine NDA was approved in 1985.

With regard to therapies for these conditions, in peripheral neuropathy, there is no approved treatment for the prevention of peripheral neuropathy from chemotherapy or diabetes, but there are treatments for alleviation of the suffering from this disorder, including duloxetine, pregabalin, and tapentadol.

Cirrhosis of the liver, there are standard treatments for hepatic encephalopathy by targeting reduced protein absorption from food, but also use of Lactulose and rifaximin for increasing the elimination of ammonia from the body. And finally, Alzheimer's disease has donepezil, rivastigmine, memantine, and galatanamine to aid in memory dysfunction.

So in conclusion, the physical and chemical properties of ACL are well characterized. The extent of ALC use in pharmacy compounding is not known. The safety profile suggests it's well tolerated when given orally up to 3 grams daily,

but it must be used in caution with anyone using anticoagulant drugs, such as warfarin, a person suffering from seizures, or a person with renal insufficiency, which is a major route of elimination.

Extensive investigation in large randomized, blinded, placebo-controlled trials fails to support its efficacy for any of the proposed uses and the disorders included in the domination of serious medical conditions for which safe and effective treatments are available in the United States.

As a result, we do not recommend that acetyl-L-carnitine be placed on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you. At this time, we will accept clarifying questions from the committee. Dr. Pham?

DR. PHAM: I'm not sure if I completely understood the slide about the carnitine pool, but

basically trying to get a sense for what is the added value of ALC to the current levocarnitine product that's on market. So is it adding -- is it working on that other cycle to potentially increase the carnitine for carnitine deficiency?

DR. BERGMANN: I think that's exactly the question. I don't know what the added benefit would be over L-carnitine. I tried to demonstrate that it's a very fluid situation, so if you feed one, you feed the other. And I think that to what we know about pharmacokinetics, that would seem to be so. So I think that's the answer.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: All right. At this time, we will now proceed with the nominator presentations. We have one presentation by Dr. Day from PCCA.

Nominator Presentation - A.J. Day

DR. DAY: Good afternoon. My name is A.J. Day. I'm with PCCA in Houston, Texas, and PCCA does provide acetyl-L-carnitine for compounding pharmacies to utilize for prescription

compounding.

Before I get started with the specific discussion on acetyl-L-carnitine, just one point of clarification that was brought up from a previous presentation with Ms. Kieffer on D-ribose. There is a dietary supplement monograph that will be official August 1st in USP39NF34. So that has been -

MS. DAVIDSON: Food?

DR. DAY: Food, yes.

MS. DAVIDSON: Not dietary supplement?

DR. DAY: Yes, a food monograph. Yes.

I would like to thank Dr. Bergmann and the FDA for a very thorough presentation on acetyl-L-carnitine. I might be referring to it as ALCAR, as is commonly done in the industry.

Before we get started on the clinical presentation here and review of the data that's presented, just out of curiosity on this particular committee, we're talking about how these substances get utilized in compounding. And in the committee discussion prior to lunch, we talked about how it

may be promoted for patient utilization for physicians to write the prescriptions.

Have any of you on the committee had an opportunity to visit a compounding pharmacy? I know in our June meeting, this is something that Mr. Mixon had suggested. So as just a matter of understanding the industry and how these compounding pharmacies operate, actually going in and visiting them, interviewing them, finding out how these prescriptions are coming in, what are their marketing practices and how do those prescriptions -- how does awareness of these prescription opportunities come about, I think that that process is going to be vital to how we make decisions, how you make decisions as voting members of this committee.

Now, as the FDA's presentation stated, the concerns with acetyl-L-carnitine, or ALCAR, in large part look at the efficacy side. The physical and chemical characterization is not in question. The toxicology of it is not in question. There was one point about the physical stability that came up

with regards to its aqueous stability and the potential for an instability in an aqueous media.

There is published literature in a peer reviewed journal, this is available, you can find this on PubMed, and it's the International Journal of Pharmaceutical Compounding, where they look specifically at acetyl-L-carnitine stability in an aqueous vehicle, and they found that there was quite good stability at room temperature or at refrigeration.

In a compounding environment, this particular formulation, if followed exactly according to the study, would get about 30 days at room temperature.

Now, in compounding, we're often changing the concentrations, and there may be variations from the specific formula, in which case we would default to the USP guidelines for stability, and then for beyond use dating of the preparations, and 14 days refrigerated is the standard for aqueous oral preparation.

A big part of the conversation from the

previous presentation looked at how is levocarnitine different from ALCAR. Is there a difference? Why might we need one versus the other or have both of them on hand?

Now, this is a piece of literature that specifically looked at that. This is a non-human study. This is looking at young versus old rats and the effect of acetyl-L-carnitine on oxidative stress, ambulatory activity, and the biomarkers of that oxidative stress in the brains of old rats.

What they actually conclude is that ALC was effective, unlike levocarnitine, in decreasing oxidative damage, including these biomarkers of oxidative damage in old rat brains. These data suggest that acetyl-L-carnitine may be a better dietary supplement than levocarnitine.

Here are some of the data that they found in that study. You can see on the first column is young rat brain versus the old rat brain. Then when you look at the addition of acetyl-L-carnitine versus simply levocarnitine, you can see the statistically significant difference in markers of

oxidative stress; again, further data with some of the other markers of oxidative stress in the rat brain showing a marked difference when utilizing acetyl-L-carnitine versus simply using levocarnitine. There is a clinical difference that this study is showing.

So the study does go on to conclude that acetyl-L-carnitine and levocarnitine increase ambulatory activity similarly in old rats and elevated carnitine levels in old rat blood and brain, so this speaks to that balance between the two. However, acetyl-L-carnitine did decrease MDA, nitrotyrosine and oxo8dG/oxo8G in the old rats' brain. And this data suggests that ALC is a more effective dietary supplement than levocarnitine.

Now, if we look back to the FDA's briefing document on acetyl-L-carnitine, they talk about the DeGrandis publication, the double-blind, randomized, placebo-controlled pharmaceutical sponsored trial. And the authors themselves put this finding of the increase in nerve conduction velocity as it being relatively small. And as was

mentioned earlier, that it did not, in itself, have relevance, this nerve conduction velocity change.

What the actual study concludes, though, is that after 12 months of treatment -- because they're not overall looking at patients and nerve conduction velocity as a measure of treatment outcomes. You're obviously looking to see that the treatment is effective for treating the pain. And after 12 months of treatment, mean visual analog scores for pain were significantly reduced from baseline by 39 percent in acetyl-L-carnitine treated patients versus 8 percent in placebo patients.

ALC was well tolerated over the study period. It was effective and well tolerated in improving neurophysiological parameters and in reducing pain over a 1-year period. Acetyl-L-carnitine is therefore a promising treatment option in patients with diabetic neuropathy.

This is the quote, this is the screenshot from that trial. The trial is not about nerve

conduction velocity, and here is that data that they present, again, reaching statistical and clinical significance.

In addition, we have a recommendation from the Australia and New Zealand College of Anesthetists and Faculty of Pain Medicine. This is their review of scientific evidence and their recommendation for acute pain in patients with HIV infection. And they do indicate that for the medication induced neuropathic pain in HIV and AIDS patients, it is treatable with acetyl-L-carnitine. This is their official treatment algorithm and recommendation.

The study that they utilized to come to this conclusion was analyzed by the FDA, and the actual treatment professionals, the specialists in the field have determined that it is not a trial that should be dismissed, but it does provide a baseline for how we can approach our patients in a more compassionate manner.

In addition, the FDA's briefing information talks about there's no evidence from

methodologically sound clinical studies showing the efficacy of acetyl-L-carnitine for the treatment of disease. And an extensive investigation of acetyl-L-carnitine in large randomized, blinded, and placebo-controlled trials, it also supports efficacy for any of the proposed uses and that there are multiple safe and effective treatments available for those uses.

Now, this study by Sima and colleagues is a review of two randomized, blinded, placebo-controlled trials. Right here, we have the abstract, but I'm going to go into some of the details in the next few slides.

They have 1,257 patients, intention-to-treat. It was an analysis of two randomized, double-blind, placebo-controlled trials. Each trial was 52 weeks, 1 year in length. Both of the trials were multicenter. One of them used 28 U.S. and Canadian centers -- this was the UCS arm -- and the other trial had 34 centers throughout the United States, Canada, and Europe. This is the UCES arm.

They actually enrolled a total of 1,346 patients. Now, their inclusion criteria included men and non-pregnant women between the ages of 18 and 70 years old, with diabetes for 1 year and an HbA1c of 5.9 percent.

The differences between the UCS, the United States and the Canadian data, was very small, however there was a difference between the UCS and UCES data, and that's mainly due to the European patient cohort. This is according to the authors.

So we're going to focus on the UCS data because, frankly, we're in the United States, and this is an FDA meeting, so that's what we're concerned about. So the UCS data does show statistical significance using the higher dose of acetyl-L-carnitine over a period of months, both at the 26-week change and the 52-week change.

The most common emergent adverse events were pain, paresthesia, and hyperesthesia. And in total, in the total population, pain, paresthesia, and hyperesthesia were reported by significantly fewer patients taking the 1,000 milligrams

acetyl-L-carnitine compared with placebo. So your adverse events were lower in the patients that were on the treatment versus placebo. The incidence of other adverse events did not differ between placebo and patients on an active drug.

Now, as I analyzed this data, I looked back, and this trial is listed in the bibliography section of FDA's analysis from the briefing information, so I needed to kind of analyze it a little bit more thoroughly to understand why it was not included in their document.

I don't pretend to have that answer for you. What I can tell you is that I did not identify any particular shortcomings with this data to justify it not being discussed by the FDA. So hopefully, we can find out a little bit more in just a little while.

So this article is published in a high impact factor journal. Diabetes Care has an impact factor rating of 8.57, which means that it meets high standards for robust methodology and instrumentation. The design of this trial is

sound. The pertinent patient population, the lack of bias, all of those factors have been considered.

The overall conclusion is supported by the data produced. There was some extrapolation of the results with regard to improvements in vibratory perception and nerve regeneration, yet, there is no extrapolation or interpretation for the clinical outcomes or the adverse events reported. So while the conclusions of the trial do state that longer trials need to be conducted, two studies of 52 weeks each is very good evidence.

This next study, Campone from 2013, assessed patients with chemo-induced peripheral neuropathy. Patients with ovarian cancer in this study had less incidence of grade 3 and 4 peripheral neuropathy. So while the overall incidence of drug-induced neuropathy was not reduced for all patients, it was less severe for the ovarian cancer patients. You had fewer incidence of those higher grade neuropathies.

Similarly, we have a study the following year, 2014, by Callander and colleagues. They

assessed 32 patients with chemo-induced peripheral neuropathy. Again, the acetyl-L-carnitine patients had less grade 3 or 4 neuropathy and those patients lived longer.

There has been some discussion on risk of clotting factors and monitoring INR. These patients did not have any different incidence or measurements of hemoglobin or platelets. So this is a table specifically looking at frequencies and percentages of treatment associated toxicities.

In their discussion, they do talk about the response time. So the median duration of response was 3 months in the control group versus 10 months in the acetyl-L-carnitine treatment group. And the survival was 22 months in the control group versus 28.3 months in the acetyl-L-carnitine treatment group.

They also talk about the attempt to mitigate the incidence and severity of peripheral neuropathy through the use of prophylactic acetyl-L-carnitine. That is the goal. They weren't trying to eliminate, but rather to mitigate the severity.

Our studies suggest that the addition of acetyl-L-carnitine did not eliminate treatment related peripheral neuropathy, although there appeared to be fewer cases of grade 3 or 4 neuropathy among patients receiving the prophylaxis as reported by the treating physicians.

Given the observed continued high responses to the treatment combination, it is clear that the inclusion of this agent in the treatment regimen did not diminish the response rate of the cancer therapy, and that acetyl-L-carnitine was very well tolerated.

Now, this trial utilizes a very specific chemotherapy regimen, so in a later paragraph of their conclusion they say it is also conceivable that the incorporation of acetyl-L-carnitine and bortezomib containing regimens earlier in the treatment course might offer a protective advantage against the development of peripheral neuropathy.

This next study looks at HIV associated antiretroviral toxic neuropathy. So still neuropathy, however instead of chemo induced, we're

talking about HIV associated drug induced. And this is getting back to something that we referred to in one of the earlier trials, so the Hart study, and I'll talk a little bit about that in just a moment as well.

What they do talk about is that although not formally documented, those who stopped acetyl-L-carnitine treatment suffered rapid symptom worsening, including the return of dysesthesia. Acetyl-L-carnitine treatment was well tolerated with no side effects, no adverse events, or wound complications.

So again, the Hart study was cited by FDA in their bibliography. It was not mentioned in the briefing information. So I wanted to do that thorough analysis again to understand what are the potential downsides of this literature, that it was not included.

Again, it's published in a journal with a high impact factor, which is quite reputable. The length of the study was 33 months, almost 3 years, which appears sufficient to determine the long-term

effects of acetyl-L-carnitine, both positive and negative effects.

Controls were used and results were compared to baseline and control. Researchers took measures to reduce variabilities in results when processing the biopsies. And though clinical scores were used to evaluate improvements, quantification of the components of neurofibers were also conducted.

It was a relatively small trial. There were only 19 participants in the end, started off with 21. Three patients changed antiretroviral therapy, their medication changed during the course of the study, which might have affected some of the study results.

So although there were some weaknesses of the study, we do not feel that those were strong enough to exclude the data showing the benefits, and again, looking back to the Australian guidelines of HIV medication induced neuropathy, the treatment benefits for acetyl-L-carnitine from baseline.

In the nominating information that was

submitted to FDA for acetyl-L-carnitine, there were other indications. There were quite a few in fact, and I understand that it's difficult to go through all of those. However, the ones selected by the FDA to present were not fully inclusionary of everything that was nominated.

So here we have some data on how it's utilized in compounding for fertility, male fertility specifically. This study from 2005 was a placebo-controlled, double-blind, randomized trial on the use of levocarnitine, acetyl-L-carnitine, or the combination of those in men with idiopathic asthenozoospermia.

Now, the result section does talk about sperm cell motility. It's looking at overall motility as well as forward motility, specifically the ability of the sperm to move forward in the correct direction.

Here you can see the placebo at the bottom of the chart, not having much variance from baseline, your treatment group with levocarnitine having modest increase, acetyl-L-carnitine having

greater increase in forward sperm motility, and the combination of levocarnitine and acetyl-L-carnitine having the greatest increase. The conclusion is actually that the supplementation with a specific ratio of that combination is very important to forward motility of sperm.

Here we have total sperm motility at each time, and group 1 are patients treated with acetyl-L-carnitine alone or combined with levocarnitine, whereas group 2 is patients treated with just levocarnitine or placebo. And you can see the significant difference that this makes in sperm motility. The implications for male fertility are dramatic.

Specifically forward sperm motility, again looking at group 1, the treatment of acetyl-L-carnitine alone or combined with levocarnitine versus group 2, just levocarnitine or placebo. This is further evidence that the two substances are not simply interchangeable. There is a difference in clinical outcomes and in patients when using acetyl-L-carnitine versus

levocarnitine.

Another indication that was nominated with acetyl-L-carnitine is ALS. This trial is conveniently titled, Randomized, Double-Blind, Placebo-Controlled Trial of Acetyl-L-carnitine for ALS. It was published in 2013. This is a phase 2 clinical trial showing that median survival was 45 months in ALC versus 22 months in placebo. They do conclude that ALC may be effective, well tolerated, and safe in ALS. A pivotal phase 3 trials is needed.

This was a non-for-profit, multicenter, randomized, placebo controlled, parallel-arm, pilot phase 2 trial. They talk about the specific dosing regimen that they initiated patients with. They talked about how they dosed the packets. Symptomatic and palliative treatments were given during the study and were permitted and recorded.

There was some discussion about how difficult it is to blind some of these studies due to a unique body odor, amongst other things, that a lot of patients with the medication receive.

However, if you review that study, that is specific data to levocarnitine. None of that is mentioned in any of the data for acetyl-L-carnitine, any of the trials.

So all adverse events encountered and any serious events were to be recorded using the coding system for the source of adverse reaction terms. Severity was graded according to the modified WHO criteria for toxicity where applicable. You can see the various parameters for the demographic and clinical characteristics.

All of this is showing that there is a trend, that there is consistent data showing that acetyl-L-carnitine and levocarnitine are not one in the same, and they don't simply just feed into the same metabolic pathway, but they do provide distinct clinical benefits.

So the FDA's conclusion is that the disorders that we've nominated acetyl-L-carnitine for are serious medical conditions for which safe and effective treatments are available in the United States.

As we all know, as treating clinicians, the medications that are available are important. Having a product that has gone through the vigorous and rigorous FDA approval process is important. Those are the standards of therapy.

However, in many of our patients, those therapies underperform. They do not provide the relief our patients need and deserve. And it doesn't take a journal article from the Journal of Pharmacoeconomics to tell us that we need better options, and we need adjunctive therapy options.

Many of these patients are already burdened with high pill burden, so adding on extra supplements that you're saying now just go get it from an unknown source at a vitamin store versus a pharmaceutical grade supplement that can be combined with their standard of regimen, so that they're not adding additional medications and having to remember additional pills, these are important aspects for quality of life and for patient compliance to their regimens. Thank you very much.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will now accept clarifying questions from the committee. Dr. Pham?

DR. PHAM: So when you've seen the prescriptions for acetyl-L-carnitine come through, has there been an attempt -- has the provider tried to use the L-carnitine products and seen failure, or is this been -- like is this the drug of choice before they even go to that product?

DR. DAY: The requests for acetyl-L-carnitine have been traditionally for very specific conditions. Acetyl-L-carnitine is not a first-line therapy for many patients. Typically, when we see it in a pediatric population, it might be for a mitochondrial disorder for a patient who has difficulty acetylating and converting. Because again, the acetylated form of levocarnitine is what contributes most into that metabolic pathway. So if there's a diagnoses that establishes the need for the acetylated form to be supplemented, then that's what they go to first and foremost.

Beyond that, for neuropathic conditions,

oftentimes yes, they will go for levocarnitine, identify if the patient has seen any benefit, or if not then they will go for other therapies.

The treatment algorithm for neuropathic pain, because there's so many different causes for it, is very complex. And it's up to each specific patient with their concomitant disease states and other medications as well.

With regards to fertility, male fertility, the information that I've seen has typically focused on the specific ratio of levocarnitine combined with acetyl-L-carnitine so that patients get the best benefit.

DR. PHAM: Is there any -- for the -- at least for pediatric patients and the mitochondrial disorders, I think that [indiscernible] is also used for that. Is there any difference in palatability? I know that you can obviously make things palatable by compounding, but is there any complaints of palatability of the marketed product that you're aware of?

DR. DAY: None that I'm aware of. There are

several specialty compounding pharmacies who focus on pediatrics who focus on mitochondrial and cellular metabolic disorders who have -- who, again, they specialize in this, and they are very successful at treating their patients. And I've not heard of any complaints or an inability for the patient to tolerate the medication.

DR. GULUR: Dr. Carome?

DR. CAROME: So one has to be cautious when you cherrypick data from various studies. The Sima study which you showed, could you go back to the table where you showed the pain results from the Sima study?

So it's important to recognize the Ns for the patients -- for the subjects in this trial. So the trials combined involved 1346 subjects, and you see that this is just a small subset of the subjects who were enrolled, where we're looking at the pain scores. And it's, I believe, about 25, 27 percent of the total subject population.

All they're looking at here is that subset of patients where pain was the most bothersome

symptom that they reported, which I believe implies that there are other patients or subjects who had pain in this study that aren't being reported, which suggests that in order to show some statistically significant result on the pain scale, they polled out a population that supported what they were trying to show. And I think that's very important when analyzing studies carefully to consider details like this.

I'm curious if the FDA has a view about this pain data and whether it's meaningful in assessing the drug.

DR. BERGMANN: I think what you say is a very good point. In general, in these reviews, we have tried to look at the highest level of data that's available, and then we look to see is it credible in supporting its findings. And we look for things like multiplicity, selective reporting of the population, blinding, adverse events, especially adverse events because the absence of proof is not proof of absence. Rare events happen rarely, and so a small trial wouldn't come up with

them.

I think the blinding remains an issue. I think body odor has been reported in ALC trials. Before FDA, I was a clinical trialist for 30 years. And if you have -- tell that a patient's on an active substance, it changes things. And I think that that's something that you have to take into account with all of these trials.

I think it's also important to be careful and mindful of the jump from a finding to clinical significance. And in all drugs that are approved, clinical significance, the meaningfulness of a result is taken into account.

That's especially true of pain. Pain is terrible. And if you have a person who has pain and you reduce it 40 percent by a scale, and you ask that person, is this important, it may not be because 40 percent less of a terrible pain is still a terrible pain. So that's an important part of the equation of effectiveness.

Then, with regard to indications, or not indications but uses that we didn't look at -- we

have backup slides if people want to see -- there's a whole list of things that were asked of us to review but could not be assessed because there is either no meaningful data or it was never used in humans, or they were for uses that really didn't indicate a disease. And I would point out the antioxidant feature of many compounds.

It's very difficult to -- it's very easy to show in an animal that something might have an antioxidant effect, but to translate that to human efficacy, well, there have been very large trials looking at very potent mitochondrial antioxidants that did not bear fruit.

So it's one thing to see a biochemical finding in an animal and to see an actual physiologic benefit in humans. So these were all some of the considerations that we had in looking through the documentary support of the nominations.

DR. GULUR: Thank you. Dr. Cohen on the phone has a question.

DR. COHEN: Thank you. Can you hear me?

DR. GULUR: Yes.

DR. COHEN: Okay, good.

Dr. Day, thanks so much for the presentation. A quick question. As you were concerned that Dr. Bergmann didn't address all of the conditions, discuss why he didn't discuss Alzheimer's. And I guess the follow-up question to that is, as far as compounding, what's the most common indication of ALC? Thank you.

DR. DAY: Thank you. Very good questions. So the utilization in compounding does not really reach much into Alzheimer's. I haven't -- personally from the prescriptions I've dealt with, as well as the compounding pharmacists that I've networked with and asked as preparation for this meeting, we are not using it much in Alzheimer's, if at all. In fact, nobody -- let me rephrase that to say at all. That's why I did not address it.

So throughout this process, throughout these meetings, we will see a lot of instances where the FDA's presentation addresses several different indications and utilizations, potential

utilizations, that are not necessarily utilized commonly in compounding. And I think in our October meeting, we discussed this as well.

So some of these indications were put forth in the nomination process back in the months following the 2013 signing of the law when we were asked to nominate the substances, how might it be used.

So we put together all sorts of information from literature that was available, clinical trials that had been done previously or were currently underway, or had been proposed as potential uses. We did not really have a good roadmap for this process, and what the expectations are by way of levels of evidence, and what the process looks like.

So there are a number of potential uses that a substance was nominated for that I don't have clinical data, and that the compounding community does not have clinical data to provide to support those potential uses. If it would be of benefit to the committee and to FDA staff in reviewing the

materials, we'd happily have a debrief with FDA prior to the materials being reviewed by their internal divisions so that we can help them narrow it down.

That may not be possible because it may be a formality that since it was submitted for certain uses that it has to be reviewed for those uses. I don't know. But it's something that we are definitely open to discussing.

Specific to the second part of your question on acetyl-L-carnitine utilization in compounding, I think it goes back to what Dr. Pham asked with the first question. We do primarily see it for drug-induced neuropathies, whether it's chemo, HIV, or even diabetic neuropathy, which is not necessarily drug induced.

We've seen it more recently utilized a little bit for male fertility, but the data is very promising, and the patient outcomes seem quite good. And then there is a small cohort that is utilizing it for pediatric mitochondrial and metabolic disorders.

DR. GULUR: Any further questions?

(No response.)

Committee Discussion and Vote

DR. GULUR: Thank you, Dr. Day.

Since the agency did not receive registrants for the open public hearing session, we will move on to the committee discussion and voting. So we will now begin the panel discussion portion of the meeting. We will start with aloe vera.

Dr. Pham?

DR. PHAM: Just to recap because the sequence of the FDA presentation then the nominator presentation, it seemed like some of the questions from the FDA came back to how is it defined. So after hearing the definition of the aloe vera, 200 to 1, is there still that valid concern from the FDA side?

I'm trying to get a feel for the risks that are still now present with that definition from the nominator.

DR. TAYLOR: Hi. I'm Cassie Taylor. I'm on the botanical review team. We appreciate that the

nominator did explain that it was the gel that they were using, but it's still a concern for us because it's not well characterized. Even if it is just the gel as we looked at before the USP monograph only talks about the aloin, which is the anthraquinone, which is not sufficient from a quality perspective.

DR. GULUR: Any further questions?

(No response.)

DR. GULUR: Moving on to D-ribose.

(No response.)

DR. GULUR: If there are no further questions on that, we'll go on to chondroitin.

(No response.)

DR. GULUR: Any questions for acetyl-L-carnitine? We have a question from Dr. Cohen on the phone.

DR. COHEN: Yes, it's not so much a question as much as a comment. You know, I've seen a lot of medications used for diabetic neuropathy as well as ALS. This is what I do as well as chemotherapy induced peripheral neuropathy. And there's a lot

of initially promising results with compounds. A lot of literature gets published, but the follow-up on it unfortunately for me, and particularly for my patients, is disappointing.

In reviewing the papers that were listed in the bibliography, the nerve conduction studies I think we can forget about. The changes are within, I feel, a margin of error.

Visual analog scale is something that a lot of times ends up being positive initially and not subsequently. In the study of the use of ALC in ALS, I know the investigators and I know the study. And as much as we were initially excited about it, unfortunately, that really hasn't panned out.

So I understand the enthusiasm of Dr. Day and the hope that it would be something that would really change clinical course. I mean, I feel the same way. But unfortunately, a lot of these are just [indiscernible], I think, as Dr. Bergmann said. So thanks.

DR. GULUR: Thank you, Dr. Cohen.

If there are no further questions, we will

now end our discussions and start the vote.

(No response.)

DR. GULUR: 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 3 times. After everyone has voted, the vote will be complete.

Voting will be on the four drug products just presented. All vote questions relate to whether these products should be included on the 503A bulk list. 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.

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

corresponding button again.

Starting with the first question, vote yes, no, or abstain for this question. FDA is proposing that aloe vera freeze dried 200 to 1 not be placed on the 503A bulk list. Should aloe vera freeze dried 200 to 1 be placed on the list?

So just for clarification, if you vote yes, you are recommending placing these drugs products on the difficult -- allow me to read you the right one.

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

Do the committee members have any questions on how to answer?

(No response.)

DR. GULUR: Thank you. So the vote again,

FDA is proposing that aloe vera freeze dried 200 to 1 not be placed on the 503A bulk list. Should aloe vera freeze dried 200 to 1 be placed on the list?

(Vote taken.)

DR. GULUR: We're just waiting for Dr. Cohen's vote to come in by email. Having been on the other side, I can assure you it takes time, so thank you all for your patience.

DR. HONG: So question 1 for aloe vera. It is 1 yes, 9 noes, zero abstain.

DR. GULUR: We will start with the member comments. We'll start with the voting members.

Dr. Wall, would you like to start?

DR. WALL: I voted yes. I thought that there is a use for it, and I thought that the risk or the safety -- the risk was very minimal.

DR. CAROME: Mike Carome. I voted no because of a lack of characterization of what is a complex mixture of compounds. There's some animal carcinogenicity data, and there's really a lack of data in humans on pharmacokinetic safety and

efficacy and quality.

DR. GULUR: Thank you.

DR. VAIDA: Allen Vaida. I voted no because it would be hard to ensure the quality and consistency of the product.

DR. PHAM: Katherine Pham. I also voted no based on not really seeing enough data or significant benefit to balance the hesitations we have on its aloin content and the quality issues.

MS. JUNGMAN: Elizabeth Jungman. I voted no for similar reasons. I wasn't convinced that there was a clinical need that the product fills that make it worth the uncertainties that are created by the poor characterization and the lack of evidence specific to wound care.

DR. DIGIOVANNA: John DiGiovanna. I voted no because of the lack of characterization. However, it is a little unusual to have such a widely used drug orally, and a drug that quite frankly is thought by so many people to be useful for these indications.

So I wonder if there could be a better

characterization or a better understanding of exactly what the compound is, if perhaps this might be reconsidered at some point with a specific characterization.

MR. HUMPHREY: William Humphrey. I voted no for the lack of characterization of the product as well.

DR. HOAG: Steve Hoag. I voted no for the lack of characterization. And also there are products available on the market.

MS. DAVIDSON: Gigi Davidson. I also voted no because of the lack of characterization. And I wasn't really clear on the role of the aloin and the lack of anthraquinone activity in the freeze-dried product. I wasn't clear on that.

DR. GULUR: Padma Gulur. I voted not to put it on the list for similar reasons that have been stated, lack of characterization, available alternatives, and unclear clinical benefit.

So we will move on with that to the next vote. Vote yes, no, or abstain for this question. FDA is proposing that D-ribose not be placed on the

503A bulk list. Should D-ribose be placed on the list?

(Vote taken.)

DR. HONG: Okay. For D-ribose, we have 1 yes, and 10 noes, and zero abstain.

DR. GULUR: Thank you. We'll follow a similar pattern. If the voting members could please, starting with Dr. Wall, give us their comments.

DR. WALL: I voted no because even though my heart went out to the chronic fatigue folks, I just didn't feel like the data was there.

DR. CAROME: I voted no primarily because of the lack of any good efficacy data for the two proposed uses.

DR. VAIDA: I voted no because can't control the indication and there really wasn't really good data for the heart disease.

DR. PHAM: I also voted no. I do appreciate the recommendation for chronic fatigue, but ultimately went with the recommendation from the Office of New Drugs and the fact that it would be

still available through another way to purchase.

MS. JUNGMAN: Elizabeth Jungman. I also voted no. While concerned about the unmet medical need, I felt like the balance of factors weighed against it.

DR. DIGIOVANNA: John DiGiovanna. I voted no because I agreed with the FDA assessment.

MR. HUMPHREY: William Humphrey. I voted no for similar reasons already stated.

DR. HOAG: Steve Hoag. I voted no for reasons already stated, and I was concerned about the efficacy.

MS. DAVIDSON: Gigi Davidson, and I voted yes because of the chronic fatigue patients. I felt like it couldn't hurt. And I also am concerned about the quality of the products that are on the market. There seems to be quite a variable quality on what's available.

DR. GULUR: Padma Gulur. I voted no for reasons already stated with regards to the efficacy. The chronic fatigue indication did show there was a recommendation to add it, however, I

felt the data was not compelling enough.

DR. BUCKLEY: Lenore Buckley. I think there's a tremendous unmet need, but I thought that the data essentially was totally inadequate.

DR. GULUR: Moving on to our third question, please vote yes, no, or abstain. FDA is proposing that chondroitin sulfate not be placed on the 503A bulk list. Should chondroitin sulfate be placed on the list?

DR. HOAG: A point of question. Did the previous say for topical or is that --

DR. GULUR: This says just for any indication. Am I correct? The question currently is asking if chondroitin sulfate should be placed on the 503A bulk list or not, not a particular indication. Correct?

(Commander Muniz nods affirmatively.)

DR. GULUR: So to reaffirm -- yes?

DR. HOAG: Well, the documents are nominated for topical use, so we're changing this to general?

DR. GULUR: I believe they covered other uses, but I'll allow the FDA to comment.

MR. FLAHIVE: This is Jim Flahive. Since it was looked at for topical, then we should vote on it for topical. Yes, we will change the question to topical.

DR. GULUR: All right, so we will change the question. Do you want to do that?

FDA is proposing that chondroitin sulfate not be placed on the 503A bulk list for topical use. Should chondroitin sulfate be placed on the list for topical use?

(Vote taken.)

DR. HONG: For chondroitin, we have zero yeses, 10 noes, and zero abstain.

DR. GULUR: Thank you. Starting again with Dr. Wall, if we could have your comments.

DR. WALL: I voted no for the reasons as mentioned by the FDA.

DR. VAIDA: I voted no because of I didn't think there was enough data to show it works and good data on the strengths.

DR. PHAM: Katherine Pham. I also voted no for similar reasons and also for the existence of

other safer and effective alternatives.

MS. JUNGMAN: Elizabeth Jungman. I voted no because there are other alternatives available with more demonstrated effectiveness.

DR. DIGIOVANNA: John DiGiovanna. I voted no because I agreed with the FDA assessment.

MR. HUMPHREY: William Humphrey. I voted no because of the lack of clinical evidence as a topical dosage form.

DR. HOAG: Steve Hoag. For all those reasons, I voted no. And also, I think every textbook on transdermal absorption would have to be rewritten if polymers that big would be actually absorbed.

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

DR. GULUR: Padma Gulur. I voted no for, as Dr. Hoag pointed out, clearly it's unlikely to be absorbed.

DR. BUCKLEY: Lenore Buckley. I voted no for lack of efficacy data.

DR. HONG: Dr. Vaida, could you just state

your name and vote for the record one more time? I don't think you stated your name in the beginning.

DR. GULUR: Dr. Vaida? If you could please state your name for the record.

DR. VAIDA: Pardon me?

DR. GULUR: They would you like you to state your name for the record and your vote.

DR. VAIDA: Allen Vaida, I voted no.

DR. GULUR: Thank you.

Moving on to our last question. Vote yes, no, or abstain for this question. FDA is proposing that acetyl-L-carnitine not be placed on the 503A bulk list. Should acetyl-L-carnitine be placed on the list?

(Vote taken.)

DR. HONG: For question 4 for acetyl-L-carnitine, we have 1 yes, 10 noes, and zero abstain.

DR. GULUR: We will start with the member comments again with Dr. Wall.

DR. WALL: Donna Wall. Although there's a lot of interesting things with the

acetyl-L-carnitine, until I know more answers with renal elimination and this problem with seizures, I don't feel I can yes.

DR. CAROME: Mike Carome. I voted no, again because of concerns of a lack of good evidence of effectiveness.

DR. VAIDA: Allen Vaida. I voted no because of lack of evidence for effectiveness, and also the various dosage forms, dosage routes.

DR. PHAM: Katherine Pham. I voted no because it has the same toxicities and drug interactions as the L-carnitine that's currently marketed. So although I appreciate the expanded uses, perhaps it's something that the currently marketed product could also investigate scientifically for labeled use.

MS. JUNGMAN: Elizabeth Jungman. I voted no because I wasn't persuaded of the clinical need or effectiveness.

DR. DIGIOVANNA: John DiGiovanna. I voted yes because I was persuaded by the difficulties with chronic pain for peripheral neuropathy and in

particular HIV disease, where standard measures tend to be inadequate occasionally. And I think this is a potentially useful for some patients.

MR. HUMPHREY: William Humphrey. I voted no because I wasn't convinced by the clinical efficacy.

DR. HOAG: Steve Hoag. I voted no for concerns about the efficacy.

MS. DAVIDSON: Gigi Davidson. I voted no because although it's slightly more bioavailable than L-carnitine, I believe that L-carnitine is better characterized and might have similar effects at a higher dose.

DR. GULUR: Padma Gulur. I voted no for reasons that have already been stated regarding the efficacy of the drug and the safety profile.

Dr. Cohen?

DR. COHEN: Yes, Jeffrey Cohen. I voted no because of the lack of clear efficacy.

DR. GULUR: Do we have any words from the FDA officials as we conclude day 1?

MS. AXELRAD: No, except to thank everyone

for their thoughtful questions and deliberations. And we very much appreciate the time that you've taken, and we look forward to talking about a different subject tomorrow.

DR. GULUR: Yes, Dr. Davidson?

MS. DAVIDSON: I just wanted to make a point of clarification about the various USP monographs that are out there. This afternoon's session, there were two monographs referenced as dietary supplement monographs, 1 proposed and 1 existing, for D-ribose and L-carnitine.

Those are food monographs in the food chemicals codex. And I wanted to make the distinction between those, that a dietary supplement monograph and a drug monograph are in the book in USPNF. Food monographs are in the FCC, and I don't know if FDA cares to make comments on the applicability of food monographs.

MS. AXELRAD: I don't think we think that they're applicable monographs. As we've said, it has to be a drug monograph for us to consider it an applicable USP or NF monograph.

Adjournment

DR. GULUR: Thank you for that clarification from both of you. I think it was helpful for most of us to have that.

With that, we will adjourn for today and reconvene tomorrow morning at 8:30, and look forward to another interesting day. Thank you.

(Whereupon, at 4:06 p.m., the afternoon session was adjourned.)