FOOD AND DRUG ADMINISTRATION CENTER

FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Monday, November 20, 2017

1:48 p.m. to 5:11 p.m.

Afternoon Session

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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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

(1:48 p.m.)

DR. GULUR: Welcome back, everyone. As had been decided, we will be starting the meeting at this point. We will now proceed with the FDA presentation on astragalus by Dr. Brave.

FDA Presentation – Michael Brave

DR. BRAVE: Good afternoon. I'm Michael Brave, a clinical reviewer from CDER's Office of Hematology and Oncology Products, and I reviewed the nomination for astragalus.

I'd like to acknowledge and thank my colleagues listed here who participated in this review. Astragalus extract 10:1 has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act.

The suffix 10:1 presumably implies a water or aqueous ethanol extract with 10 grams of the astragalus root producing 1 gram of the extract, although this is unclear.

The uses for which astragalus extract 10:1

has been nominated are diabetes mellitus, allergic rhinitis, wound healing, asthma, and herpes simplex keratitis. The nominator did not propose more narrow indications within any of these disease categories. The proposed route of administration is oral. The references provided in the nomination contain both clinical and non-clinical information.

In traditional Chinese medicine, astragalus preparations were made from the root of 1 of 2 plant species. The nominator clarified, in response to an FDA information request, that the nominated substance is derived from the root of astragalus membranaceus. However, the process to determine the consistency of the compounds in the nominated substance was not specified. For example, growing conditions like temperature, and rainfall, and the harvesting process all affect the final botanical substance.

Approximately 100 potentially bioactive compounds have been identified from the astragalus root and its extracts. These include polysaccharides, saponins, flavonoids, amino acids,

and trace elements. Known compounds account for a small percentage of the whole astragalus plant.

In vitro data suggest that some astragalus components have biological properties, including immunomodulatory antioxidants, antitumor, antidiabetic, antiviral, hepatoprotective anti-inflammatory, anti-atherosclerotic, and neuroprotective properties. We found no data linking any particular class of compounds to a given clinical effect.

Astragalus is listed in the pharmacopeia of the People's Republic of China as well as the Japanese pharmacopeia and the European pharmacopeia. Astragalus roots and extracts are widely marketed in the U.S. as dietary ingredients of dietary supplement products, including mixtures made from astragalus root and other botanical and non-botanical ingredients.

These products are often complex without characterization and quantification of even the most abundant classes of molecules. Potential impurities or contaminants in a given astragalus

extract include residual organic solvents used in the manufacturing and purification process, heavy metals such as lead, arsenic, or mercury linked to the source of the starting material, and microbes such as yeast or mold and their metabolites, such as aflatoxins.

To summarize the characterization of astragalus, its root and extracts are used in traditional Chinese medicine and contain a complex mixture of compounds. Insufficient information was provided to fully characterize the nominated substance.

In the next several slides, I will discuss publicly available information regarding the non-clinical toxicology of astragalus. Astragaloside-IV is a saponin isolated from astragalus membranaceus. It is purported to be one of the biologically active substance in astragalus based on non-clinical studies. Pharmacokinetic studies of Astragalus IV in the rat and dog have been published.

The review team found no toxicity studies

conducted with the nominated substance, astragalus 10:1. We did, however, find repeat-dose toxicity studies of an extract of the astragalus root and of cycloastragenol, a triterpene aglyclone extract of the astragalus root.

Yu and colleagues conducted a study in the rat in which an astragalus root extract was administered via the intraperitoneal route, 2 rats, at doses between 5.7 and 39.9 grams per kilograms daily for 90 days, and to beagle dogs at doses between 2.85 and 19.95 grams per kilogram daily for 90 days. It was reported that toxicity was not observed in either species.

Szabo and colleagues administered cycloastragenol orally to rats at doses between 40 and 150 milligrams per kilogram daily for 91 days, and again, no toxicities were reported.

The review team found both positive and negative published results of Ames' chromosomal aberration assays of various astragalus extracts. No information was found specifically for the nominated astragalus 10:01 preparation, and we

found no published carcinogenicity studies.

Regarding reproductive toxicity, we identified two published studies in which Astragaloside-IV was administered to the rat and/or rabbit at key times before mating, during gestation, and/or during lactation. These studies reported a decrease in body weight gain in dams compared to untreated controls, increased incidences of fetal death and developmental delay in offspring. No teratogenic effects were observed.

To summarize published non-clinical information on astragalus, there are no toxicology data that we can specifically associate with the nominated 10:1 extract. No toxicity was observed in repeat-dose studies of unspecified astragalus extracts in the rat or dog.

The genotoxic potential of astragalus is unknown. We identified no carcinogenicity data. And finally, fetal deaths were observed in the rat and rabbit dosed with Astragaloside-IV.

Now, I will discuss published clinical

information on the use of astragalus, starting with safety followed by pharmacokinetic, and finally clinical efficacy data.

Regarding safety, most published reports of the clinical effects of astragalus do not analyze or discuss adverse reactions. Whether most clinical studies systemically collected this data is uncertain. The FDA adverse event reporting system, or FAERS, contained no reports specific to astragalus.

Much of the information available about the clinical toxicity of astragalus comes from the Center for Food Safety and Nutrition's adverse event reporting system, which receives adverse event reports related to food, cosmetics, and dietary supplements.

On June 27, 2017, the review team searched the CAERS database for adverse events associated with astragalus. This search retrieved 547 cases. Four deaths were reported. None of these 4 deaths were associated with astragalus as the sole active substance in the ingested product or products.

In only seven reports was astragalus the sole active substance ingested. Most cases reported multiple organ systems affected simultaneously. Many of these reports described what sounded like a generalized acute illness characterized by malaise plus symptoms from several organ systems such as diaphoresis, nausea, vomiting, diarrhea, headache, palpitations, dyspnea, et cetera.

In conclusion, few published reports of the clinical effects of astragalus analyzed or discussed adverse reactions. Whether most clinical studies systematically collected such data is uncertain.

The Center for Food Safety and Nutrition's adverse event reporting system contained 547 cases as of June 27, 2017. Many of these reports described what sounded like an acute systemic illness with multiple simultaneous symptoms.

The review team found no published pharmacokinetic data for astragalus 10:1. We did, however, find a pharmacokinetic study of

Astragaloside-IV, the previously mentioned saponin extracted from astragalus, and thought to mediate some of its pharmacological activity.

Xu and colleagues studied the pharmacokinetics of Astragalus IV in a dose escalation trial of 40 Chinese healthy volunteers. Each volunteer received a single dose of Astragaloside-IV between 200 and 600 milliliters.

Single-dose oral pharmacokinetics were linear over the 200- to 500-milliliter dose range. Only 4 percent of Astragaloside-IV was excreted unchanged in urine and accumulation was not observed in a subset of 16 volunteers, given 500-milliliter doses daily for 7 days.

The next several slides describe reports of clinical trials with astragalus. In general, these reports provide little detail about trial methodologies such as the astragalus preparation used, the patient population enrolled, or the statistical analysis plan. Their conclusions generally suggest minor treatment effects on subsets of assessed endpoints. As such, we cannot

conclusively interpret these findings as substantive to clinical benefit.

Tian and colleagues performed a meta-analysis of 13 clinical trials enrolling a total of 1,054 subjects, comparing astragalus by oral or intravenous administration to usual care in patients with type 2 diabetes mellitus.

All 13 trials were conducted in China. The analysis concluded that astragalus by either route of administration reduced fasting plasma glucose, postprandial plasma glucose, and insulin sensitivity. Only the aqueous decoction reduced hemoglobin A1c levels.

Li and colleagues performed a meta-analysis of 21 randomized controlled trials and 4 uncontrolled trials of unspecified mixtures of astragalus, which enrolled a total of 1804 patients with diabetic nephropathy. All trials were conducted in China. The analysis concluded that astragalus may improve proteinuria and serum creatinine levels in these patients.

Kim and colleagues reported one case of a

62-year-old man with diabetic nephropathy who obtained short-term improvement in proteinuria and glomerular filtration following an unspecified regimen of astragalus membranaceus extract.

Chao and colleagues randomized 43 patients with newly diagnosed type 2 diabetes mellitus to traditional Chinese mixtures of 3 herbs, including astragalus versus placebo 3 times daily before meals.

At 3 months, patients in the investigational arm were reported to have improved insulin resistance compared to baseline. It's not possible to conclude which components of the ingested mixture was responsible for the observed effects.

Lien and colleagues performed a retrospective analysis comparing 416 Taiwanese patients with type 1 diabetes mellitus, whose treatment included traditional Chinese herbs, some of which contained astragalus, to 1608 matched case control patients with diabetes mellitus who did not use traditional Chinese herbs. The analysis concluded that in patients with type 1 diabetes

mellitus, Chinese herbal therapy may reduce the incidence of diabetic ketoacidosis.

Pang and colleagues performed a meta-analysis of 16 randomized controlled trials which enrolled 1,173 total patients of a traditional Chinese mixture of several herbs, including astragalus root, for the treatment of patients with diabetic peripheral neuropathy.

All trials were conducted in China. The analysis concluded that patients in the investigational arms had improved neurologic symptoms and nerve conduction velocities.

Matkovic and colleagues randomized 48 adults with seasonal allergic rhinitis to 6 weeks of treatment with an herbal mineral complex containing astragalus membranaceus versus placebo. The authors found patients in the active treatment group to have a trend toward symptomatic improvement, but no significant changes in serum immunoglobulin levels or nasal eosinophils. It is not possible to conclude which compounds or components of the herbal mixture was responsible

for the observed effects.

Ko and colleagues randomized 16 patients with type 1 or type 2 diabetes mellitus and mild diabetic foot ulceration to a traditional Chinese mixture of 2 roots, one of which was astragalus versus placebo twice daily.

At 6 months, patients in the investigational arm showed a trend toward improved wound healing. Again, the active treatment here composed multiple herbs, so one cannot conclude which was responsible for the observed effects.

Wong and colleagues randomized 85 children with asthma who were using inhaled corticosteroids to receive a daily oral combination of 5 herbs, including non-specified astragalus species versus placebo for 6 months. The trial failed to show a reduction in steroid dose, improved lung function, or effects on biochemical markers of disease.

A meta-analysis by Bang and colleagues of 18 randomized controlled trials of pharmacoacupuncture, which is the injection of herbs via syringe at specific points, included four

studies using the astragalus root. The authors suggested that the treated groups had improved lung function compared to the groups receiving conventional asthma therapy.

We found no published reports of astragalus affecting clinically meaningful endpoints in patients with herpes simplex keratitis.

In summary, published reports have concluded that astragalus, or herbal preparations which include astragalus, may favorably affect certain aspects of diabetes mellitus, allergic rhinitis, wound healing, and asthma. Most of these reports appear in alternative or traditional Chinese medical publications.

Most involved the administration of multiple herbs, none of which appear to have been the nominated 10:1 substance. Few reports had specified statistical analysis plans to analyze clinically meaningful efficacy endpoints, and we found no reports of long-term efficacy or safety of astragalus for any indication.

Astragalus has been used in traditional

Chinese medicine for thousands of years. Insufficient information is available to determine if the nominated substance astragalus 10:1 has been used in compounding. A chief reason for this uncertainty is that the manufacturing process to produce this substance is essentially unknown. Since these processes determine the chemical ingredients, the nominated substance cannot be well characterized.

In summary, because the manufacturing processes used to produce astragalus extract 10:1 are unknown, the substance cannot be adequately characterized. Non-clinical safety data are incomplete, but fetal deaths were observed in the rat and rabbit dose with Astragaloside-IV, a component of astragalus.

Although no efficacy or safety studies have, to our knowledge, been conducted with the nominated formulation, astragalus extract 10:1, a review of the Center for Food Safety and Nutrition's adverse event reporting system contains many reports of an acute systemic illness.

In non-clinical models, certain astragalus extracts and astragalus-containing herbal mixtures seem to show limited treatment effects and suggest potential therapeutic value for patients with diabetes mellitus, wound healing, asthma, and herpes simplex keratitis. However, these effects have not translated into conventional measures of clinical benefit in any of these patient populations.

While astragalus preparations have been used in traditional Chinese medicine, we do not have information to determine whether the nominated substance has been used in compound.

Based on a balancing of the four evaluation criteria, the review team found that astragalus is not a suitable substance for compounding under Section 503A of the Food, Drug, and Cosmetic Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you. Clarifying questions from the committee? Dr. Carome?

DR. CAROME: Mike Carome. For a product

like this, what would FDA require or like to see in terms of characterizing it normally?

DR. BRAVE: If the product were a drug going through the additional NDA process, the requirements would be extensive. I'm not a chemist, so I don't want to specify exactly, but there would be a lot of requirements.

DR. GULUR: Dr. Burman?

DR. BURMAN: It seems like the main potential utility is for diabetes, and yet all of the standard measures, such as hemoglobin A1c, lipid profile, urine, microalbumin, and retinopathy, nephropathy, et cetera, are all lacking from these studies. And they don't appear to be controlled, either.

DR. BRAVE: Yes, that's correct.

DR. GULUR: Questions from our members on the phone?

(No response.)

DR. GULUR: Thank you very much.

DR. BRAVE: Thank you.

DR. GULUR: We have one nominator

presentation, Mr. Wynn.

Nominator Presentation – Tom Wynn

MR. WYNN: My name is Tom Wynn, and I was here earlier, so I know you all know my background. And I promise not to pick on Charles and his drink choice with this particular talk.

So we did nominate astragalus, so with that, astragalus membranaceus is a small bushy perennial plant, also referred to as Huang Qi, if I'm saying that right. The root is traditionally used for medicinal purposes. And pretty much the FDA went over that same. It's definitely a traditional Chinese medicine.

So for characterization, I do have a little bit to speak about that in that, right now there is currently a USP designation for astragalus. It is not in the regular database. It is in the nutraceutical database for that, but at least that does give some idea of what factors we're looking at for astragalus and where we want it to fall, and here that it contains not less than 99 or 100 percent of labeled amounts of the cell

[indiscernible] and isoflavonoids calculated on a anhydrous basis.

So at least now, we have some idea of what we'd be looking for as a supplier or manufacturer of the powder, we'd be looking for to try to get a better handle on that particular extract.

I also was able to find in characterization 2 that they have put together -- as far as the GAP, which is the good agricultural practices, they started to look at that in China in 2002. And to what we were talking about or what was mentioned about monitoring the management of the growing field and controlling disease and pests and harvesting, packaging, storing, transporting, all that was looked into. And as of 2010, they actually had adopted 99 different traditional Chinese medicines to adhere to these standard operating procedures for growing agricultural practices.

So they're trying to put together a way that they can keep this characterization under control. And they also had, as of 2010, 22 different Chinese

provinces that were adhering to these practices.

So I think there is some information out there that astragalus membranaceus is now in that good agricultural practice. So it's one that is being helped to be characterized by controlling these different environmental factors in the growing of the actual plant.

Also, I did find a study where they were looking at, again, methods for analyzing the different Chinese herbal complexes. And in this particular study, they were looking at astragalus again as well.

They tried to put together kind of a flow chart of how you go about pulling out the different components to try to do an HPLC measurement and get an idea of the different components that are in there using everything from pure water to methanol and water and isopropyl methanol, different combinations. This is the process that they put together, they felt was best, and they called it the HPLC unified method.

So there are methods out there where they're

trying to help characterize, again, the different traditional Chinese medicines, and astragalus was instituted in this particular program as well or looked at for this process as well.

As far as safety goes -- and I think a lot of these studies were talked about with the FDA, too. This one that we found was actually done in rats, and they were actually given 5,000 milligrams from the astragalus, but it was also a combination of three standard extracts there, so again, I guess it wasn't necessarily just the one particular extract.

They did the combination, but they did not really see that there were a lot of adverse effects in the mice when putting that together. So I still think it kind of talks to the idea of safety with astragalus.

This next study here, again, it was a treatment of patients for allergic rhinitis, and they didn't find any adverse events with this. They did treat 48 different patients for 6 weeks. It was a double-blind placebo-controlled. Again,

the astragalus was just a component of the complex, but again, it does go to show, as far as safety, anyway, not necessarily if we were trying to look at effectiveness in this particular study, that even though it was in the complex, there were not any adverse effects associated with the study. So it's again adhering to at least the safety component of astragalus.

Here's another study where they were looking at allergic asthma again. This particular one, the purpose was to determine whether herbal injections could suppress allergic-induced mucus secretions in mice. And the results indicated that it does have a potential role in treating allergic asthma.

This particular one was an injection, which is not necessarily the more common way we might see this as a compounder to utilize it, but it does show that there was some potential in helping with allergic asthma with the astragalus.

Then this second study also with allergic rhinitis again, this particular one was with 48 adults. And this study revealed a number of

positive signals indicating therapeutic effectiveness. But again, this one was compared to placebo. This one was, again, another herbal complex, though. And I realize that this drug has been in there. We are showing the effectiveness, but again, we have the other group in there as well, which could possibly dilute some of that data.

For herpes simplex, I know this was one that they mentioned that they felt that there wasn't a very significant amount of data from it. They did actually treat 62 patients in this particular study. Or I should take that back. There were 106, but then 62 were healthy individuals.

In this particular one, they did see improvement in immune function that showed some significant improvement for herpes simplex. So I thought there was a little bit more significance than what maybe might have been mentioned.

There was a fair number of people that they actually treated and compared to some of the other studies, even some of the other studies we saw

today at 100 participants anyway, so I think it was still worth mentioning.

Wound healing is probably the one where I think astragalus might find its most potential use. I know there were a lot of things that were nominated. At the time that we did nominate this particular chemical or Chinese herbal medicine, we kind of put down everything that we thought it potentially could be treated for.

So wound healing was one that I felt was probably more of its niche, if you will.

As far as wound healing goes, there's a few things out there that maybe you can utilize that are commercially available, but a lot of times, wounds don't necessarily respond to all the treatments that we have available, so it's nice to have another option.

In this particular study, they were looking at astragalus again, and they saw they had a high potential in wound healing. This mechanism is associated with inhibiting inflammation, accelerating cell cycle, and promoting secretion of

repair factors. So this is just a nice example of another option that we could have for wound healing.

Again, this second study here, this one here, was actually done in animals. This particular one, again, was IV treatment, but again, I think we're getting the chance to see that the product was helping with both healing and had some anti-scar effects as well in the wound treatment, but this one was an animal study.

In conclusion, astragalus does have a monograph now. It has a USP dietary supplement monograph, so it does get specifications as to what it needs to be, which will help with the characterization of the product.

Astragalus has shown some safety, both animals and human studies that we have presented. I think that, as far as effectiveness, again, wound healing I think has its best place, but herpes simplex, allergic rhinitis are both areas to where it did show some efficacy in the studies that we presented.

Clarifying Questions from the Committee

DR. GULUR: Thank you. Clarifying questions from the committee members? Dr. Davidson?

MS. DAVIDSON: What is the significance of the 10 to 1 ratio? I read through the nomination and FDA's follow-up message for clarification. What is that, and why did you nominate that instead of one of the other three forms of astragalus that has dietary supplement monograph? I'm just curious.

MR. WYNN: I think the 10 to 1 was just the way that it was actually provided to us from the actual manufacturer of the powder. And so we included that on because that was its designation to us. They were letting us know it was a 10 to 1 extract, that they were taking 10 parts of the root to 1 part.

I guess, in hindsight, I almost wish that we would have just left that off because it's something that provides from -- they're telling us that's where the powder comes from, how they're doing it. And that's the only reason that we put

it on there, because when it comes to us from that particular supplier of the powder, they called it a 10 to 1 just showing us what they had done.

DR. GULUR: Dr. Hoag?

DR. HOAG: Quick question. Is what you're proposing the same as what's in the USP, the same in the JP, and the same as the Chinese? Are they all the same thing? Are there differences?

MR. WYNN: Do you mean is the 10 to 1 the same as the powder? The 10 to 1 from my knowledge is what the compounders are going to be able to get. My colleague might have an answer to that question, if I could have Kim come up. She was involved in helping me put this together.

DR. GULUR: Could you come to the microphone, please? And please introduce yourself.

MS. KIEFFER: Hello, I'm Kim Kieffer from Fagron North America. The material that we were supplying is astragalus membranaceus. The 10 to 1 is how they standardize. They take 10 parts of the root to make 1 part of the extracted powdered material.

So as long the monographs, and the JP, and USP, et cetera are for the membranaceus, then yes. And actually, I think the USP specifies some other forms of astragalus as well.

DR. HOAG: Does that imply that you have a variable extraction process? Did you get that 10 to 1 ratio? Do you worry about the phytochemical profile in there at all? The USP had something like not less than.

MS. KIEFFER: Right. At this point, we don't supply that material anymore, but if we're going to continue to supply it, we would source USP material at this point because that USP monograph now exists.

DR. GULUR: Could you clarify? The USP monograph now exists?

MS. DAVIDSON: There are actually three, but they're all dietary supplement monographs, which are not applicable to this process.

DR. GULUR: Dr. Johnson?

DR. JOHNSON: The folks from the botanicals review who reviewed astragalus would like to make a

comment.

DR. LI: This is Jing from the botanical review team. Based on my understanding, and the knowledge, and searching from the different pharmacopeia, including USP pharmacopeia for the astragalus, there is only the powder for the root and extract and no specific mention about the extract of 10 to 1.

DR. GULUR: A question for you would be, on this paper that you had brought -- I'm sorry, this is for the speaker -- on Zhao [ph], the wound healing effect of astragalus.

Could you comment on what they had used as their materials? When I read that description, it seems to indicate multiple materials were in there.

MR. WYNN: Right. I mean, it was the astragalus, but I think it was a complex as well of other -- I'd have to go back and look at that.

DR. GULUR: When I read it, there seems to be streptomycin, penicillin, a few other substances in there, and I'm just wondering how they came to the conclusion that the astragalus was the active

ingredient that resulted in wound healing.

Did you have a chance to look at that in further detail?

MR. WYNN: I'm afraid I did not.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: You described the good agricultural practices as a way of giving ourselves some assurance with regard to the characterization. I'm just curious about how you assure yourself that those practices are being followed, being implemented and following as a purchaser of them?

MR. WYNN: Sure. That's a very good point. You would have to be assured when you go to interview a possible supplier of that particular powder, how do you come about it; what kind of things? And I'm sure that the ones that are under those are going to present that we are part of this good agricultural practicing

So it's more or less before you're going to buy, something you're going to inquire about. And Kim wants to --

DR. GULUR: I guess a clarification we're

seeking is how would you compare this to the GMP practices, GAP [ph] practice there, and how are compounders here in the United States informed that they should be looking for these aspects when they interview Chinese manufacturers?

MR. WYNN: The compounders probably themselves are going to directly go to the manufacturer. They're going to go to a supplier, so then a supplier is the one that's going to make sure that they're following -- whether it be GMCP, FDA-approved, or anything of that nature. So I don't think there are too many compounders who are going to go directly to a supplier.

DR. GULUR: How many suppliers are there here in the United States?

MR. WYNN: Of astragalus?

DR. GULUR: Or who might potentially?

MR. WYNN: That I don't know just because we don't carry the preparation anymore at this time. We did at the time it was nominated, but now, we actually don't have it in stock.

DR. GULUR: Can you elaborate on why you no

longer carry this?

MR. WYNN: I don't think it was anything that was an issue of a problem with it. It was more or less, again, depending upon the usage possibly, how much that we were utilizing out. And then of course with changes that's gone with the monographs, we would want to change how we're going to search out those particular suppliers as well.

DR. GULUR: Thank you.

Any further clarifying questions, Dr. Jungman?

MS. JUNGMAN: I just want to understand the relationship between the nomination and the monograph. So are you suggesting that probably the thing to put on the bulk substance list wouldn't be this 10 to 1, but would be actually something that you'd find in the dietary supplement monograph?

MR. WYNN: What we're saying now is, at the time it was nominated, you didn't really have that to go by. Now, when you're going to want to go and search out a supplier of that particular API or powder, you're going to want to -- since that's

what you have, you're going to want to focus on that monograph to make sure that it's compliant with that.

MS. JUNGMAN: But we're voting on the 10 to 1. Is that different than what's in the dietary supplement monograph? Yes. Thank you.

MS. DAVIDSON: Just for clarification, the three dietary supplement monographs are astragalus root, astragalus root powder, and astragalus root extract.

Committee Discussion and Vote

DR. GULUR: We do not have any open public hearing speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion for astragalus.

The first question I'd like to pose to the FDA is it appears that the nominated substance is not something the nominators, for that matter, intend to move forward with. Is that of any pertinency, or are we expected to vote just on 10 to 1 and move forward with that?

MS. BORMEL: That was what nominated, so we evaluated that, and we would move forward with it because it is in the docket as a nominated bulk substance.

DR. GULUR: Thank you.

Any other clarifying questions from Dr. Davidson?

MS. DAVIDSON: If a traditional herbalist or Chinese medicine practitioner wanted to refer a patient for treatment with astragalus, would that be a problem if we don't put it on the list? Would they still be able to obtain the substance as a botanical or dietary supplement and still use it on their patients?

MS. BORMEL: Yes.

MS. DAVIDSON: I thought so, but I just wanted to clarify.

DR. GULUR: Dr. Desai?

DR. DESAI: Just to follow up on Dr. Gulur's question for the FDA, since we're only looking at 10 to 1, if the nominators or a future nominator wanted to revisit this on a different formulation,

that would go through the process again. Correct?

MS. BORMEL: Correct.

DR. GULUR: We will now end our discussions and start the vote. Do we have a question? I apologize.

MS. BORMEL: I just wanted to follow up on what Dr. Desai asked. We would look to see if that particular nomination was supported adequately by information that we hadn't yet evaluated.

DR. GULUR: Thank you. We will now end our discussions and start the vote. The question before us, FDA is proposing that astragalus extract 10 as to 1 not be included on the 503A bulks list. Should astragalus extract 10 as to 1 be placed on the list?

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

If there is no further discussion, we 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.

(Voting.)

DR. CHEE: We have zero yeses, 13 nos, and zero abstain.

DR. GULUR: Dr. Carome, if we could start with your comments.

DR. CAROME: I'm Mike Carome. I voted no. I was most concerned about the complexity of the compounds in this preparation and the lack of adequate characterization, and secondly data to support. Its long-term safety and effectiveness just doesn't really exist.

DR. HOAG: Steve Hoag. I voted no. The main reason was the characterization. There was

all these pharmacopeias, and it wasn't really clear how this materially relates to the pharmacopeia forms and things. I think the pharmacopeia has put a lot of thought and effort into defining what the material is and this lacked that.

MS. JUNGMAN: Elizabeth Jungman. I voted no for similar reasons. I would just add that the poor characterization made it unclear how the formulation in the available studies related to the formulation that would be used in practice.

DR. BOGNER: Robin Bogner. I voted no because there is now a monograph, and it wasn't clear what the 10 to 1 formulation was.

DR. PATEL: Kuldip Patel. I voted no due to the lack of comparative efficacy and also the physical and chemical characteristics.

DR. DESAI: Seemal Desai. I also voted no. I actually found the data presented both by the FDA and the nominator, particularly for diabetes and wound healing, to be interesting. But what wasn't really clear was how the 10 to 1 formulation would really interact with the studies and the different

versions that were presented, so I voted no for those reasons.

DR. GULUR: Dr. Wall, on the phone, if you could, give us your comments.

DR. WALL: I voted no because of the complexity of the physical and chemical properties and for the other reasons that were mentioned.

DR. GULUR: Dr. Humphrey?

MR. HUMPHREY: William Humphrey. I voted no for many of the same reasons, the lack of clinical efficacy and the confusion about the formulation.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: Gigi Davidson. I voted no. I still am not sure what 10 to 1 means, and I would have been more satisfied with the substance if it had been one of the ones that was monographed in the dietary supplements because those are very well characterized.

I was also influenced about the lack of knowledge about which of these forms were used in the clinical studies and was not convinced of efficacy and very compellingly was the fact that

the nominator no longer offers this substance for sale.

DR. GULUR: Padma Gulur. I would have to agree with everything that's been said so far, poorly characterized 10 as to 1 is unclear. What formulations actually have been used in the studies appears to be unclear. Efficacy, even in those studies, is questionable given the fact that multiple substances were used. So for all those reasons, I voted no.

Dr. Venitz on the phone?

DR. VENITZ: Jurgen Venitz. I voted no. Criteria number one, the lack of characterization, was kind of overriding anything else.

DR. VAIDA: Allen Vaida. I voted no for all the reasons that have already been mentioned, especially that the nominator doesn't even offer the product any more.

DR. BURMAN: Ken Burman. I voted no for basically the same reasons, the poor characterization physically and chemically. The extract is not well characterized and has not been

used alone in most studies. There are no long-term studies, safety not established, and with regard to diabetes, there's a lack of significant endpoints that we need to know.

DR. GULUR: Thank you very much. With that, we will not be taking the break that has been scheduled after this. We will take it after the next section. We will now proceed with the FDA presentation on EGCg by Dr. Johnson.

FDA Presentation – Susan Johnson

DR. JOHNSON: Good afternoon. I feel like my charge today is to echo what other folks have said with a slightly different effect. So I'm going to say similar things, but they're not the same, so I'd just encourage us again to think about the transitions between these.

My name is Sue Johnson. I'm from the Office of Drug Evaluation IV in CDER's Office of New Drugs. The nominated substance we're talking about now is epigallocatechin gallate or EGCg.

I'd like to thank members of the review team, especially contributors from the Division of

Metabolic and Endocrine Products, and Dr. Chambers from the Division of Transplant and Ophthalmology Products, who is an ophthalmologist if we have any specific questions.

EGCg has been nominated for inclusion on the 503A list. There are seven proposed uses, including weight loss and the treatment of obesity, diabetes, cardiac hypertrophy, corneal neovascularization, non-alcoholic fatty liver disease or NAFLD, Parkinson's disease, and wound healing. The proposed routes of administration include oral, ophthalmic, and topical.

EGCg is a polyphenol compound, specifically a catechin, which is a type of flavonoid. EGCg itself is a well-characterized compound. The nomination for EGCg states that the substance is intended to be added to the 503A list as a substance that contains at least 94 percent EGCg.

The components of the other 6 percent or up to 6 percent of the substance have not been identified to FDA. We considered the nominated substance and subject of our review to be EGCg.

This is not considered a botanical product. EGCg is soluble in water, but is unlikely to be stable under ordinary storage conditions, either as a solution or a solid.

EGCg can be chemically synthesized, but due to the complexities and expense of the process, it's typically extracted from green tea leaves. As we've noted in the other reviews, compounders should use the information in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues.

In conclusion, EGCg is well characterized, and the nominated substance has up to 6 percent impurities. EGCg is unlikely to be stable in the proposed formulations under normal storage conditions.

EGCg is abundant in green tea leaves, but the content of EGCg in green tea is very low. As such, it's difficult to provide a reliable estimate of the comparative amount of EGCg in a dietary supplement product containing 200, for example, milligrams of EGCg per capsule and the average

intake of EGCg from green tea beverage consumption.

In 2005, the U.S. Department of Agriculture conducted a survey of green teas on the market in the United States and found that the content ranged from 2 to nearly 54 milligrams of EGCg per gram of dry tea leaves. That provides some insight that, depending on how much tea an individual may consume, ingestion of EGCg from green tea as a beverage or from a dietary supplement, and also from the clinical studies we will discuss, could be comparable amounts.

Extraction of green tea can produce nearly 100 percent pure EGCg. So for simplicity in this presentation, we're referring to studies using substances containing approximately 94 to 100 percent EGCg as EGCg studies. We found very few of these.

Studies of substances with lower EGCg content we're calling green tea studies. We do not exclude the possibility that safety or efficacy data derived from green tea formulations are pertinent to EGCg itself, but we do not have

sufficient information to assess the validity of an extrapolation.

We also note that EGCg is a component of an FDA-approved product. Veregen is a topical product indicated for the treatment of genital and perianal warts. Veregen contains 15 percent sinecatechins, which is a proprietary extract of green tea containing 55 percent EGCg.

EGCg is often referred in the literature to be the most bioactive component of green tea and is generally considered to be an antioxidant. It's therefore often theorized to be the component of green tea that would be most likely to have pharmacologic activity, and that's why it is specifically studied separately from astragalus preparations.

Some in vitro and in vivo data that we found might suggest that pharmacologic mechanisms related to the activity of EGCg exists for all of the various proposed uses. For example, various aspects of wound healing, such as reepithelialization were found to be improved by

topical application of EGCg in a mouse model of type 2 diabetes.

The pharmacokinetics of EGCg have been studied in animals and humans. EGCg has very low bioavailability, which is somewhat increased by fasting conditions. But there are multiple pre-systemic mechanisms active in the small intestine to prevent absorption, such as extensive metabolism and an efflux transporter.

EGCg undergoes first-pass metabolism and is also metabolized by gut flora in the large intestine. Given the limited bioavailability, there are reports in the literature about strategies being investigated to improve the systemic delivery of EGCg via the oral route. We found no information about pharmacokinetics associated with a topical application.

We did find a study that describes a drug interaction with boronic-based proteasome inhibitors, specifically Velcade, in vitro and in vivo in a mouse model. In this study, the investigators had undertaken it to determine

whether or not EGCg consumption would be of benefit to their cancer patients, and they were surprised to find that, in fact, it actually blocked the activity of the specific drug.

I use this as an example of what you don't know when there are impurities. There was a direct covalent bond formed between the boronic-based proteasome inhibitor and EGCg. And in retrospect, the investigator said they should have been able to predict it based on the polyphenol chemical structure, but they were actually investigating for the opposite reason. And that's just an example of one of the things you couldn't know unless you started to investigate at this level.

This slide shows the results of our search for non-clinical safety studies from EGCg studies. At high dose in acute toxicity, EGCg shows hepatotoxicity and death. We found no studies of these various types with the 94 to 100 percent EGCg studies.

We also looked at non-clinical safety studies that use green tea formulations. Here are

the results from a series of studies from the National Toxicology Program using a preparation of less than 50 percent EGCg. There are other studies described in the review of green tea, but this series from the NTP provides an overview of the effects of a consistent formulation.

In repeat-dose toxicities, the NOAEL was 100 milligrams per kilogram. At higher doses in rats, hepatic and stomach mucosal necrosis was observed as well as increased mortality, And mice showed liver inflammation and hematopoietic cell proliferation. The Ames assay was positive only in two bacterial strains in the presence of metabolic induction.

There were only minor findings in three-month developmental and reproductive toxicity studies from NTP, and carcinogenicity findings based on a two-year study were considered to be of questionable relevance.

Looking at clinical safety, the FAERS database was searched to include EGCg and green tea, but to exclude reports of Veregen and

Hydroxycut. Briefly, Hydroxycut is a dietary supplement product line that contained green tea extract and was recalled in 2009 due to 23 reports having been received by the FDA of adverse liver effects. These include asymptomatic hyperbilirubinemia, jaundice, liver damage, liver transplant, and death.

FDA stated at the time of the recall that we could not determine the exact ingredients that might be associated with the liver injury. The product line was reformulated and no longer contains green tea extract.

From FAERS, one report was of a possible drug interaction was cyclosporine and the other three were of hepatotoxicity. The CAERS database contained 200 reports associated with EGCg or green tea products; 72 of these were about Hydroxycut products, the other 128 contained 11 reports of liver injury or liver failure. There were also two cases of dermatologic reactions to a moisturizer topical product containing green tea.

We found safety data in two EGCg clinical

studies. And just a reminder, these are products that are 94 to 100 percent EGCg rather than green tea. Both studies assess liver function and neither identified abnormalities.

The nominator has identified that a study cited in our review that was considered a green tea study actually included EGCg treatment of 16 healthy adults taking either 400 or 800 milligrams of EGCg daily for 4 weeks. Adverse events were reported to be mild and included various gastrointestinal symptoms, dizziness, headache, and muscle pain.

In addition, we did not find safety data from studies of other proposed uses, but there has been a study of EGCg used as a topical ophthalmic product in which no side effects of treatments were observed. The indication there was dry eye.

We note that our review of green tea studies includes reports of serious hepatotoxicity. Again, that's with green tea products.

In conclusion, we found limited safety data available from EGCg formulations. Hepatotoxicity

was seen in non-clinical and clinical data associated with green tea preparations, and the association of these events to the EGCg content of these preparations cannot be fully assessed.

Our efficacy review focuses, again, on EGCg studies. Additional information about efficacy studies of green tea formulations, including several meta-analyses for obesity and diabetes is contained in the review. We found two placebo-controlled EGCg studies in overweight or obese women in which doses of 300 or 150 milligrams of EGCg daily were dosed for a period of approximately 3 months. No clinically important differences were seen between groups.

In a study of gestational diabetes in which 404 pregnant women received EGCg during their last trimester of pregnancy, EGCg appeared to be associated with a treatment effect. The EGCg group had significantly lower fasting plasma glucose and other positive effects.

In an 8-week study, placebo controlled, of 88 overweight or obese men, no clinically

significant difference in various parameters related to glucose or insulin were found. I will just note that the studies of obesity and weight loss also had parameters related to diabetes as part of their protocol.

One study of green tea polyphenols formed in 10 newly diagnosed Parkinson's patients was found on clinicaltrials.gov. We did not find a publication of the results of this trial, although the website for Michael J. Fox's Foundation for Parkinson's Research has a high-level summary of a study that could be the same trial.

The summary states that mild symptomatic benefit was observed in untreated patients, but we have no details in which to assess this conclusion. And when I say untreated patients, I mean patients that were not receiving a treatment other than the EGCg.

No clinical efficacy data were identified for the use of EGCg in cardiac hypertrophy, corneal neovascularization, NAFLD, or wound healing.

Based on the consultation with our

dermatology colleagues, we noted that clinical studies of wound healing would not generally include treatments of dermatitis or keloids unless, in particular, dermatitis had progressed to the level of ulceration.

Although EGCg was isolated from green tea decades ago, it's unknown how long or the extent to which it's been used in compounding. EGCg is available as a dietary ingredient in dietary supplement products.

In conclusion, EGCg is well characterized and makes up at least 94 percent of the nominated substance. EGCg is not likely to be stable under ordinary conditions for oral, ophthalmic, or topical formulations. We found little safety data specific to EGCg.

Non-clinical and clinical safety data for green tea formulations show a consistent evidence of an association with hepatotoxicity. We cannot identify or rule out a causal relationship between green tea component EGCg and hepatotoxicity.

We found a treatment effect suggested in a

single study of gestational diabetes, but no evidence of clinical efficacy for EGCg in weight loss, Parkinson's disease, cardiac hypertrophy, corneal neovascularization, non-alcoholic fatty liver disease, or wound healing.

It's unknown how long or the extent to which EGCg has been used in compounding. Overall, a balancing of the four evaluation criteria, in FDA's opinion, weighs against EGCg being added to the list of bulk drug substances under 503A. Happy to take questions.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will accept clarifying questions from the committee.

Dr. Desai?

DR. DESAI: Thank you very much, Dr. Johnson. Just a technical question. When you mentioned the Veregen, which has the sinecatechins already in it, is the reason that EGCg is not exempted under the fact that it's already an approved drug is because that is a component of sinecatechins. Is that correct?

I guess it's more of a technical question. My understanding was, if we already have an ingredient that's approved as an FDA drug, then it would be exempt from the list. Is that correct? And since sinecatechins contains 55 percent EGCg --

DR. LAWSON: The answer is correct, that this is a component of sinecatechins.

DR. DESAI: So because it's a component of the actual approved ingredient, that it's not exempt.

DR. LAWSON: We consider it not the same.

DR. JOHNSON: If I could clarify just a little further, it's a component of a botanical --

DR. DESAI: Correct.

DR. JOHNSON: -- and that's really the distinction here. If it were just 1 of 6 ingredients in a drug substance, in a drug product, and all of them were drugs and not botanicals, then you still would be allowed to be compounded, but this was a botanical. It was the first NDA botanical approved.

DR. DESAI: Again, just a technical, but

it's because it's a component of a botanical or a component of the ingredient, not the ingredient itself?

DR. JOHNSON: Aside from botanicals, if I had a cream made up of A, B, and C drugs --

DR. DESAI: Got it.

DR. JOHNSON: -- A, B, and C would be allowed to be compounded.

DR. DESAI: Then the second question I had is when you talked about wound healing under general pharmacology, one of the studies that was discussed was the type 2 diabetic study that showed improvement in wound healing, but you mentioned something about high-dose toxicity.

Can you just clarify that?

DR. JOHNSON: So that was in an animal study. I don't remember which rodent. EGCg was soaked out to a sponge. The sponge was applied to the wound. And at high doses, there was actually irritation of the wound.

DR. DESAI: Irritation of the wound. Got it.

DR. GULUR: Yes?

MS. BORMEL: I just wanted to further clarify what Dr. Johnson and Dr. Lawson said. With respect to the Veregen, the sinecatechins is the active ingredient in that, and the EGCg is just a component --

DR. DESAI: A component of that.

MS. BORMEL: -- of the sinecatechins. It's not the sinecatechin.

DR. DESAI: It's not the same thing.

MS. BORMEL: Yes, correct.

DR. DESAI: I just wanted to make sure that was a technicality that was clarified. Thank you.

MS. BORMEL: Correct.

DR. DESAI: Thank you.

DR. GULUR: Dr. Bogner?

DR. BOGNER: I just want to clarify the relationship between EGCg and this Hydroxycut that was removed from the market.Was the EGCg the main ingredient, an ingredient? And what was the relationship between that and its removal from the market?

DR. JOHNSON: Looking through the FDA information that's on our website about what happened during that circumstance, the actual recall was for the Hydroxycut product line, and there was no explanation offered because we did not have sufficient data to point to an ingredient or ingredients.

So we did not point to green tea extract, which was a component of Hydroxycut, or EGCg specifically. And I don't believe I saw any place where EGCg was quantified in the Hydroxycut line. There is still Hydroxycut marketed. It's no longer marketed with green tea extract. So all of those links lack data.

DR. BOGNER: One follow-up question if I may. Was green tea extract the only active ingredient in the Hydroxycut that was removed?

DR. JOHNSON: No. Most of them are multi-ingredient supplements to my knowledge. Thank you.

DR. BOGNER: Thank you.

DR. GULUR: Any further clarifying questions for members on the phone?

(No response.)

DR. GULUR: Thank you, Dr. Johnson.

We will now proceed with the nominator presentations. We have one presentation, Ms. Kimberly Kieffer from Fagron.

Nominator Presentation – Kimberly Kieffer

MS. KIEFFER: Good afternoon. I'm Kim Kieffer from Fagron North America. I wanted to speak a little bit to the purity of the EGCg since we're talking very technically in this meeting. Upon review of our C of A for this particular material, 94 percent is the minimum purity. It's typically in a range from 94 to 100 percent. It can also contain up to 5 percent water as part of its specification. So a current C of A, for instance, has an activity of 97 percent with 3 percent water content. That might speak a little bit to some of the impurities that are unknown.

In addition, this material is assayed for heavy metal content, mold, yeast, et cetera, with specific specifications for those heavy metals, not just pass. And if you would like, I can supply

that example to you at some point later on.

Thank you, FDA, first of all for your extensive review of this. There were a lot of conditions that were nominated or indications nominated for this particular substance.

I wanted to specify again for everyone that, when we created these nominations three years ago, we weren't really sure exactly what FDA was looking for. We tried to pull as much information together to show that there were potential uses for it, there were some safety data, et cetera. As the supplier of the compounding materials and even the compounders themselves, we don't necessarily know what physicians are going to come and want to use particular substances for.

In addition, new publications and literature come out every single day. So in reviewing for this particular meeting, I found a lot more data on EGCg than we were able to find when we did these nominations three years ago.

I've included on this slide some of the conditions and disease states that EGCg's been

studied for, and I actually ran out of room on the slide because it goes on, and on, and on. But today, for this presentation, I wanted to specifically only focus on what we're seeing it being used for and compounded preparations.

We're not seeing it being used topically. We're not seeing it being used for eyedrops, not that the potential use couldn't exist. But what we are seeing it for is being used in the treatment of wounds and scars. EGCg has shown the potential to enhance wound healing and prophylaxis for fibrosis and scarring.

It's typically compounded into creams, gels, and ointments. A typical time that a patient might have these particular topical formulations is only 30 days. That's per USP specifications. Typical dosage range is 0.1 to 1 percent, which is fairly consistent with the data that we do have that supports this use.

It's most often compounded in combination with other ingredients, so corticosteroids, anesthetics, skin lightening agents, things that

you would typically use in the treatment of scars. And typical length of therapy is usually -- my research and discussions with clients is typically 1 to 3 months.

So just some highlights in terms of when we're looking at this data, or physicians, or compounders are looking at the data that is available, EGCg has been shown to be potentially effective in regulating the secretion of cytokines in the activation of skin cells; has been shown to have anti-inflammatory and antioxidant properties.

EGCg has been shown in studies to affect the role of TGH beta 1 or F-beta 1; enhances wound healing by accelerating reepithelialization and angiogenesis; improves the cellular reorganization of granulation tissue. EGCg has been shown in in vitro and in vivo studies to reduce fibrosis and the contractions often associated with scarring.

I wanted to talk about safety since that was a big part of the FDA's review. This is the pharmacokinetics and safety of green tea polyphenols after multiple dose administration of

either the EGCg itself or as polyphenon E. Polyphenon E as a dietary supplement that contains a specific amount of EGCg.

This was done in 40 healthy men and women. One of 5 treatments was given 800 milligrams EGCg once a day, 400 milligrams EGCg twice a day, 800 milligrams EGCg as polyphenon E once a day, or 400 milligrams EGCg as polyphenon twice a day, or placebo. That was a 4-week-length study. Adverse events were excess gas, upset stomach, nausea, heartburn, stomach ache, abdominal pain, dizziness, headache, muscle pain.

This is just a chart of the distribution of the treatment arms.

Adverse effects were rated as mild events. Common events included headaches, stomach ache, abdominal pain, and nausea. All adverse events noted were reported in subjects receiving green tea polyphenol treatment as well as placebo. No significant changes in blood counts and blood chemistry were observed, and the conclusion was that oral administration of EGCg or polyphenon E at

a dose of 800 milligrams a day for 4 weeks was safe and tolerated.

This is another study, another oral study in humans, randomized placebo-controlled trial, evaluated in the safety of one-year administration. So this is 49 men randomized to the treatment arm and 48 to the placebo group. They were administered in a fed state, 200 milligrams of EGCg per day for 12 months. No liver or other toxicities were observed. A single report of grade 3 nausea was reported. No other dose-limiting toxicities were observed.

Conclusion. Daily intake of standardized catechin mixture containing 200 milligrams EGCg taken twice a day with food for one year did accumulate in the plasma and was well tolerated and did not produce treatment-related adverse events.

This was a dermal study or just an animal study in general. There was a dermal arm to it, but there was also oral and subQ parts, but this chart shows the distribution of animal studies and the concentrations of EGCg that were used.

So the highlights. No systemic signs of toxicity were observed in any of the rats following dermal application of 93 percent EGCg. Minor dermal irritation was observed in rats and guinea pigs, but not in rabbits. Moderate dermal sensitizing in the guinea pig maximization test was observed.

Oral doses of 2,000 milligrams EGCg preparation per kilo was lethal in rats, whereas a dose of 200 milligrams EGCg per kilo induced no toxicity. In a 13-week rat study, no toxicity was observed in doses up to 500 milligrams per kilo per day. No adverse effects were noted at 500 milligrams EGCg preparation per kilo per day administered to pre-fed dogs in divided doses. However, morbidity did occur when administered to fasted dogs at a single bolus dose. However, the author asserted in the article that this model may be unrealistic when applied to humans.

From these studies, a no observed adverse effects level of 500 milligrams EGCg preparation per kilo per day was established. From these

results, a dose of 5 milligrams EGCg per kilo per day would seem an acceptable daily intake for humans, so for a 60-kilo adult, this would this would be equivalent to 300 milligrams EGCg per day, which is almost consistent with what we saw in the oral studies earlier.

This is a topical study that was done in breast cancer patients. This was a study of topical EGCg in patients with breast cancer receiving adjunctive radio therapy. Topical EGCg was prepared and a spray applied to grade 1 dermatitis as developed from radiation therapy to see if it would reverse or lessen irritation symptoms.

Twenty-four women with pathologically proven breast cancer with a planned course of radiotherapy were selected for this trial. EGCg concentrations were escalated from 40 to 660 micromoles per liter. The therapy was initiated once grade 1 dermatitis occurred from the radiation therapy, and it was applied three times a day to the entire radiation field.

The median duration of EGCg treatment was four weeks. No dose-limiting toxicity was observed. No other obvious adverse effects were observed to be related to the topical EGCg treatment. The conclusion was that topical administration of EGCg was well tolerated, and no dose-limiting toxicity was observed.

This is the follow-up to that same study. In this one, 49 women with the same pathology were selected, and EGCg concentrations were started at 660 micromoles per liter, consistent with the last study. Again, it was initiated once grade 1 dermatitis occurred from the radiation therapy and it was applied 3 times a day.

The median duration of the treatment was 4 weeks. And again, EGCg was well tolerated by all patients. Incidentally, it was also effective in treating irritation as a cause of the radiation therapy.

Evidence for use, we don't have a lot of controlled placebo studies for scarring and wound care, but we do have some ex vivo studies and some

compelling animal studies, so I thought I would bring those here today.

This is a keloid organ control model, and the tissue is maintained in either dexamethasone, 50 micrograms per mL, as a positive control, or it was submersed in EGCg 100 units per mL, dissolved in dimethyl sulfoxide and maintained for 4 weeks.

The EGCg treatment stimulated cytotoxicity and significantly reduced metabolic activity from 1 week to 4 weeks, compared with the vehicle-treated dimethyl sulfoxide control.

Dexamethasone reduced higher cytotoxicity and lower metabolic activity in comparison. However, EGCg and dexamethasone both significantly reduced collagen 1 and collagen 3 transcription. The EGCg group showed significant reductions in secreted collagen 1 and 3 compared to the dexamethasone group that did not show significant changes. The author concluded that, overall, EGCg reduced interkeloid collagen synthesis more efficiently than the dexamethasone.

This is a mouse study, promotion of full

thickness, wound healing using EGCg in a polylactic co-glycolic acid membrane as a temporary wound dressing. This study implies that EGCg regulates the secretion of cytokines in the activation of skin cells during the wound healing process.

In this study, various concentrations of EGCg were added to the electro spun membranes composed of PL/GA, and its healing effects on full-thickness wounds created in [indiscernible] mice were investigated.

Cell infiltration of mice treated with electrospun membranes containing 1 percent EGCg significantly increased after 2 weeks. Reepithelization at the wound site and formation of blood vessels also increased in the mice treated with 1 percent EGCg and PL/GA membranes in comparison with mice treated only with PL/GA membranes.

These results suggest that 1 percent EGCg can enhance wound healing and full-thickness wounds by accelerating cell infiltration, reepithelization, and angiogenesis.

Finally, one more mouse study. I think FDA already presented this one. This is enhanced wound healing by an EGCg-incorporated collagen sponge in diabetic mice. Various concentrations of the EGCg were incorporated into collagen sponges in order to investigate its healing effect on full-thickness wounds created in type 2 diabetic mice.

At 14 days, the residual wound size of mice treated with just 10 parts per million EGCg-incorporated collagen sponges decreased significantly faster than untreated mice. Significant increases in reepithelization, thickness, granulation tissue, and the density of the capillaries were observed in the wound sites exposed to 10 parts per million EGCg and collagen sponges in comparison with the others.

These results suggested that EGCg-incorporated anti-collagen sponge at low concentrations can enhance wound healing in diabetic mice by accelerating reepithelization and angiogenesis as well as improving the cellular reorganization of granulation tissue by triggering

the activity of microfiber blasts.

So in conclusion, EGCg has been used in compounded preparations for the management of wounds and scars because of this type of information. And this information suggests that topical EGCg may improve wound healing and reduce scar formation. Topical application studies in humans observed no limiting dose toxicity.

Ex vivo studies using keloid organ culture models conclude that EGCg reduces collagen synthesis, and animal studies on wound closer suggest that topical EGCg enhances reepithelization angiogenesis. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now accept clarifying questions. Dr. Wall on the phone?

DR. WALL: Thank you. Just a quick question. You had mentioned -- you said your current use when it is being made is combined with multiple other ingredients.

Is that correct, the topical creams or

ointments?

MS. KIEFFER: Typically, yes.

DR. WALL: With you and your colleagues' experience, what have you seen that contributes when you add it to those other ingredients? What changes or the clinical [inaudible].

MS. KIEFFER: Are you asking what results we're seeing?

DR. WALL: Yes. What are you seeing [indiscernible] ingredients, kind of clinical?

MS. KIEFFER: Unfortunately, I don't have that data. I don't see patients. I only see people seeking active ingredients.

DR. WALL: Thank you.

DR. GULUR: Thank you. Dr. Desai?

DR. DESAI: The study that you mentioned with the results showing that the combination of the EGCg with the PL/GA was superior to the PL/GA alone, was that a mouse model study?

MS. KIEFFER: Correct. Yes.

DR. GULUR: Dr. Patel?

DR. PATEL: Going back to the question of

stability in the FDA's report, it was mentioned that it's not a stable compound and that the stability was not documented for beyond 6 days. When you add mixing with steroids and anesthetics, how do you guarantee the potency of the active ingredient?

MS. KIEFFER: I think that's the case with any combination of ingredients. We can't. However, USP guidelines give us a very strict adherence for preparing things in that matter and that they cannot be held for more than 30 days.

DR. GULUR: Could you clarify that again? It's 30 days and yet the stability here was 6 days?

MS. KIEFFER: Without a stability study, USP allows us to compound things for 30 days beyond use dating.

DR. GULUR: Please clarify.

DR. PATEL: Is that because in reference to 795?

MS. KIEFFER: It is.

MS. DAVIDSON: To clarify, those default dates are when there is no other evidence

available, and I think there's plenty of evidence available that it's not stable in an aqueous solution past 6 days.

MS. KIEFFER: That being said, there are a number of compounding bases that can be used that are non-aqueous. So they're ointment and gels that don't contain any water. And in fact, typically, the ointments and gels are what it's being compounded in, and they are silicone and petrolatum base.

DR. GULUR: However, you had mentioned that, when you're doing 94 percent, 6 percent is water. So could you clarify how that would work?

MS. KIEFFER: All chemicals have a small amount of water in them upon their derivation.

DR. GULUR: Thank you. Dr. Bogner?

DR. BOGNER: I wanted to follow up on the water. I take it this is a crystalline compound, yes, that one, EGCg. I'm less familiar with having that high a loss on drying for a crystalline compound. I'm more familiar with having that high of a water content in partially amorphous or non-

crystalline compounds. Maybe Dr. Hoag can help clarify that.

That being said, if I am correct, and that's a very high moisture content, I'm wondering if we have here not something that's fully crystalline. Would you be able to say?

MS. KIEFFER: I would need to find out from the manufacturer if it's a fully crystalline substance, but we see high concentrations of water in quite a bit of active ingredients.

DR. BOGNER:Let me go back to the water and reactivity piece. Looking at the compound and all those phenolic groups around, it seems to me oxidations would be a big problem, which means you'd have that trouble in a silicone-based gel as well as others.

Does anybody know about the reactivity of all these phenolic groups? So if you were to combine this active with another active, would they actually react with each other?

MS. KIEFFER: I don't know all the specifics on that. That would be on a case-by-case basis.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: Just noting that the nomination was for a number of different formulations, but your presentations seem to primarily be supporting topical use for wound treatment and skin treatment, do you continue to support the ophthalmic and oral formulations, or are you really looking for the topical formulation?

MS. KIEFFER: As I was explaining earlier, when we first created these nominations, we really were unclear that specific indications were what FDA was looking for. So we tried to supply as much data as there was or at least a lot of data so that you could see, okay, there are usages, there are potential need, and that there is some safety and efficacy data here, there, and whatever.

Again, every single day, we have new literature, so maybe tomorrow, there will be a new use for EGCg that we might support. But I thought, since indication has really surfaced as what we're looking at in these discussions, it would be better to just focus on and give you some idea of what

it's actually being used for.

DR. GULUR: Dr. Desai?

DR. DESAI: Following up on Dr. Jungman's comment, I too was interested because the majority of your presentation was around the topical use. And when we heard Dr. Johnson's presentation, she mentioned several studies including a very recent one, if I'm not mistaken, on the pregnant patients who had an improvement in their glucose levels.

Can you comment a little bit? Have you seen that being used at all? Have you had prescriptions come in for that? Have you had usage in other formulations other than topical?

Also, in terms of a volume, can you give us a sense of how many topical prescriptions or how much usage you're seeing of this topically?

MS. KIEFFER: I have not seen any oral usage in the compounding pharmacy, not that there isn't some, but I have not seen any. And then in terms of volume, all of these substances sort of ebb and flow.

For a while, there was a lot of interest in

it, and I would imagine that's still consistent. But I wouldn't say it's any immense volume, but I think when we're talking about scarring, we don't have a lot of really great clinical or FDA-approved or even standard of care options, and I think people are always looking for something that's going to help attenuate some of the fibrosis, et cetera.

So that's where it really seems to have gotten most of its attention.

DR. GULUR: Thank you very much. Dr. Davidson?

MS. DAVIDSON: Can you talk a little bit more about where the not less than 94 percent came from?

MS. KIEFFER: Yes. It came from the manufacturer specifications.On their list of specifications, on their C of A, what they tested against, that that's their specification that it can't be less than 94 percent.

MS. DAVIDSON: That is their own individual specifications?

MS. KIEFFER: That is their own individual specifications. And I think you were asking about this earlier. How do we determine if we don't have a monograph? That's a very good question, and I think the manufacturers tend to make specifications for themselves if there isn't a monograph for them to look at.

If there's a monograph in another country, often those will be used, but in this case, it's the manufacturer's review.

MS. DAVIDSON: Because there is a dietary supplement monograph for green tea extract, and it requires not less than 40 percent of the epigallocatechin. So I was just curious as to what the relationship is between the 94 percent and efficacy and if degradation below that maybe isn't a bad thing. I just was curious as to where the 94 percent came from.

MS. KIEFFER: It's the pure material, so they're extracting it, and that's what they're --

DR. GULUR: Yes. Dr. Bogner?

DR. BOGNER: I'm going to go back to that

5 percent water because, frequently, the water content is specified, but purity is based on the anhydrous. Right? Once the water has taken off, now, what is the purity of the solid that's left? You seem to indicate that this is including the water.

MS. KIEFFER: It's not including the water. When we're doing an assay, as you're stating, it's based on the water being driven off, and that's what is stated. But if it's only for 94 percent, what else is in there?And the impurities are, for this one, water, it looks like.

DR. GULUR: Could you clarify that again, because I'm genuinely very confused? So is it the anhydrous? Whatever is anhydrous is 94 percent?

MS. KIEFFER: Yes.

DR. GULUR: Or are we talking about the whole thing as 94 percent with 6 percent water?

MS. KIEFFER: The whole thing is 94 percent active, and then it can contain up to 5 percent water. And when we assay for the activity, we drive off the water first.

DR. GULUR: So if you drove off the water, what is the activity that you were left with?

MS. KIEFFER: 94 percent.

DR. GULUR: So what else is in there?

MS. KIEFFER: There's probably chemical intermediates, possibly fragments. Like I said, they do assay for a number of different --.

DR. GULUR: So would you agree, then, that, as implied in the FDA presentation, when it's 94 percent there could be 6 percent impurities?

MS. KIEFFER: Not necessarily because the activity is not necessarily set that way. The activity can fluctuate regardless of whether there is a number of activities or not -- excuse me, impurities or not.

DR. GULUR: Thank you. Dr. Desai?

DR. DESAI: Just a quick question. We've seen so many studies on this in the presentations. On the wound healing presentation studies that you presented, were any of them human subject studies, any phase 3 data, or phase 2 human studies, or were they all mice? I just can't remember.

MS. KIEFFER: The studies at the end were mice. We did talk about one dermatitis study that was in humans.

DR. DESAI: And do you remember the cohort size or do you remember if it's large or medium sized by chance?

MS. KIEFFER: In the human study, there were two. It was 24 and 49.

DR. DESAI: Thank you.

DR. GULUR: Dr. Hoag?

DR. HOAG: When you say activity, how did you determine that?Is it they use the word international units for vitamins and stuff or is this HPLC?

MS. KIEFFER: It's HPLC.

DR. GULUR: Dr. Johnson?

DR. JOHNSON: Two comments on the radiation dermatitis studies. First, I tried to preempt this just to make it clear what our viewpoint is, but grade 1 dermatitis would not be considered an appropriate model for wound healing. If you were looking at -- and our dermatologic colleagues have

provided the Radiation Therapy Oncology Group scoring system. If you were up to level 3 or level 4, and level 4 being ulceration, hemorrhage, necrosis, you would be talking about a wound healing model. There were no patients in either one of these studies that reached that level.

MS. KIEFFER: Actually, I included those studies, the radiation studies, really to show more dermal safety than wound healing efficacy.

DR. GULUR: So would you say there are no human studies on efficacy for wound healing?

MS. KIEFFER: Not that I was able to find.

Committee Discussion and Vote

DR. GULUR: Thank you. Thank you very much.

We do not have any open public hearing speakers. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We will now begin the panel discussion of EGCg. Dr. Braunstein?

DR. BRAUNSTEIN: Yes. I just want to confirm that an API can be put on the list with a particular --

DR. GULUR: Concentration?

DR. BRAUNSTEIN: No, no, no. I was going to say formulation, but really it's a route of administration, is what I was going to say.

MS. BORMEL: Yes, you can restrict the route of administration. What you can't do is restrict the usage, because once it's on the list, it could be used for any particular use. But the route of administration, you can include as a restriction on the list.

DR. GULUR: Dr. Carome?

DR. CAROME: Mike Carome. So we have approved some topical drugs for dermatologic conditions and said we'd like to restrict it to that, but in all those prior cases, there was evidence of efficacy, which we don't have here.

DR. GULUR: Yes. I think even the nominators have confirmed there are no human studies of efficacy for wound healing.

If there are no further discussion points, we will move on to the vote. Yes, Dr. Jungman?

MS. JUNGMAN: Do any of the FDA chemists

have more information on reactivity, chemical reactivity of this compound?

DR. ZHANG: This is Ben Zhang from OPQ. Just I want to make a few more comments on the stability of this substance. EGCg is very sensitive to oxygen, even as a solid formulation. We only have evidence showing for stable for one week, and then 13 percent degrades after one month.

Now, the main reason for degradation is an oxidation reaction. If you know a group will oxidize, and form dimer of EGCg and then acetyl ester [indiscernible], and then you can hydrolyze the increased solutions. Hopefully that will give you information about this reactivity.

DR. GULUR: Yes, Dr. Davidson?

MS. DAVIDSON: So there is a commercially available product called Veregen that is approved, and it must be stable or you've wouldn't have approved it.

DR. JOHNSON: Correct.

MS. DAVIDSON: And it must be effective and I know it's not a drug.

DR. JOHNSON: It is a drug.

MS. DAVIDSON: It is a drug, okay. Is it a botanical drug?

DR. JOHNSON: The gel contains 15 percent of a mix called sinecatechins. And the sinecatechins is a proprietary mix. It's just a name that they have. It's 55 percent EGCg.

MS. DAVIDSON: But presumably no water.

DR. GULUR: Yes, that went away.

Any further questions, questions from our members on the phone?

(No response.)

DR. GULUR: We will then move on to the vote. The question before us is FDA is proposing that EGCg not be included on the 503A bulks list. Should EGCg be placed on the list? If you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF monograph or

component of an FDA-approved drug.

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.

(Voting.)

DR. CHEE: For EGCg, we have zero yeses, 13 nos, and zero abstain.

DR. GULUR: We will start with the comments from Dr. Carome. You'd like me to choose the other side?

(Laughter.)

DR. GULUR: That's fair. Dr. Burman?

DR. BURMAN: Thank you. Thank you, Dr. Carome. This is Ken Burman. I voted no. Obviously, the major part of the discussion by the FDA related to oral preparations, and it was clear to me that there was significant degradation

issues. There was possible toxicity, especially of liver and GI tract.

There is no long-term data. And it was not effective in most of the indications used except possibly for type 2 gestational diabetes, where the endpoints at least weren't clearly identified, so I'm not 100 percent sure about that.

With regard to, however, the presentation about the nominator, who focused mainly on topical preparation, that may be more useful. But as she herself said, there aren't any clinical human studies. I just raised the issue that may be in their future, if there were clinical studies in humans, it might in fact be beneficial. And that's a topic for a different time.

DR. GULUR: Thank you. Dr. Vaida?

DR. VAIDA: Allen Vaida. I voted no, and I thought that Dr. Burman stated the facts eloquently there. I probably just want to reiterate, too, with the safety data, it was first presented for topical 1 to 3 months and all the safety data only went up to 4 weeks in the studies that were

presented.

DR. GULUR: Thank you. Dr. Venitz on the phone?

DR. VENITZ: This is Jurgen Venitz. I voted [indiscernible].

DR. GULUR: Thank you. Padma Gulur. I voted no, stability, safety to some degree, and the lack of clinical efficacy for the indications that were presented influenced my vote.

Dr. Davidson?

MS. DAVIDSON: I voted no for all the reasons stated. I think the stability issues obviously can be overcome because there was an approved product for it, but the hepatotoxicity safety signals concern me significantly, And that's why I voted no.

MR. HUMPHREY: William Humphrey. I voted no for, again, many of the same reasons, the lack of clinical efficacy in humans and the stability issue.

DR. DESAI: Seemal Desai. I won't repeat. The previous speakers have done a great job of

going over their reasoning. I will make a comment, however, that from a topical perspective, I think the nominator did a very nice job of presenting the mouse model studies, which are encouraging in data. We just don't have any human data.

Given that Veregen and sinecatechins are a product that I use as a dermatologist very frequently, that may be something anecdotally, in listening to some of this data, which could certainly be studied down the road. But what we had here with EGCg just wasn't up to par for the data.

DR. PATEL: Kuldip Patel. Just to add to these comments that are already made, we already know the compound was highly unstable under normal storage conditions. And to add other products to that as an add mixture concerned me about how effective that product would be within days, with the current date being given 30 days out.

Added to that, impurities was a concern, we talked about a potential interaction with another drug, Velcade, and the lack of long-term data on

efficacy in humans.

DR. BOGNER: Robin Bogner. I voted no for many of the reasons that were stated. In addition, while we know that stability can be taken care of at least because there is a commercial product, it's not clear that a compounder would have at his or her disposal those same techniques and right off the top of their heads. So that's why I voted no.

MS. JUNGMAN: Elizabeth Jungman. I also voted no like most of my colleagues, primarily because of instability, concerns about liver toxicity, and lack of data of effectiveness.

DR. HOAG: Steve Hoag. I voted no. I think this, in the future, with better data has potential to be approved or moved forward. But I would just concern, like, the lack of clarification of what is in there. My gut tells me that probably there are some impurities that are making the stability problematic, so that would make me vote no.

DR. CAROME: I'm Mike Carome. I voted no for all the reasons stated by other committee members.

DR. GULUR: Thank you, Dr. Carome.

With that, we are scheduled to take a break at this point. If everyone could return at 3:45 so we can get restarted. Thank you.

(Whereupon, at 3:33 p.m., a recess was taken.)

DR. GULUR: Welcome back, everyone. We will now proceed with the FDA presentation by Dr. Ganley.

FDA Presentation – Charles Ganley

DR. GANLEY: I'm going to be talking today about trans-resveratrol. Throughout this talk, it may state resveratrol, but it's going to be referring to trans unless I other identify that.

I'm Charlie Ganley. I'm the director at the Office of Drug Evaluation IV in the Office of New Drugs. This is a list of the review team. I just want to acknowledge their work on this. I also acknowledge that there's a lot of people behind the scenes who work on all these presentations and help us with slides, and I want to acknowledge their participation. I also want to acknowledge the time

the committee takes out to assist us with this process.

Trans-resveratrol is trans-3,4,5-trihydroxystilbene and has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. The proposed use is for the treatment of impaired glucose tolerance in older adults and also for pain.

This was not a nominated use, but we reviewed it, for reasons that will become evident later, because we're aware that it is being used for this use in compounding. The reviewed routes of administration are oral for both of the proposed uses and topical for pain. There were no specific dosage forms or strengths proposed.

With regard to the physical and chemical characterization, resveratrol is a naturally occurring polyphenolic phytoalexin. You're probably most familiar with it as being an ingredient in red wine, but it also is present in many different foods that we eat and in different

plants. It is a stilbenoid with two well-characterized structural isomers, cis and trans. The trans is more abundant in the bioactive isomer. Trans-resveratrol is slightly soluble in water. It is also more stable when kept away from light.

Exposure to light causes acceleration of isomerization between the cis and trans-isomers, the cis- being the less stable isomer. Light-induced degradation of the cis-resveratrol leads to genotoxic impurities.

Physical and chemical characterization. Some plants produce small quantities of resveratrol in response to pathogens. Large-scale quantities can be chemically synthesized. The synthesized resveratrol is a mixture of the trans- and cis-isomers in the 7 to 3 ratio, and the two isomers can be isolated with chromatography.

As far as general pharmacology, I'll just go over this slide briefly because there are literally hundreds, if not thousands, of articles in the literature that talk about the biologic action potential of trans-resveratrol. All these bullets

here are referring to its anti-oxidation or anti-inflammatory effect, although the last bullet is the sirtuin 1. NAD-dependent acetylase is involved in longevity.

The one thing I do want to point out is the concentrations that are used in some of these studies, whether they're in vitro or ex vivo, we're talking in micromolar concentrations, and that will become evident later when I talk about the clinical pharmacokinetics in humans.

With regard to impaired glucose tolerance, there's mechanistic in vivo animal studies of type 2 diabetic models. It suggests resveratrol in doses of 10 to 100 milligrams orally increases insulin secretion, improves glucose tolerance, improved pancreatic islet structure and function, decreases insulin resistance, and decreases oxidative damage. On the right, there's a schematic that shows these various potential actions and the improvement of insulin secretion.

With regard to pain, pharmacology, use of polyphenol such as resveratrol attenuated

neuropathic nociceptive pain in animals; supplementation of resveratrol in several in vivo animal models with diabetes, that is, 10 and 20 milligrams intraperitoneal injections in rats and 5 to 20 milligrams orally in mice; reduced hyperalgesia, decreased serum, tumor necrosis factor alpha levels, and whole-brain nitric oxide release.

A gel formulation containing .025 percent resveratrol-reduced inflammation and edema in an in vivo rat model of pain when measured 1 to 4 hours post-injury.

The non-clinical pharmacokinetics resveratrol is detectible in plasma within 15 minutes of oral administration and reaches peak concentrations within 30. Elimination half-life is 8 to 12 hours. The highest distribution is found in the liver, followed by the pituitary muscle, stomach, intestines, and optic nerve.

Trans-resveratrol undergoes extensive conjugation during its metabolism, it does not accumulate over time, and it is largely eliminated

in the feces. Similar mode of metabolic profiles were reported for topical and/or oral routes of administration.

So with regard to the human clinical pharmacokinetics, there are many studies out there that evaluated the pharmacokinetics of trans-resveratrol, and consistently throughout the literature, it suggests that it's highly absorbed based on carbon-14-labeled drug, but has a low absolute bioavailability after oral administration, primarily due to extensive first-pass metabolism either through the liver or possibly in the gut through bacterial degradation.

I've just listed 2 PK studies here as examples. In the first study, a single-dose study of 500 milligrams, a gram, or 2 and a half grams, or 5 grams, I want to point out here that, in a liter of red wine, generally the amount of resveratrol is less than 10 milligrams. The highest amount that has been detected in red wine is 14 milligrams. Many of them are much less than that, maybe around 2, 3, or 4 milligrams. So even

in a glass of red wine, you may be lucky to get a milligram of resveratrol.

So you see here that the dose being used is rather high relative to what we would see in foods. And if you go back to the non-clinical data -- and you can remember that I mentioned a lot of these studies were using doses that were in the micromolar range.

So the Cmax values in this particular study ranged from 73 nanograms per mL for the lowest dose to 539 nanograms per mL with the highest dose. Now, 73 nanograms per mL is approximately 0.3 micromolar. So just keep that in mind. The Tmax range from 0.8 to 1.5.

In this study, 6 metabolites were identified, either sulfates or glucuronides, so they were generally primarily phase 2 metabolites. And this is consistent throughout the literature. It may not be 6; it may be less than that. The half-life ranged from 3 to 8 hours.

In a multi-dose study of 25 milligrams to 150 milligrams every 4 hours, for 13 doses, the

Cmax ranged from 1.4 nanograms per mL to approximately 25 nanograms per mL. So 1.4 nanograms per mL is probably about 0.01 micromolar.

After the 13th, the Cmax was approximately 6.9 up to 64 nanograms per mL. The volume and distribution is approximately 1.8 liters per kilogram, which suggests that it gets into the tissues. And consistently throughout the literature, it's noted that the circulating human blood levels are lower than resveratrol concentrations found to be active in vitro and ex vivo.

That's in part one of the reasons I think the larger doses are given. But you have to keep in mind also that the human blood level is in equilibrium with tissue levels, and it's not always reflective of what the tissue levels will be. So you actually may have higher tissue levels than you're seeing in the blood.

In a separate multi-dose small study of 12 subjects, there was no difference in PK between young and older subjects or males and females. But

that was at least 6 in each group based on age and on sex.

The application of resveratrol, approximately 50 micrograms per square sonometer for 24 hours to ventral forearms in 6 women without any skins disorders showed high variability and absorption by tape-stripping method. They didn't detect, and we wouldn't necessarily expect them to have detectible levels in the blood. Most of the applied product remained in the stratum corneum layers of the skin.

Orally administered resveratrol, 1 gram per day for 4 weeks inhibited cytochrome 450 enzymes, 3A4, 2D6, and 2C9. So for drugs metabolized by the cytochrome 450 enzymes, concomitant resveratrol may lead to increased blood levels and longer elimination half-life.

The other thing I'll just point out with that, it's not clear at what dose you would not see that potential interaction. Not all cytochromes have been evaluated in this type of study.

With regard to non-clinical safety,

resveratrol was non-irritating to skin and eyes, and it was non-sensitizing when topically applied in animal models. Toxicities were dosed and formulation related. Some studies reported no toxic effects. Other studies reported adverse clinical signs, dose-related increase, and therefore toxicity were noted in several species in four 13-week and 6-week toxicity studies.

Gastrointestinal, specifically diarrhea and loose stools and urinary bladder epithelial hyperplasia effects were reported in some resveratrol formulations.

Trans-resveratrol was non-mutagenic in several Ames' assays; positive clastogenic activity in a chromosomal aberration test in human lymphocytes, both in the presence or absence of metabolic activation and negative genotoxic activity in the in vivo bone marrow, micronucleus test in rats.

Other non-clinical safety, developmental, and reproductive toxicity, resveratrol binds to estrogen receptor. It's a phytoestrogen. There's

no in vivo adverse events reported -- no adverse reproductive or fetal effects were seen in embryofetal toxicity studies in rats.

As far as carcinogenicity, resveratrol was not associated with an increase in benign or malignant tumors in a 6-month transgenic mouse model study. Dose-related increase in death likely to accumulation of resveratrol at very high doses in the GI tract.

With regard to adverse events, you've heard the FAERS data and what that is. There were 7 cases found. None described the use of resveratrol as part of a compounded product, listed the adverse events reported there. It was difficult to assess causality because of a lack of information or confounding by disease in the use of multiple concomitant medications or supplements.

I'll just point out that two of the adverse events, one was persistent vomiting and diarrhea, which is not necessarily inconsistent with the side effects that you see in the literature related to higher doses of resveratrol.

The case of gynecomastia involved a 15-year-old male taking risperidone and resveratrol. The dose of resveratrol was not provided. It's simply stated it was 4 times per day. Risperidone alone can cause gynecomastia, but risperidone is metabolized by cytochrome 2C9, and resveratrol inhibits cytochrome QC9. But there's really insufficient information for us, other than to note that coincidence there of a possible drug-drug interaction.

With regard to the CAERS data, there were 377 reports identified. In most of these cases, multiple dietary supplements were being ingested. Some cases suggest a role for resveratrol in the adverse events. Many of these cases were serious in nature. In a lot of them, the number of ingredients that the individuals may be taking was 50 or more. So it's really difficult to make any conclusions about the causality related to resveratrol.

Many of the studies are short-term studies lasting several days, several weeks, or months, so

the acute adverse events are primarily mild to moderate gastrointestinal symptoms, including diarrhea, abdominal pain, flatulence, nausea, and heartburn.

There was a phase 2 trial in myeloma patients that reported nausea, diarrhea, vomiting, fatigue, and renal failure in five of the individuals. They were receiving 5 grams per day on cycles of 20 days. So these five cases actually may have been precipitated by dehydration from the gastrointestinal effects of resveratrol.

Actually, these renal failure cases prompted the investigators to stop using it in that population because they are at risk simply from the multiple myeloma to develop renal failure, and this may have thrown him into it.

There have been multiple studies of non-alcoholic fatty liver disease, and there were also increased stools, and there was mildly increased alanine and aspartate aminotransferases. In this particular study, it was simply a doubling of those. Other studies have not necessarily

identified liver toxicity.

The Susan G. Komen organization recommends that resveratrol supplementation should be avoided in women with hormone-sensitive conditions, specifically breast, uterine, ovarian cancer, endometriosis, and uterine fibroids because of its phytoestrogenic effect. And again, I want to be accurate here. It says resveratrol supplementation. It doesn't say eliminate foods that may have minor amounts of resveratrol in it.

The one thing that's not here is long-term safety. The long-term safety of resveratrol for different diseases has not been adequately studied. Resveratrol can elicit a biphasic dose response in different models such that one dose may appear to be beneficial, but a higher or lower dose is detrimental.

In a review by Calabrese from 2010, he noted that these biphasic responses were reported for numerous human tumor cell lines affecting breast, prostate, colon, lung, uterine, and leukemia. In such cases, low concentration of resveratrol

enhanced tumor proliferation, whereas higher concentrations were inhibitory.

Biphasic dose responses were also reported in animal models for the cardiovascular-induced injury, gastric lesions, ischemic stroke, Alzheimer's disease, and osteoporosis.

There was often a protective effect at a low dose, but an adverse effect at higher doses, exacerbating the disease process. Many of the effects adduced by resveratrol are dependent on dose, and the opposite effects occur at low and high doses.

I just point this out because specifically for the impaired glucose tolerance, that's a disease that the individuals are at risk obviously for developing diabetes, but they also are at risk for developing cardiovascular disease and things like that. So simply because resveratrol is available in your food, for some of the doses that we're getting into here, where we're talking about gram quantities or dose, it could be detrimental long term. And that information can only be

obtained in long-term studies.

As far as the safety conclusion, animal models show that the kidney, and gastrointestinal, and urinary bladder as target organs of toxicity. Again, in human acute studies, there were symptomatic adverse events that were primarily gastrointestinal, and in some cases at higher dose can be fairly severe, and in some populations, it can be extremely detrimental.

In clinical adverse event reports, concomitant therapies and/or underlying diseases make it difficult to make any conclusion about attribution to resveratrol.

The effectiveness in impaired glucose tolerance is not a recognized disease, at least based in discussions with the endocrine division in the Office of New Drugs. It a risk marker for future diabetes. Delaying the onset of diabetes in patients with IGT has not been shown to offer any micro- or macrovascular benefits to patients in long-term randomized controlled trials.

There was one study that we found where

trans-resveratrol was used in the treatment of impaired glucose tolerance. It was done in 10 patients who were over 64 years of age. The doses of resveratrol were very divided into 1, 1 and a half, or 2 grams per day.

The results suggested there was no change in fasting sugar. The decrease in peak and post-meal glucose and 3-hour glucose AUC was noted. There was a decrease in post-meal insulin levels, and insulin sensitivity improved in 1 of 2 scales. Insulin secretion and disposition index did not change significantly.

It's important to note that the authors in their conclusion stated that subtle changes in diet and exercise could have contributed to the observed effect. These were not controlled for in this study.

With regard to pain, there were no clinical trials, either by oral or topical routes of administration, that we identified where resveratrol alone was used for the treatment of pain.

We did find one study where resveratrol was used in conjunction with contraceptive medications. It was a Brazilian study, uncontrolled, open label. Patients were initially treated with drospirenone and ethinylestradiol for 6 months. Resveratrol 30 milligrams was added at 6 months because patients were not completely pain free.

Pain was significantly relieved with the contraceptives, using a categorical pain scale of 0 to 3. After 2 months of resveratrol treatment, there were significant improvements in pain scores.

Again, this is a small open-label uncontrolled study using an unvalidated pain scale that does not support clinical effectiveness. In these types of situations, it is important to have a control arm simply because the women in this study may have continued to improve simply on continuing the contraceptives. So they were taking contraceptives and resveratrol during the improvement.

The conclusion with regard to effectiveness, impaired glucose tolerance is a risk marker for the

development of diabetes. The benefit of treatment of IGT is unclear, for the American Diabetic Association notes that for impaired glucose tolerance, the mainstay of treatment is an intensive behavioral lifestyle intervention program to achieve and maintain at least 7 percent weight loss within the first 6 months of intervention and increase physical activity to at least 150 minutes per week.

We found only one study evaluating the effect of resveratrol in the treatment of impaired glucose tolerance, but is insufficient to support effectiveness. Resveratrol has not been adequately studied for the treatment of pain.

With regard to the historical use in compounding, resveratrol was first identified from the roots of white hellebore in 1940. It is available as a dietary supplement. There is really insufficient information available about how long resveratrol has been used in pharmacy and compounding.

The last item here was what prompted us to

look at pain because we became aware of this information. This was a letter from Congressman Scott and Cummings in a response to a notice in the Federal Register that was really directed to what involved prescriptions being written and paid for by the Department of Labor for individuals that were on workman's comp.

This is a quote from the letter, "The Postal Inspector General provided data which show payments for over 5,000 prescriptions for resveratrol totaling more than $16 million." And I also note that resveratrol is a dietary supplement, which has been prescribed for use in compounded drug creams for back pain.

So if you can do the math there quickly, 16 million divided by 5,000 is around $3200. The letter did also note that in some cases over $32,000 was paid for an individual prescription.

In summary, trans-resveratrol is well characterized. The acute safety concerns are primarily related to gastrointestinal adverse effects observed in clinical studies and possible

drug interactions related to inhibition of cytochrome P450 enzymes.

The non-clinical data suggests the kidney, gastrointestinal tract, urinary bladder to be target organs of toxicity. Clinical effectiveness has not been established. There is limited data in patients with impaired glucose tolerance in pain. There is poor absolute bioavailability due to extensive gut and liver metabolism.

The history of compounding is limited, and it's been available as a dietary supplement. And just again to note, the long-term safety of use in these products for serious conditions has not been established. The recommendation is a balancing in the four evaluation criteria weighs against resveratrol from being added to the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Ganley. We will now take clarifying comments and questions. Dr. Vaida?

DR. VAIDA: I'm just trying to follow a history here. This was nominated for various indications, and then it came back for just glucose intolerance, which I guess was oral. But then you did a study on glucose intolerance and pain, but you found that its real use right now is topical for either pain or aging skin.

So even with the oral for glucose intolerance, you didn't find anything that supported that, and it doesn't even look like it may be used for that.

DR. GANLEY: Well again, we don't have a lot of data on how these products are being used. We are aware of it being used for pain simply because of what was in the public domain here with regard to that letter. We were not aware of that.

I actually don't know how it's being used orally. This is what it was nominated for. The nominator can provide information on what it's being potentially used for.

You mentioned anti-aging. If you go on the internet, you can find products that contain

resveratrol, and they generally have cosmetic-type claims, either anti-aging or improving the appearance of your skin. Some have used the term "anti-wrinkles," although I'm not sure that's allowed under the cosmetics standard.

DR. VAIDA: Thank you.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: That actually gets to my question, which is the briefing materials note that it's sold as a dietary supplement, and it says capsules, tablets, powders, and cream formulations. And it was my understanding that you couldn't have a dietary supplement that wasn't adjustable.

So the currently available topical formulations that are not compounded, what are those? Cosmetics?

DR. GANLEY: I believe they're cosmetics. If you go online and do a search for resveratrol in a topic, you'll pull up products. It doesn't specifically state what the concentration is, but it has various cosmetic type uses for it. So it's not a dietary supplement, but it could be marketed

under the cosmetic regulations.

MS. JUNGMAN: I'll admit knowing almost nothing about the cosmetic regulations. I know there's no pre-approval. Is FDA looking at those at all, or what does it mean that it's a cosmetic?

DR. GANLEY: They don't look at the safety of those.

DR. GULUR: Dr. Ganley, I do have a question with regard to -- and I apologize if I missed that somewhere here, in the reproductive toxicity. And we've basically seemed to indicate that, at least in my studies, there wasn't any real risk to the fetus per se.

Did I understand that correctly, or there is risk to the fetus?

DR. GANLEY: Yes. I'm going to let Dr. Harrouk answer that. We did try to look at that specifically because this is a similar structure to diethylstilbestrol, so she can address that. But I think the issue with regard to the Susan G. Komen Foundation has to do with a phytoestrogen effect.

DR. GULUR: I'm specifically also referencing the paper, a pregnant primate study that was done, that actually showed that the fetus had a 42 percent increase in their pancreas size. I'm just wondering about the impact of that on glucose tolerance.

DR. HARROUK: Hi. My name is Wafa Harrouk. I did the pharmacology on resveratrol. So as Dr. Ganley mentioned, because of the receptor similarity to another product, which is DES, obviously the researchers were interested in knowing whether it has any reproductive toxicity effects.

So there were studies that were conducted in vitro, and resveratrol does bind to the estrogen receptor. It's an estrogen receptor agonist. There were other studies that were done on estrogen receptor responsive cell lines, and it binded there, so, in vitro, there were effects.

Now, when they went into the actual embryo fetal studies, they didn't have really much of an effect. In terms of -- they did

embryofetal [indiscernible], and it was kind of clean.

So the only thing were the in vitro findings that were positive. However, we don't have a lot of information about the studies. Usually, the studies have a lot more information, and these were reported in a review, so we didn't have access to the individual data points.

So there could be some effects. We just don't have the full picture. But on the surface, in a review article, it says there were no effects.

DR. GULUR: Could you clarify for me this particular study, which I didn't see mentioned much? Basically, it's out of Oregon, and it's a 2014, I believe, article, where it's pregnant non-human primates, Japanese monkeys, basically, that they did this study on. And they found some beneficial effects to the mother, but the fetus had a 42 percent increase in the size of the pancreas, which sounds very concerning to me, especially because the beta-to-alpha cell ratio changed, and there were much fewer alpha cells there. And I'm

just thinking of what implication that has as we are considering glucose tolerance here.

DR. HARROUK: Right. Again, this could be taken into account. We have to figure out the dose that was used also, and response to the effect. So I'll have to see the doses the mothers were exposed that induced this effect in their fetuses to really make a safety risk assessment kind of call on it.

But overall, there weren't a lot of studies that we could find that we can say, okay, the liver, or the pancreas, or whatever is a targeted organ in fetuses.

DR. GULUR: The primates were given pretty much constant infusions of resveratrol through their diet, really, added on continuously.

DR. HARROUK: During the pregnancy.

DR. GULUR: I would appreciate it if you could look at it and comment as well if you could.

DR. HARROUK: Okay.

DR. GULUR: Any other questions, clarifying questions? Dr. Patel?

DR. PATEL: Yes, I had a question regarding

the dose-response relationship and whether there is any information about prediction on what dose gives what kind of response, especially when you are talking about a biphasic dose-response relationship.

DR. GANLEY: Those are generally in vitro or cell models, so you still are getting up into the micromolar ranges. The difficulty is, when you look at these studies and then you're trying to relate them to humans, it's difficult to relate.

In this Calabrese study, it was actually the lower micromolar doses that stimulated tumor cells, but once you got it into higher doses, 100 micromolar, 200 micromolar, which is fairly high, you saw a decrease in the tumor cell stimulation, or there was no stimulation. It was inhibition.

So that's where it's important you have to understand the long term -- what is the concentration of the tissue relative to the blood. And again, they've gone to higher doses here, I think largely in part because seeing the micromolar

doses that were needed to elicit a biological activity and then seeing decreased absolute bioavailability in humans. That's how you end up with doses, a single dose per day, that's equivalent to drinking 50 bottles of red wine or something in a day.

But it's evident -- even though there's been a lot of research done in the last 30 years, there's an enormous amount that's not known. I think the long-term safety is one of the issues, particularly if you're getting into the treatment of potentially serious diseases or populations that are at risk for serious disease.

DR. HARROUK: Dr. Gulur, can I follow up on the conversation?

DR. GULUR: Yes, please.

DR. HARROUK: So the study that you were discussing, can you point me to where you're getting the data from?

DR. GULUR: That's, yes, the FASEB Journal.

DR. HARROUK: So you pulled it off the internet?

DR. GULUR: Yes. You can search it.

DR. HARROUK: Yes. I was just wondering whether it was something that was submitted later on or not.

DR. GULUR: No.

DR. HARROUK: The studies that we reviewed were on two separate formulations, and that's what I wanted to say when I was standing there. Depending on the formulation, there's been two groups of researchers, some that reported no adverse events whatsoever and another group that reported some fetal events. But those were done in the rat in both cases.

The ones that did say there were adverse clinical effects, they didn't say what they were because the data were summarized in a review article by Iled [ph].

DR. GANLEY: We can pull the article up.

DR. GULUR: I'm happy to share that with you.

DR. HARROUK: Yes.

DR. GULUR: It's out of Oregon National

Primate Research Center, and it's basically been done on Japanese monkeys, as I said. I'll be happy to pass that link around.

DR. HARROUK: Yes. I'll be happy to look at it. Thank you.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Questions from our members on the phone?

(No response.)

DR. GULUR: We can have you come back to that during the discussion if that would be okay.

Thank you, Dr. Ganley.

We have one nominator presentation by Dr. Jeffrey Johnson.

Nominator Presentation - Jeffery Johnson

COL JOHNSON: Thank you, ma'am.

Again, I'm Colonel Air Force Retired Jeffrey A. Johnson. As you can see from there, I am a pharmacist, and I am also a naturopath, so that's kind of an interesting thing to sit here and listen to some of this.

To answer a couple of questions, someone was asking about some of the compounds as far as topicals. There is an interesting website called Into the Gloss.

The person that's writing this, I don't know what their documentation is, but they said there was a study called SkinCeuticals Resveratrol B, and it says, "Improve skin elasticity, firmness, and radiance," but it doesn't go into the evidence of it.

It does give some interesting names of the compound, Vine Vera Resveratrol Pinot Noir; 100 percent Pure Red Wine Resveratrol Scrub Mask Luminous Primer; CorDel Wine [ph] Expert. I think it's supposed to be vine expert, but I'm just trying to sound like I'm French; Firming Serum Radiance Day Cream; SPF 15 Eye and Lip Serum. And then I thought this one was interesting, Bite Beauty High Pigment serum; and then Sunday Riley Bionic Anti-Aging Cream.

Okay. Enough of that. So I'm up here to talk about resveratrol. I am representing two

groups today. And just to give my disclaimer of what I am, I am a paid consultant by MEDISCA.

I'm also speaking on behalf of the National Community Pharmacists Association. If you don't know about the NCPA, they represent 22,000 independent pharmacies across the country. That's an $80 billion a year healthcare market, and 88 percent of their pharmacies that they represent do some form of compounding. So that's one reason I think that's important to be aware of.

This nomination came up on September 30, 2014. As we've been talking about, it's resveratrol. Dr. Ganley, thank you very much for your excellent presentation. And I'm not going to read all this to you. You can see the description of the strength, quality, stability, and purity. We saw that as he was discussing that.

The PCCA database has a really good MSDS on it as well. It is very chemically stable. Both air and heat sensitivity was mentioned, that there is some light oxidation that we have to be aware of, and the ingredient format is in powder form.

It is recognized in pharmacopeias. I did find that the USP had proposed a monograph back in 2015, but I can't find if that was ever voted upon to make it an official USP pharmacopeia. And it is sold OTC in the United States.

Here was some of our biographies on safety and efficacy. Again, I won't read through those; you can see those on the screen, and we can come back to that.

The anti-oxidant is what we are looking for, also anti-inflammatory. It is a natural compound found in more than 70 plant species, including nuts, grapes, and pine trees. And as Dr. Ganley mentioned, you would have to drink a lot of wine, so I am going to have a glass of merlot tonight when I get home, but just one.

It is thought to play a role in preventing heart disease as a plant source, and it is a natural polyphenol derived from the root of the Japanese knotweed. It was actually discovered in 1940 and has been used in traditional Chinese medicine and oriental medicine since that time.

And again, looks like that combination formula is designed to help maintain protection against free radical oxidated damage to tissues, and again, anti-inflammatory.

Here were just some clarifications that the FDA had asked for us, again, going through that.

One of the things I want to point out -- and Dr. Ganley mentioned the uses that we had submitted back in 2014 -- I just kind of want to go over a little bit more, though, what some of those other additional uses are.

It does have anti-inflammatory properties. It's antioxidant. You've already heard about the anti-aging thoughts from the dermatology part. It does seem to indicate that there are some studies that show lowering the LDL, cardiovascular protection. It has been used in some studies with cancer, in Alzheimer's disease, diabetes, and weight management.

So I apologize for the small print. I'm going to try and give you the summation of what these studies said. The one we've got up there

right now is from Neurology 2015.

I'm sorry. As you can tell, I'm over 60 now and I probably need to be using more resveratrol so my eyes get better.

So this one is the randomized double-blind placebo for resveratrol in Alzheimer's. It was by Turner and Company. It had an N of 119. The most common side effect they had at this point was nausea, diarrhea, and weight loss. Overall, the study shows that it was fairly safe and well tolerated. It did cross the blood-brain barrier very, very well, and it did seem to have some positive effects on altering an Alzheimer disease biomarker trajectories.

So bottom line up front, we felt like that -- or at least the studies showed that there was some promise in the Alzheimer's therapy.

Again, as you find with dietary supplements and with nutraceuticals, a lot of the problem we have is there really hasn't been enough good, solid clinical studies done, and that's one of the things that you see, that we do need to encourage that

research.

The next one is from the British Journal of Nutrition back in September of '14, and this one was the effect of resveratrol on cardiovascular risk in non-alcoholic fatty liver disease. This was by the folks you can see there at the top of the screen.

It had an N of 50, and the bottom line up here was there didn't seem to be any significant changes in the blood pressure, nor in the insulin resistance, or tag. It did reduce the level of ALT, and also there was a reduction in hepatic steatosis.

Our next one was from the Archive of Medicine Research, and this one was back in May of '15, the anti-inflammatory effects of resveratrol on ulcerative colitis. The review here was the use of resveratrol as an anti-inflammatory and antioxidant. The N was 50, and there was significant positive reduction in the plasma levels of T and F and of hsCRP.Also, it seemed to have a positive effect on the activity of the NFKB.

The bottom line up front for this one was that resveratrol seemed to improve the quality of life and the diagnosis of the ulcerative colitis activity through the reduction of the inflammation.

The next one, this is the Experimental Gerontol [ph] from 2014, and this was the safety and metabolic outcomes of resveratrol supplementation in older adults. Anton was the primary researcher on this. The N on this one was only 32, but it was a triple-blind study, and they broke it into three arms. There was the placebo arm. There was one at 300 milligrams per day and 1,000 milligrams per day.

One of the things that Dr. Ganley pointed out that I think is very pertinent is the fact that the dosing range on these ranged anywhere from 10 milligrams a day up to 5 grams a day. And some of the places they saw some of the toxicities really start to happen was when they got over the level of 2500 to 5,000 milligrams a day. That's where the toxicity seemed to really hit. If they stayed below that 1500 level per day, it seemed to

not have as much impact along those lines.

On this one, we were seeing that the blood glucose was significantly lower in the resveratrol group and that it was well tolerated. Again, there was improved cardiometabolic health overall in both the arms that were taking resveratrol, and there was positive support and use. And again, the writers encouraged there be larger studies.

Our next one was from Cardiovascular Drug Therapy in 2013, and this was where they really took a hard look at the great resveratrol and how it increased the serum adiponectin, decreasing regulatory inflammatory genes. This was Tome and his crew.

The N on this group was 75. This was, again, a triple-blind study, which I found very interesting to read. The results was there were changes in the circulating inflammatory and fibrinolytic genes were analyzed. And it really just showed that the transcription profiling and inflammation genes were decreased and actually good.

The bluff or the bottom line up front is that it did increase the anti-inflammatory effect. It did decrease the thrombogenic plasma and activity, and the daily use seemed to show positive cardiovascular protection.

Our last study that we're going to look at is from Current Medical Chemicals of 2013, and this was the anti-inflammatory antioxidant effects of resveratrol in healthy smokers. The N on this one was 50, and they blocked it into 25 and 25. There were 25 using resveratrol and 25 not.

The bottom line up front for this research was that the resveratrol seemed to significantly reduce the CRP. It also significantly reduced the triglyceride concentration, and it increased the total antioxidant status of the patient. And the conclusion was that it seemed to reflect positive anti-inflammatory and antioxidant effects within the smoker, helping the smoker overall.

We wanted to also share Dr. Luis Martinez-Rivera, who is a regenerative medicine, cell, and gene therapy physician. He was going to be with

us. Unfortunately, he couldn't clear his patient schedule to join us today, but he sent us some quotes that I think are very, very important. He has been using resveratrol in his practice, so I'll read these off for you.

"For resveratrol, I've been using it for over seven years. Although starting doses are usually in my experience 100 to 200 milligrams, I have found that 500 to 1,000 milligrams are usually needed to achieve measurable results.

"I have used resveratrol mostly to aid in reducing inflammation, for example as related to arthritis and to help with cardiometabolic disturbances. As an example of the higher doses, I could observe reductions in CRP, improvements in glycemia, and also in blood pressure.

"Patients on resveratrol usually can cope better with exercise regimes and they feel more energized. My dosing approach to resveratrol is that of a sliding scale, where I would titrate up to 1,000 milligrams daily to achieve results.

"My experience is that resveratrol was

usually well tolerated. The most common side effects I've observed has been headaches and diarrhea, particularly with the higher doses.

"I consider that resveratrol has sufficient placebo-controlled studies for the FDA to consider allowing it to remain as an ingredient for compounders."

One of the things I wanted to kind of hammer home -- and we talked about this throughout the day -- is looking at the dietary supplements that are on the shelf, that we can just go in and buy at GNC or wherever versus the compounded pharmacy versions of these products, and basically, there are four things I think we need to keep in mind.

First off is the purity. As we've talked about, with a certificate of analysis that we get as a compounding pharmacist from our suppliers, whoever it may be, we're guaranteed -- and I know we've heard of one instance today that that didn't happen, but that will occasionally, but it's very, very much not the norm. The norm is when we get the certificate of analysis, we can depend on it,

so the purity is there.

We also know that we are the ones compounding it. I'm not worried about whoever it is that's making it down the street. I know what I'm doing.

We've also heard that there are standard operating procedures, that we make sure that we take a batch every so often to send it out for analysis to ensure that it is exactly what we said. That goes along with a strength assurance because we're the ones doing the compounding. So we know what we put into the product, which gives us superior quality versus what we know we have on some of the shelves where we may not have that quality in some of the products we're buying.

Then there's professional support by the compounding pharmacists and their staff as well, which we provide both to provider and patient. We've been talking about the triad, or the triad, or the triangle, or the stool of the provider, the pharmacist, and the patient. And I think that's just critical for us to remember, that we're doing

that.

I gave you some additional studies. Again, I'm not going to read through these. It's just that I wanted you to see that there were some other ones. And the key one I wanted to point out is the one at the very, very bottom, which is the therapeutic potential of resveratrol, the in vivo evidence by Baur and Sinclair.

What was interesting with them was, at the end of their study, they also referred to an additional 248 published studies in support of resveratrol in a variety of different ways. So I just think those are interesting to look at.

A couple of other last comments I just wanted to make, I did make about the USP. I mentioned the toxic doses, that when you get to those higher levels, that's part of the problem. The other thing with a compounding pharmacy we need to keep in mind is that this is the individualized, personalized therapy that we can provide our patients; that when the doc calls us, the provider calls us, we're able to both counsel with the

provider and find out exactly where he or she is wanting to go in treating that patient.

It's not that we're going to market that necessarily to the provider, but if he or she calls and asks me, "Jeff, what can I do? Where can we go with this? This is my patient. What do you think," we can work together to try to achieve that. And I think that's one thing that you don't get when you say to the patient, "Just go buy it off the shelf and see what happens."

With that, I will open that up for discussion.

Clarifying Questions from the Committee

DR. GULUR: Thank you very much. We will take clarifying questions at this time from the committee. Dr. Ganley?

DR. GANLEY: Yes. I just wanted to point one thing out, and it had to do with, I think, slide 6 of the presentation. That was the randomized, double-blind, placebo-controlled trial in Alzheimer's disease. It gets to the point that I've raised with regard to long-term concern about

safety.

In this study, patients with Alzheimer's disease were titrated from 500 milligrams up to 2 grams a day.

COL JOHNSON: Right.

DR. GANLEY: It was a 52-week study. In the results section, one of the things they were measuring as an outcome was brain volume. With Alzheimer's disease, you have brain volume loss. In their results section, the last --

COL JOHNSON: Got it. Yes.

DR. GANLEY: -- sentence it says, "Brain volume loss was increased by resveratrol treatment compared to placebo." I'm not sure how that's a good signal. I think if it had gone in reverse, where they said that resveratrol delayed it, they would be making a claim that there's some benefit there.

So that's the point I'm trying to make in the long-term safety of making an assumption because you have this in your food that dose doesn't matter. Dose does matter.

COL JOHNSON: Yes, sir. And I completely agree with you. Dose does matter, and I think that's another reason to go to a compound pharmacist and have the provider very, very much involved with that versus telling our patients just to go buy it off the shelf and go from there.

DR. GANLEY: I guess my point is, I don't want a clinician necessarily prescribing 2 grams a day to someone with Alzheimer's because they think there's some benefit here --

DR. BRAVE: Sure, understood.

DR. GANLEY: -- when in reality it may hasten their demise. That's my point.

DR. BRAVE: Got it, sir.

DR. GULUR: Dr. Desai?

DR. DESAI: I actually did have a comment that was unrelated to what Dr. Ganley just said, but I do want to comment on what he just said. I agree with you that the results say that of that study, but we don't necessarily know if that means that their disease worsened per se because apparently what they've studied here are

biomarkers.

DR. GANLEY: I don't disagree, but that is a hallmark of patients --

DR. DESAI: Correct.

DR. GANLEY: -- with Alzheimer's, and there's a progression to death, of declining brain. So this is a question --

DR. DESAI: Yes. I think it's not clear.

DR. GANLEY: -- that has to be answered.

DR. DESAI: Right.

DR. GANLEY: And that's my point, not only with Alzheimer's disease, but with all these other diseases. You're giving very high doses of something that was found, a chemical in food, and you think it's safe. But when you get into a bimodal dose-response effect in some of these situations, it could be deleterious over the long term. And that's my point I wanted to make.

DR. DESAI: Yes. I think we're on the same page. And that leads me to my question, which is, if we were to look at the average amount of systemic dosing on all the studies you presented,

can you say that there would be one safe dose that you've seen used or that you think would be optimal across all indications of what we're looking at?

COL JOHNSON: Sir, I think I would defer this one to Dr. Martinez Rivera, and I would say that what I've seen is along the line of what he's saying, starting out with that sliding scale of 100 to 200 milligrams, and like is said on slide 13, up to 1,000 milligrams daily.

From what I've seen in the studies, that seems to be. Although going back to what Dr. Ganley is saying as well, part of the problem with this is with the bioavailability and getting across into the bloodstream.

So I think the 1,000 milligrams would be where I would hang my hat, but I still think, starting out, the sliding scale. Because as he very well pointed out, the fact is that, at too low of a dose, it may actually be more detrimental than helpful, whereas at too high of a dose, it may, again, start becoming detrimental. So finding that sweet spot, so to say, is what becomes the

challenge.

For him, as you can see in his practice, that's where he is found, that up to that 1,000 milligrams a day seems to be that sweet spot for his patients, and I would kind of hang my hat on that.

DR. GULUR: I would like to clarify on that. That's anecdotal. How many patients is that? How long was the safety data --

COL JOHNSON: You're absolutely right, ma'am.

DR. GULUR: -- followed on those patients?

COL JOHNSON: Right. I could not answer that, ma'am. That's why we really had hoped he would be able to be here, but he wasn't able to, because he would be able to answer that question. I cannot.

DR. GULUR: I do have another question. As you've reviewed all of this, have you found any negative studies, where resveratrol has not shown the benefits that are being touted?

COL JOHNSON: Actually, ma'am, I kind of ran

across the same studies that Dr. Ganley did. So I would say that, as he was reviewing them, I had reviewed those same studies as well; and so, yes.

DR. GULUR: Could you comment on the Semba study that was in JAMA, which showed no benefit?

COL JOHNSON: That one I have not seen. I'm sorry. I have to apologize. We were looking at a lot of different studies, so that one unfortunately slipped past me.

DR. GULUR: I think the studies that I saw, Dr. Ganley, you had commented on were more related to impaired glucose tolerance and pain. This is more cardiovascular benefits and mortality.

Did you have a chance to review that?

DR. GANLEY: If I had spent time reviewing all the possible studies -- when we did the literature search, if you just go into PubMed and put in resveratrol, you get over 10,000 reports. If you do resveratrol in humans, it's over 5,000. If you do resveratrol in clinical trials, it's about 150.

So you could pick your diseases however you

want, but there are certain limits as to our capability to review all of them.

DR. GULUR: No, I totally understand, which is why your indications have been very specific, the impaired glucose tolerance and pain that you had reviewed. But since cardiovascular was brought up in the nominator presentation, I just wanted to bring up that particular article, which is in a well-published journal and received quite a lot of publicity, actually, since it contradicted information that was pretty much taken for granted for benefits of red wine, per se.

COL JOHNSON: Yes, ma'am.

DR. GULUR: I just wanted to bring that up.

Thank you very much. Any other comments from members on the phone? Dr. Bogner?

DR. BOGNER: So the solubility of resveratrol in water is .003 percent, at least by PubChem. So it's not surprising to me, actually, that you'd get some high dose, some low dose. It's not very clear what the dose is.

How does one control the bioavailability?

Why would one give a gram of resveratrol when the solubility is so low, you wouldn't expect to get half of that in?

COL JOHNSON: I think Dr. Ganley was kind of pointing to that as well, that part of the problem with bioavailability -- and that really is the challenge of trying to get it into the bloodstream and get it going because, as you're pointing out, either, A, it's going to get stuck in the tissue, and therefore not going to get in, or it's going to get in and get out real quick through the first pass.

DR. BOGNER: Actually, I'm saying it's not even going to get past the GI tract, and I'm wondering if we know anything about the formulations in the supplements because that could change actually the dose that the patient gets from exactly the same milligram strength.

COL JOHNSON: I think from the supplement point of view, ma'am, your point is exactly right because we don't know.I can't tell you because most of those are proprietary. I couldn't tell you

what they put in them to begin with. I know, when we compound them, I can tell you exactly what I put in. And I know the powder that is used is usually 99 percent pure. But it's an excellent point. It's a very excellent point.

DR. GULUR: Dr. Desai?

DR. DESAI: I just want to make one comment before we forget since it's brought up several times throughout the discussions, in Dr. Ganley's and the nominator's presentation.

Resveratrol is available in cosmeceutical products topically, and it's not obviously been studied in the same way that it would as a drug, but some of the products mentioned, we actually sometimes use as adjuvant treatment in topical aesthetic dermatology, specifically the one he mentioned by SkinCeuticals.

So it is available in multiple ingredient-based cosmeceuticals, specifically the ones that oftentimes are combined with tretinoin and retinol-based products in an OTC cosmeceutical formulation. So I just did want to mention that, that it has

been used and it has been studied in small cohorts, usually by the companies that are making them.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: Thank you very much for your presentation.

COL JOHNSON: Yes, ma'am.

Committee Discussion and Vote

DR. GULUR: We do not have any open public hearing speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion.

Any comments from the committee members? Dr. Burman?

DR. BURMAN: Just a quick comment that I think everybody realizes is that the studies that were just gone through by the nominator, we didn't have time to look at, to analyze critically, or to really see whether there were control groups, et cetera.

DR. GULUR: Dr. Bogner?

DR. BOGNER: I have a question to the FDA folks, and this may not be fair. If you had to rank your safety concerns regarding the compounds, I guess the potentially listed materials we've talked about today, where would this rank?

DR. GANLEY: I'm not sure how to really respond to that. That's not how I think about things. I think in this situation, I think there's an assumption in the public, because it's in food or it's in red wine, that it's okay. But it really does get down to clinical pharmacokinetics and pharmacodynamics and what is an effective dose and what is a detrimental dose.

I think there's clearly literature in the in vitro and ex vivo literature that suggests that there can be a bimodal effect. So it behooves us to make sure that we actually know what the dose is.

When you're getting up to grams per day -- and I think a lot of these diseases that have been mentioned are serious diseases. Inflammatory bowel disease is a very serious

disease. I'd love to have a drug that worked great on it, but I think we ought to know what the dose is and what the long-term consequences of use are.

I think it's very concerning when you see a study like this in Alzheimer's, and there's a signal which they would have reported differently had it gone in the other direction, that it's just sort of dismissed as not being relevant as a concern. I think there's this lore out there that these things can be used and prevent cancer or whatever, and I think you have to be cautious about that.

To me, it's not a word to the compounder. It's a word to the clinicians who are prescribing this. Compounders are just making what they're told to make. I'm more concerned about clinicians who are going to write prescriptions for this stuff, who absolutely had no understanding that there's drug interactions with this when you get to a certain dose.

Doses that were studied in this clinical study was a gram per day for 28 days, where they

used probed drugs to help determine whether there were drug interactions, and they did establish that. We don't know if half that dose would have the same effect. Obviously, more would have an effect and maybe even a greater effect.

So when you're starting to get up to hundreds of milligrams per day to grams a day, you have to think about what benefit are you providing to a patient. These drugs can be prescribed for long periods of time, and you ought to know something about the safety of it.

Again, that's not directed at the compounders; it's directed at clinicians.

DR. GULUR: Dr. Carome?

DR. CAROME: Just to follow up on the point Dr. Burman made, I agree we didn't have time to look at the studies in detail, but from what I could tell, from reading the abstracts that were posted up, most of the endpoints that they were measuring were not clinically meaningful outcomes as far as I can tell.

DR. GULUR: Dr. Desai?

DR. DESAI: Just to clarify, the nomination is for impaired glucose tolerance, so what we will be voting on is specifically for impaired glucose tolerance. And if I remember from Dr. Ganley's presentation, you've mentioned some good data, or some studies -- I don't think we went into specific references -- that it did help increase insulin secretion, decrease or improve --

DR. GANLEY: Those were in animals.

DR. DESAI: So that was my question. Are there any that we found in humans related to insulin levels or glucose secretion?

DR. GANLEY: There are studies in diabetics where they look at these various markers. I don't know if the endocrine folks here are here to answer.

DR. DESAI: Dr. Burman may know this.

DR. GANLEY: He can try.

DR. DESAI: I was just curious because since we're voting on that -- and the one mention that we had in your presentation did show --

DR. GULUR: Dr. Desai, I just wanted to

clarify that we will not be voting on the one indication, because once this drug is on the list, it can be used for any indication.

DR. DESAI: Correct, correct. I just wanted to make sure we had clear data on the human aspect of that because that's what the nominators had initially presented.

DR. GULUR: Dr. Burman?`

DR. BURMAN: Just a quick comment on impaired glucose tolerance tests, it is not necessarily these days the standard test to determine whether someone is going to get complications from diabetes or whether they will progress to diabetes. It's a 70-gram glucose ingestion followed with blood sugars two hours later that, in this case, would be 140 to 199 or have a fasting glucose between 100 to 125.

The test is not reliably reproducible. That amount of glucose is not what we normally eat during regular meals, and we would use, these days, insulin and glucose levels with hemoglobin A1c, maybe even a 24-hour glucose monitor to better

assess glucose homeostasis.

DR. CHONG: Hi. William Chong from the Division of Metabolism and Endocrinology Products. To address your question about human studies, there have been some reported studies in patients with diabetes. I believe Dr. Ganley also referenced a small study in patients with impaired glucose tolerance.

We've not viewed the studies in the patients with diabetes to show clear results. There have been some mixed reporting of some effect or no effect. In the study that Dr. Ganley presented, that was a small study. There was a small effect on the glucose level following the standardized meal that they used. But as he also mentioned, it's not really clear what that means in terms of clinically meaningful benefit.

DR. GULUR: So I would just like to put one point out here. So far, we've had two indications, a narrow therapeutic narrow index that appears for the dose, given the know bioavailability of this substance and also the fact that we are

recommending doses or we are seeing dose ranges that may or may not, A, have efficacy and can potentially at higher doses have significant side effects.

Two other concerning markers that I've seen is the Alzheimer's study, where this medication given for whatever duration caused a decrease in brain volume size, which is pretty significant, and yet not commented on.

The other study that I was referencing was actually referred to a primate study in which they gave the female primates medication, and this, resveratrol, as part of their diet at just a higher dose than you would normally consume. And the fetus had a 42 percent increase in the pancreas size, even though there were benefits seen in the female primates themselves.

So given the questionable safety signals in this, without any real supportive literature to contradict it otherwise, it appears concerning.

Dr. Mixon, you had a question?

MR. MIXON: I just have a comment. We're

spending a lot of time debating the clinical efficacy of this drug. The drug is going to be prescribed by or recommended by practitioners, whether we can compound with it or not. Because it's over the counter, it's a supplement.

So just keep that in mind. I mean, you're not going to change the minds of people that are recommending this substance by placing it or not placing it on the list of bulk drug substances.

DR. GULUR: Is it available as a dietary supplement at 1,000 milligrams per day?

DR. GANLEY: You can buy 500-milligram capsules or tablets. And I'll just take exceptions to your comments, because there is a big difference in whether it's a dietary supplement and standards with regard to safety, because the agency does not review the safety unless -- and, again, the hurdles to get over, for us to declare something as unsafe are very high for dietary supplements.

On the drug side, we look at things differently. We look to see whether long-term use and short-term use causes potential harm simply

because we don't have a lot of studies. In fact, we do have 1 study in Alzheimer's disease that suggests there's going to be harm.

My point of view is that's problematic to characterize as this should be something on a drug list that a healthcare provider can prescribe. I don't think most healthcare providers would have even 1 percent of the knowledge that was presented to you today with regard to the potential drug interactions with cytochrome P450 enzymes.

I think we don't know the situation of the 15-year-old child who was taking risperidone and also resveratrol 4 times a day. It just seems odd that someone would take that as a dietary supplement 4 times a day and that there's a potential drug interaction there. They shouldn't be prescribing it.

MR. MIXON: And it's even less likely that the prescriber is going to know it when they're just going to the drug store, or to Walmart, or whatever, or Amazon.

DR. GANLEY: I know. But the way our laws

are set up in this country, dietary supplements are as they are. People can make a conscious decision of whether they want to take it. It's very different to throw that into the drug realm, though.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: I was just going to comment on that. I think that's right. I get frustrated -- and I said this on our earlier vote, with regard to these votes -- for products that are also available as dietary supplements. But I really don't think we can just throw up our hands when we're considering something that's available in dietary supplement form and just assume that the vote means nothing.

It does seem significant to me. We've been given 4 factors to consider. And if this committee recommends, and FDA ultimately concludes, that the balance of those factors is in favor of the substance, that strikes me as different. We're saying that the characterization, and the balance of safety and effectiveness, and the historical use

of the product support its use as a drug.

There's already a big business in resveratrol, and I think you can see that if we put this on the list, we will see. The nominator presented a whole host of indications that were therapeutic claims that you could make for a compounded version of resveratrol that you would not be able to make, at least as I understand it, for the dietary supplement.

So I would just say that I think we've got four factors that we've been given to consider, and it's not insignificant if we conclude -- our conclusion either way on this, even if it's available as a dietary supplement.

DR. GULUR: If there is no further discussion -- yes, we do. Dr. Braunstein?

DR. BRAUNSTEIN: Hi. I would just like to maybe turn the question on its head. After this committee perhaps has voted down whether certain APIs that are available as over-the-counter nutraceuticals should be on the list, maybe the FDA could compile that list. And, in fact, you could

go challenge Congress to take a look at why substances that a panel of scientists don't feel should be made available by prescription are available over the counter for sale in an unregulated way to people who are not well informed about the risk-benefit of the products that they're purchasing.

DR. GULUR: Thank you all very much for this discussion. We will move on now to the vote. We end our discussions and start the vote.

The question before us, FDA is proposing that resveratrol not be included on the 503A bulks list. Should resveratrol be placed on the list? If you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF monograph or component of an FDA-approved drug.

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.

(Voting.)

DR. CHEE: For resveratrol, we have zero yeses, 12 nos, and zero abstain.

DR. GULUR: Dr. Burman before Dr. Carome corrects me again, would you mind?

DR. BURMAN: Yes.

DR. GULUR: Thank you.

DR. BURMAN: Thank you very much. First of all, thank you to the nominator and the FDA for a great discussion. This is Ken Burman, and I voted no basically because of the possible adverse effects, GI and renal, because the studies are relatively short term; lack of history regarding compounding; insufficient clinical studies regarding pain and diabetes; and issues regarding the bioavailability.

As I already mentioned, the diabetes study or the impaired glucose tolerance study was related to oral glucose tolerance tests, which isn't necessarily reproducible or a measure of long-term effect. Thank you.

DR. GULUR: Thank you. Dr. Vaida?

DR. VAIDA: Allen Vaida. I voted no, and I agree with my colleague here. But also, I think it really came to light with the indications again with the nominator. After looking at pain and glucose intolerance and their bringing up studies with Alzheimer's, ulcerative colitis, and heart disease, just really shows that you have limited control over how these drugs could be used.

DR. GULUR: Dr. Venitz on the phone?

(No response.)

DR. GULUR: My apologies. Dr. Venitz did not join us for this discussion.

Padma Gulur. For reasons stated both in this discussion and before, long-term safety and the therapeutic index of this drug influenced my vote.

MS. DAVIDSON: Gigi Davidson. I voted no for many of the reasons stated. I'm particularly concerned about the number of potential drug interactions. Here, there are more than 40 drugs alone that are substrates of CYP that are very significant drugs therapeutically.

I've been counseled often and counseled off and on to avoid drinking grapefruit juice when certain medications are given, but I've never been counseled, nor counseled, to avoid resveratrol. So I think that more discussion in the lay public and the prescribing public is warranted.

DR. GULUR: Dr. Humphrey?

MR. HUMPHREY: William Humphrey. I voted no as well. I have concerns about the safety concerns, the unclear dosage recommendations, and the lack of clinical efficacy.

DR. GULUR: Dr. Desai?

DR. DESAI: Seemal Desai. I also voted no. I want to thank the nominator for an interesting presentation. I think botanical ingredients like this certainly are interesting and certainly offer

some interesting therapeutic insights potentially for unmet needs in our patients, but the drug interactions in particular were one of the things that worried me the most with this, as well as the renal toxicity.

DR. GULUR: Dr. Wall on the phone?

DR. WALL: I voted no. I think this drug has a lot of hope and there's a lot of people who want it to work, but there's too many unanswered questions to say that we can safely just put it out there for anybody for anything.

I would have liked to have seen the physician who they had read his comments to, really -- if he's working on it that much, to have compounded it as a study, present the data.

It's really easy to prescribe something and just sort of put it on your checklist, but it would be so helpful for all of us, for people to really document, and know, and to put it together, put NCPA and other people where they can put their data together and really have good data so that we can have even better discussions than we had today.

Thank you.

DR. GULUR: Thank you, Dr. Wall.

Dr. Patel?

DR. PATEL: Kuldip Patel. I support all the comments made earlier and would just add to those comments that I continue to have concerns about the dose-effect relationship, which I had questioned earlier. Toxicity, especially if it's approved post-marketing, would be difficult to manage; lack of efficacy data, particularly in clinically meaningful outcomes.

Lastly, translating the data that was presented, that was in favor of the product and the animal dosing studies, would be difficult to translate into human use.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted no because the data were so contradictory here and there, and I'm concerned about the unknown unknowns.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: Elizabeth Jungman. I also

voted no. I just didn't think that the balance of safety and effectiveness worked in favor of the substance here.

DR. GULUR: Dr. Hoag?

DR. HOAG: I voted no for all the reasons listed.

DR. GULUR: Dr. Carome?

DR. CAROME: Mike Carome. I voted no for many of the reasons stated, and I was particularly concerned about the potential for adverse drug-drug interactions.

DR. GULUR: Thank you all very much. Would the FDA officials have any closing remarks?

MS. BORMEL: I'd just like to thank everybody for their participation today and for staying longer, and we'll look forward to tomorrow's meeting.

Adjournment

DR. GULUR: Thank you. This will end the session for today. We will resume in the morning.

(Whereupon, at 5:11 p.m., the afternoon session was adjourned.)