FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Wednesday, September 12, 2018

1:17 p.m. to 4:36 p.m.

Afternoon Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jay R. Fajiculay, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Robin H. Bogner, PhD

Professor

University of Connecticut

School of Pharmacy

Department of Pharmaceutical Sciences

Storrs, Connecticut

Michael A. Carome, MD, FASHP

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Seemal R. Desai, MD, FAAD
President and Medical Director
Innovative Dermatology
Plano, Texas

Padma Gulur, MD (via phone)
Vice Chair, Operations and Performance
Duke University School of Medicine
Department of Anesthesiology
Duke University Medical Center
Durham, North Carolina

Stephen W. Hoag, PhD
Professor
Department of Pharmaceutical Science
University of Maryland, Baltimore
Baltimore, Maryland

William A. Humphrey, BSPharm, MBA, MS
Director, Pharmacy Operations
St. Jude Children's Research Hospital
Memphis, Tennessee

Elizabeth Jungman, JD
Director, Public Health Programs
The Pew Charitable Trusts
Washington, District of Columbia

Kuldip R, Patel, PharmD
Associate Chief Pharmacy Officer
Duke University Hospital
Durham, North Carolina

Allen J. Vaida, BSc, PharmD, FASHP
(Acting Chairperson)
Executive Vice President
Institute for Safe Medication Practices
Horsham, Pennsylvania

Jurgen Venitz, MD, PhD (via phone)
Professor and Vice Chairman
Virginia Commonwealth University
School of Pharmacy, Department of Pharmaceutics
Richmond, Virginia

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

William Mixon, RPh, MS, FIACP

(Industry Representative)

Former Owner

The Compounding Pharmacy

Hickory, North Carolina

Christopher J. Smalley, MS, MBA

(Industry Representative)

Compounding Pharmacy Consultant

ValSource

Downingtown, Pennsylvania

TEMPORARY MEMBERS (Voting)

Thomas Chelimsky, MD

(Participation in alpha lipoic acid, coenzyme Q10, and creatine monohydrate discussion)

Tenured Professor of Neurology

Medical College of Wisconsin

Milwaukee, Wisconsin

Marc Gregory Ghany, MD, MHSc, FAASLD

(Participation in alpha lipoic acid, coenzyme Q10, and creatine monohydrate discussion)

Investigator

Liver Diseases Branch

National Institute of Diabetes and Digestive and Kidney Diseases

National Institutes of Health

Bethesda, Maryland

Hrissanthi (Chris) Ikonomidou, MD, PhD

(Participation in alpha lipoic acid, coenzyme Q10, creatine monohydrate, and pyridoxal 5 phosphate monohydrate discussion)

Professor of Child Neurology (Tenured)

Department of Neurology

University of Wisconsin, School of Medicine and Public Health

Madison, Wisconsin

Sandeep Khurana, MBBS

(Participation in alpha lipoic acid, coenzyme Q10, and creatine monohydrate discussion)

Medical Director

Liver Transplantation

Geisinger Health System

Danville, Pennsylvania

Jeanne H. Sun, PharmD

(U.S. Pharmacopeia Representative)

Manager, Compounding

U.S. Pharmacopeial Convention

Rockville, Maryland

FDA PARTICIPANTS (Non-Voting)

Julie Dohm, JD, PhD

Senior Science Advisor for Compounding

CDER, FDA

Frances Gail Bormel, RPh, JD

Director

Division of Prescription Drugs

Office of Unapproved Drugs and

Labeling Compliance (OUDLC), OC, CDER, FDA

Rosilend Lawson, VMD, JD

Lead Regulatory Counsel (Acting)

Pharmacy Compounding Advisory Committee Team

Division of Prescription Drugs

OUDLC, OC, CDER, FDA

Susan Johnson, PharmD, PhD

Associate Director

ODE IV, OND, CDER, FDA

Ruey Ju, JD, PharmD

Senior Advisor for Compounding

Office of Compliance (OC), CDER, FDA

Sara Rothman, MPH

Senior Policy Advisor

OUDLC, OC, CDER, FDA

Charles Ganley, MD

Director

Office of Drug Evaluation IV (ODE IV)

Office of New Drugs (OND), CDER, FDA

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

(1:17 p.m.)

DR. VAIDA: We're going to get started with Susan Johnson, once again, for creatine monohydrate.

FDA Presentation - Susan Johnson

DR. JOHNSON: Well, good afternoon. I hope everyone had a nice lunch. Once again, my name is Susan Johnson, and I'm from the Office of Drug Evaluation IV in CDER's Office of New Drugs, and we're now discussing the nomination for creatine monohydrate.

Again, I'd like to thank the review team and express their thanks to you for participating in this process and for reviewing the dense reviews that we put out to you. We prepare them with care, and we appreciate you paying attention to the details of them.

Creatine monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A. It's proposed for oral use in the treatment of

mitochondrial disorders. We also evaluated it for use in the treatment of creatine deficiency syndromes, which were not proposed in the nomination.

Creatine monohydrate and creatine are considered the same active pharmaceutical ingredient or API, and I'll be referring to them both as creatine. Creatine is a nonessential amino acid with a well characterized structure. It's slightly soluble in water.

Based on published literature, we find it's likely to be stable at room temperature in solid dosage forms if kept away from moisture. Aqueous solution, including those intended for oral administration, are likely to be unstable.

We are aware that the nominators may have more information about the stability of liquid formulations similar to the ALA scenario that we talked about this morning, and we will certainly take it, the committee's comments, and other public comments that we receive through the docket into consideration as we proceed through subsequent

rulemaking.

The synthesis of creatine as a bulk substance is illustrated here. In summary, we find creatine is well characterized and likely to be stable in solid oral dosage forms. In healthy humans, creatine is endogenously synthesized from other amino acids at a rate of up to approximately 2 grams per day. The synthesis process involves the kidney, pancreas, and liver. Once synthesized, creatine is transported to other tissues in the body that use energy, including the brain.

Creatine supply can also come from ingestion of animal products. Creatine helps to ensure the energy supply to muscle and other tissues. When muscles are at rest, the high energy phosphate bond from ATP is transferred to creatine, and creatine phosphate is then stored. During submaximal exercise, ATP is generated through aerobic glycolysis, and creatine is less involved. During intense exercise, creatine phosphate stores are used in the anaerobic glycogenolysis process.

Pharmacokinetics from rodent models of oral

dosing with creatine show that it's quickly absorbed but has low bioavailability that may be due to solubility issues. In humans, absorption is thought to be dependent on both -- we're on slide 8 if folks want to proceed with the paper copies.

Slide 8. Let me just begin again on slide 8. Pharmacokinetics from rodent models of oral dosing with creatine show that it's quickly absorbed but has low bioavailability. In humans, absorption is thought to be dependent on both active and passive transport through the intestinal wall, although information about bioavailability is not available.

Cellular uptake of creatine relies on a creatine transporter. Creatine storage in muscle is a saturable process. Excess creatine from dietary intake or supplementation is excreted in the urine. In muscle tissue, creatine is slowly converted to creatinine, released from the muscle, and eliminated in the urine. We found no information about the pharmacokinetics of creatine in patients with mitochondrial disorders or

creatine deficiency syndromes.

We're on slide 9. In a 15-day toxicity study in which rats and chickens were given creatine in their drinking water, no adverse event findings were noticed. In rodent models, conflicting findings have been observed. In one study, rats showed no adverse effects, while in another study, rats with existing kidney disease showed additional reduced renal function.

Similarly, in adverse events of the liver, inflammatory changes were seen in liver studies of mice but not in rats. So both in hepatic and renal toxicity realms we have conflicting animal data.

The standard Ames assay was negative for creatine. You may remember the public discussion about creatine as a component of meat being heated to high temperatures and becoming mutagenic. While that's unlikely to have relevance to pharmacy compounding, we mention it here because folks may actually remember the public discussion of creatine in that context. We found no developmental or reproductive toxicity and no carcinogenicity data

for creatine.

Moving to slide 10, with regard to clinical safety, the FAERS system contained four reports, including two serious cases. Given the animal toxicity data suggesting renal or hepatic safety issues, we're just providing some additional detail about these cases.

One case reported the death of a 42-year-old male who experienced cardiac arrest while on hemodialysis due to acute renal failure. The patient had recently been diagnosed with diabetes and had been prescribed Metformin. He developed lactic acidosis, a known side effect of Metformin, and the reporters said it's unclear whether his renal failure may have been related to preexisting diabetic nephropathy, although some suspicion of the contribution of creatine was described in the report.

A 38-year-old male who had been taking creatine supplements for several years was diagnosed with cholestatic hepatitis. Since he was also taking anabolic steroids, it was thought that

those were most likely causal.

Creatine is sold as a dietary ingredient in dietary supplement products often taken with the intent of increasing muscle strength. The CAERS database contained 139 reports, including 4 deaths that appear unrelated to creatine. No renal toxicity was reported among those cases.

Moving on to slide 11, we found no reports of serious adverse events from studies of patients with mitochondrial disorders, and there were no studies in patients with creatine deficiency syndromes. We identified one case report of a patient with creatine deficiency syndrome who experienced urinary crystals at a dose of 800 milligrams per kilogram per day -- I'm sorry, 800 milligrams per day. I was correct the first time; 800 milligrams per kilogram per day. The condition resolved with a dose reduction.

In another published case report, an 18-year-old male with mitochondrial disease and preexisting nephropathy experienced increased renal insufficiency with urea retention and reduced

creatinine clearance. The patient admitted to having used creatine for a period of time during the decline of his condition. And because the decline was gradual, the reporting clinicians attributed it to his underlying disease but also cautioned about the potential for safety issues associated with the use of creatine in patients with mitochondrial disorders.

In 2012, Gualano and colleagues undertook a review of the considerable volume of published information about creatine and renal toxicity. The review concluded that doses up to 5 grams per day over a period of months in healthy individuals appears to be safe. Doses higher than 5 grams per day were not recommended. And it was observed in their review that data in special populations, particularly those with disorders that may affect renal function, have not been well studied.

With regard to the safety of creatine, we conclude that in healthy adults, it's generally safe. Urinary crystals may be associated with high prolonged dosing, but this was reported in patients

with creatine deficiency syndrome. There's also sufficient information to support a clinical concern of the possibility of renal toxicity, particularly in patients at risk for renal impairment from their underlying disease. This includes patients with mitochondrial disorders.

Creatine deficiency syndromes are rare diseases caused by autosomal recessive inborn genetic errors. They are not considered mitochondrial disorders, and they result in a diminished brain pool of creatine.

There are three creatine deficiency syndromes, and there are no FDA-approved treatments for any of them. No prospective clinical trials have been conducted, but there is evidence that for at least two of these syndromes, creatine has a beneficial effect. These two syndromes are associated with the deficiency of one of two enzymes in the creatine synthesis process.

L-arginine-glycine amidotransferase deficiency, or AGAT deficiency, appears to be somewhat less common than guanidinoacetate

methyltransferase deficiency or GAMT deficiency. Doses of up to 800 milligrams per kilogram per day have been shown to increase brain creatine levels and improve symptoms. A third syndrome in which there is a deficiency of the creatine transporter may respond to creatine supplementation in some cases, but the evidence is inconsistent.

We found 3 placebo controlled trials that were crossover studies of creatine's use in mitochondrial disorders. One of these studies showed minor improvement on a subset of endpoints only under conditions of intense exercise. The 2015 guidelines from the Mitochondrial Medicine Society do not provide a recommendation on the use of creatine.

There's a small amount of clinical information that establishes that creatine is effective in treating AGAT or GAMT deficiencies. There are no compelling data we find that support the use of creatine treatment in mitochondrial diseases.

Having said that, we are aware that creatine

can be used in various mito cocktails, those mixes of vitamins and supplements that we've described that are tailored by clinicians to treat mitochondrial disease patients, but we were unable to find sufficient data to establish how long and to what extent creatine has been used in compounded products.

In summary, creatine is well characterized and can be stable under normal conditions in solid oral dosage forms, and we expect to receive additional information about the use in aqueous forms. It is generally safe, however, there are data that suggest a concern that creatine can be associated with renal toxicity, particularly in patients with diseases that predispose them to renal impairment.

Based on literature reports and clinical practice, creatine is effective in treating the rare disease creatine deficiency syndromes, AGAT deficiency, and GAMT deficiency. We have not found information about compounding with creatine, but we are aware that it is used in the treatment of

mitochondrial disorders.

A balancing of these factors weighs in favor of creatine monohydrate being added to the list of bulk drug substances that can be used in compounding under Section 503A. Thank you very much, and I'm happy to take questions.

Clarifying Questions from the Committee

DR. VAIDA: Thank you, Dr. Johnson.

We'll now have opportunity for any clarifying questions from the committee. Yes, Dr. Ghany?

DR. GHANY: Can you comment on the safety of the recommended dose of 3 to 5 milligrams in patients with renal insufficiency?

DR. JOHNSON: The only safety information that we had that limits dosing -- and as I understand it, this is completely an empirical process and doses are titrated up until patients experience some relief of symptoms. The only experience we have with dose limiting is the urinary crystal toxicity.

So we can't say what the optimal dose would

be, and I think it's likely patient dependent.

DR. VAIDA: Dr. Sun?

MS. SUN: I noticed that there were some things in the FDA report that they were concerned about the stability in liquid formulations. Did you find any uses on any compounded formulations that were not solid oral dosage forms?

DR. JOHNSON: If I could have the one backup slide that we prepared? I just want to go over the information that we have that was public at the time of the review. Based on published literature, stability concerns are most prominent at low pH's. And you'll note that these are very old references, so there isn't a lot of newer information in the literature. And that's why we're looking to the nominators to clarify.

We also noted in these papers that degradation occurs in solution at higher pH's. The degradation process is slower, but it is relevant to compounded formulations. So we are recommending that we consider at this meeting solid oral dosage forms and that we use information that we received

from the nominator, and elsewhere perhaps, to look at liquid formulations.

Does that answer your question?

MS. SUN: Yes. I guess in some of the case reports that you saw on efficacy and maybe even the adverse event reporting, were there any liquid formulations in there?

DR. JOHNSON: I don't know if I can say that for sure. I will look back through the review as we're talking and see if I can find that, but I don't believe that in all cases the formulation was described.

DR. VAIDA: Dr. Chelimsky?

DR. CHELIMSKY: Just a dose clarification. So that was truly 800 milligrams per kilogram per day, which translated for a 70-kilogram person would be somewhere around 50 grams per day? That's 10 times more than -- that's a good thing. If the only thing that happened was urine crystals, that means even at that dose, it seems reasonably safe.

DR. VAIDA: Dr. Khurana?

DR. JOHNSON: Let me make sure I have that

accurate, and I will pull up the original paper just to make sure. Thank you.

DR. VAIDA: Dr. Khurana?

DR. KHURANA: I just have a couple of questions, ones directed to the speaker and for the FDA. One is that the two syndromes that are described for these enzyme deficiencies in the creatine synthesis process, what's the incidence of this disease? Even in comparison to other mitochondrial diseases, how rare are they?

DR. JOHNSON: These are extremely rare. There were surveys done globally to assess the number of patients, and they identified families. In AGAT deficiency, a review was done in 2015 looking globally at the number of patients, and they found 16 patients in 8 families. If there can be a rare-rare disease, that's the one. GMAT is slightly more common. There were 48 patients from 38 families in a review done in 2014.

DR. KHURANA: The other question is to the FDA. If anybody has looked at the supplements, the majority of the currently available over-the-

counter supplements are not just pure isolated creatine supplements. They're invariably a cocktail of something added with caffeine and whatnot with it.

So when we vote here, are we voting -- is that a vote to let that combination supplement stand or is this a vote purely for supplements on creatine alone? That's a concern because a lot of these supplements are overloaded with -- they say creatine, but they are creatine plus with a lot of caffeine in it.

DR. JOHNSON: You can clarify. But what we're voting on is whether solid oral dosage forms of creatine, starting with the compounding from a bulk drug substance, can be added to the 503A list. We're not making a recommendation about the use of dietary supplements as creatine alone or with any other vitamins or supplements.

DR. KHURANA: Great. Thank you.

DR. HOAG: Steve Hoag. I have kind of a similar question. I might have heard you wrong, but did I hear you say that the monohydrate and the

anhydrous were the same, or did you say -- I didn't quite hear what you said.

DR. JOHNSON: They're considered the same active pharmaceutical ingredient, and I'm going to let Dr. Zhang comment on that. We do an evaluation at the start of these reviews to understand how the literature can be amalgamated. So in some cases, we have to keep the substances separate, and in some cases we can use data from each.

DR. HOAG: Yes. If you look at the USP, there are situations where a certain salt is needed for the product to be efficacious.

DR. JOHNSON: Correct, yes.

DR. ZHANG: Just to be clear -- this is Ben Zhang, FDA -- the monohydrate or non-hydros forms, they're just different polymorphisms. In this case, the active pharmaceutical moieties aren't the same. So in order to consider the medical indications and the efficacy, in this case, we consider them as the same.

DR. VAIDA: All right. Thank you.

We'll now move on to the presentation by the

nominator, and it's Dr. A.J. Day from Professional Compounding Centers of America.

Nominator Presentation - A.J. Day

DR. DAY: Good afternoon. Once again, I'd like to thank you for allowing me to address this committee and the FDA regarding the use of creatine monohydrate in compounded formulations for support in patients with mitochondrial diseases. We're not going to spend a lot of time going through all of the different characterizations that Dr. Johnson just went through.

Again, from the FDA's assessment, they do note that while it's well characterized physically, they do have a concern about aqueous stability. They went through the safety data in depth. They also mentioned concern regarding the amount of literature and published peer-reviewed trials that addresses the efficacy of creatine in patients with mitochondrial disorders, and then the historical use of compounding is not a concern.

So first let's start with the safety concern. Again, we talked about level of evidence,

so when we get to the efficacy component, we'll remember this stuff right before lunch, hopefully. When we talk about the stability component of it, FDA cited three studies. Two of them, which were just shown on that slide, were from the 1920's, 1925 and 1928. They were looking at not the stability of creatine or creatine monohydrate. These studies were designed to find an equilibrium point between creatine monohydrate and creatinine.

So they were intentionally trying to degrade the creatine to force it to form an equilibrium point with creatinine. It was not a stability study to begin with.

FDA cites another study, Ganguly and colleagues from 2003, where they found that the pH had an impact on the stability, on the degradation of creatine. And they showed that after 4 days, they noted rapid degradation.

Something that is important to note is that that study did not look at creatine monohydrate. They use creatine citrate, which forms a weak acid, forcing the pH into a more acidic environment.

This is not a form that we are nominating. This is not a form that we have proposed for use in compounding, and thus, we are not addressing anything about those specific studies.

What we are addressing -- and this is some data about the articles from the 1920's where they found that equilibrium point. Their conclusion that in alkaline to neutral environments, the conversion to creatine is slowed. And at some point in the alkaline environment, it forms an almost irreversible formation of creatine.

Then we move on to some actual data on creatine monohydrate. This is an independent test result from an FDA-registered analytical laboratory on a compounded formulation of creatine monohydrate. This pharmacy that created this and had this preparation tested is utilizing a 30-day beyond-use date, which is a completely acceptable and common shelf life in the world of compounding. While it may be considered too unstable for typical manufactured drugs, in the world of compounding, that is a very reasonable beyond-use date.

They did this potency test. They stopped the test after about 43 days because they got the results that they needed to provide these prescriptions for individual patients on a monthly basis. They did note also -- let me go back to that slide -- the pH of this formulation. It was in the range of 4.9, 5.3 throughout the duration of the study, and it was stored at a refrigerated temperature.

When I read the FDA's briefing information and we saw their concern regarding aqueous stability of creatine monohydrate, and we saw the specific notes within the studies, the primary literature that looked at the effect of pH on that conversion of creatine to creatinine, we wanted to identify what is the likelihood of that happening spontaneously in compounded formulations.

Just at a 1 percent concentration added into purified water USP, the pH of creatine monohydrate solution is between the range of 7.5 and 7.68. I had to submit these slides last week, but it's 23 days. I checked with our analytical division this

morning. And at 23 days since we created that solution, it's stable. The pH has stayed within that narrow range, and there is not expected to be any conversion.

There's, tangentially, a project going on with an analytical laboratory, the same one that conducted the initial trial, for that other pharmacy to verify the stability of this under full stability indicated forced degradation studies.

Further, there is data from a number of dietary supplement manufacturers about the stability of their formulations in an aqueous environment. This set of data comes from one of these dietary manufacturers, and their formulation is buffered at a pH of 6.5 to 7.5, stored at room temperature. You see their pH range. They do note that when they get rid of that buffer and actually put it into a more acidic buffer, that they get degradation at the 3-day mark down to 80 percent, so 20 percent degradation.

That same company that recommends their product be stored at refrigeration when they keep

the pH around 6 to 7 notes remarkable stability. Even beyond the 30-day mark, they're at greater than 98 percent on their potency.

This is from yet another dietary supplement manufacturer. I redacted the names of these manufacturers per their request, but this is creatine monohydrate in an aqueous liquid format, and their buffer keeps the pH at an alkaline pH greater than 7, less than 8. And they have real-time testing as well as accelerated shelf-life testing showing 36 and 48 months. You can see the actual data that they have there.

So I present this simply to state that there is data, while it may not be from a clinical trial, showing that the formulations of creatine monohydrate in an aqueous media are stable, at least for the durations of therapy that we're talking about for specific prescriptions in compounding. A 30-day supply or even a 14-day supply is very common for these formulas.

Next, we're going to look at the efficacy data that FDA has identified. This is just a

screenshot from the FDA's briefing material. The article from 1997 by Tarnopolsky, as you heard in the previous open public hearing session on CoQ10 with Dr. Korson, some of this research is very critical to the practice standards that we see out in the real world.

They used 5 grams of creatine monohydrate twice daily for 2 weeks, followed by 2 grams orally twice a day for 1 week. They also had a placebo control in this study. They concluded that creatine's effects were limited to high intensity aerobic and anaerobic activities, and there is no effect on lower intensity aerobic activities.

When we look at the specific demographics of the patients that were included in this study, the phenotype of mitochondrial disorder that they all had, or for the most part all had, is MELAS. Again, they specifically state that creatine seems to have the most benefit in high intensity activities such as sports and manual labor, and it's not necessarily about activities of daily living. They do also say that it may possibly be

very effective or beneficial in weaning from a ventilator an already fatigued patient.

The type of activity that we're looking at and the type of measurements that clinical trials are primarily studying should be really focused on the types of activity that utilize creatine as a primary source of ATP generation. And I'm really glad that the projector is working right now because in the slide, this color doesn't come out all that well.

The utilization of creatine as a source for the generation of ATP is in a very specific time line, and it's more highly utilized for specific types of muscle utilization. So we need to keep that in mind when we look at these other studies and what kinds of biomarkers, what kinds of activities they were looking at in assessing the efficacy of creatine in these patient populations.

Here we have a publication by Hagenfeldt from 1994. Usually, I don't include letters to the editor in these presentations and these discussions here, however, I think that this one in particular

is notable because we have a 25-year-old patient who was diagnosed with MELAS at the age of 5. So it's well established in this patient. He's had a number of different therapies. His present treatment before starting creatine involved a carbamazepine, aspirin, dipyridamole, carnitine, CoQ10, thymine, and vitamins K1 and vitamin C.

Creatine was given orally at 5 grams twice a day for 2 weeks and 2 grams twice daily thereafter, so a similar loading-dose protocol as we saw in the previous study by Tarnopolsky. The patient and his family reported reduced headaches, less weakness, better appetite, and an improved general well being during treatment.

They went through the graded exercise test. They talk about the level of improvement that this patient was able to experience at the 3-month mark with creatine and how that improvement was able to have an impact on his quality of life.

Again, another patient with MELAS. This one was cited by Dr. Johnson in her presentation just a moment ago. In the safety evaluation, this

18-year-old male patient with MELAS had two previous episodes of cerebral stroke.

Prior to the patient's degradation, which was gradual due to the severity of his disease and the kidney disease that he had preexisting, they noted that after 7 days of creatine supplementation, the symptoms of psychomental regression and aggressive behavior improved significantly, and they had disappeared completely after 4 weeks of treatment when the patient had regained all his previous mental abilities. Six months later, there was a clear improvement in his vocabulary, his concentration, and alertness.

Next, FDA brought to the table the article by Komura and colleagues in 2003. This is an interesting study specifically because of the way that they designed it. Note the phenotypes that were chosen for this study are a little bit different. They're not all MELAS patients, but these have a variety of different phenotypes of mitochondrial disorders.

From the discussion part of the study, they

also note, patient 1, they did an on/off trial. They noted specifically that when they removed the creatine, the improvements that they got disappeared. And when they re-initiated creatine supplementation at double the dose, the impact that they were able to observe on their ergometry doubled. When they reduced the dose down to the original dose, the impact on the outcomes reduced as well. They saw a similar dose outcome relationship in patient number 2 and 3.

Here, we have another case study. This is yet another phenotype of mitochondrial disorder. That says Leigh syndrome patient. This was a toddler who was not fully able to stand up independently, or when they were, they had their legs splayed quite broadly.

Soon after the initiation of vitamin B1 and B2 therapy, she was able to walk up and down a slope. Three months after starting creatine therapy, she was able to climb up and down stairs; fine motor function. She was initially only able to put a small ball into a hole if her wrist was

fixed so as to prevent involuntary movements, but after 3 months of creatine therapy, she could put 2 balls into the hole without needing to have her wrist fixed.

Komura had a follow-up article in 2006 -- sorry. This case study was the follow-up article from 2006, and again, the conclusion of this article is that creatine monohydrate supplementation improved gross and fine motor skills and respiratory and cardiac function in the present Leigh syndrome patients.

Next, FDA assessed two different trials that looked at creatine. What we noticed about these patients is that, for the most part, the phenotype of mitochondrial disorder was all CPEO.

When we look at the conclusion and the discussion of these articles from Klopstock in 2000, creatine supplementation is most effective in subjects with low endogenous muscle creatine concentrations. As these concentrations are normal in CPEO patients, these patients may benefit less than patients with other mitochondrial diseases.

They go on to talk about the specific measures, the outcome measures that they had in their study design. Their study, most variables measured low-intensity exercise, which may be more relevant for daily life, however, creatine, again, does not necessarily impact those types of activities. So the authors also conclude that we cannot exclude an effect of creatine in high-intensity exercise.

These outcomes are supported by the results of the Kornblum study, where again they studied primarily patients with CPEO, and they noted that the failure to improve muscle energy metabolism in our patients with mitochondrial disorders may therefore be attributed to the inefficacy of creatine supplementation to increase intramuscular phosphocreatine contents.

They weren't actually measuring the activities of daily living or the high-intensity muscle exercise. They were measuring phosphocreatine in the muscle. So they were looking for a biomarker rather than a clinical

outcome.

As blood concentrations of creatine significantly increase under oral creatine treatment, disturbances of creatine uptake into muscle cells should be considered. Creatine is transported into the cells by a specific creatine transporter.

So again, the impact that they're looking at here, again, within the CPEO patients has to do with the level of endogenous creatine that might be intramuscular as well as a transport mechanism when you have normalized endogenous creatine levels in these CPEO patients.

Another article that the FDA addressed in their briefing information is Rodriguez trial from 2007, and they talk about how difficult this study is to assess the specific therapy or outcomes of the utilization of creatine. It's an article to utilize a combination of creatine, CoQ10, and alpha lipoic acid. I would like to point out that this is one of the most clinically relevant studies because this is more realistic to how patients are

treated in the real world.

Again, the cocktail of medications, the cocktail of therapies that these patients are typically on is multimodal, and it's not just creatine, nor is it just coenzyme Q10 or alpha lipoic acid. These are patients who are on combination therapies to help address the various modalities that contribute to the lack of mitochondrial function.

Also, when we look at this study, they had the most broad subset of phenotypes of mitochondrial disorders. It wasn't just CPEO, it wasn't just Leigh patients, it wasn't just MELAS patients. But they had a cross section from a variety of these phenotypes.

Here's a table that summarizes the primary literature that FDA cited, as well as PCCA cited in our nomination. You can see that all of those in green are the ones that showed positive clinical outcomes. While the studies were not necessarily designed specifically to look at the safety of creatine in the human population, they do talk

about the adverse event profile of the patients that were involved, and they were universally pretty well tolerated.

The Klopstock and the Kornblum study, both of them were primarily focused on patients with CPEO phenotype of mitochondrial disease. And even they noted that it was primarily well tolerated, a few incidences of muscle cramps or flatulence being a primary side effect profile. And then of course the Rodriguez study that looked at a multimodal approach for these patients.

So that's the primary literature. Again, similar to coenzyme Q10, we also look at the guidelines and expert opinions that have been published on this topic. In 2009, the Mitochondrial Medicine Society had a publication that stated, based on our clinical experience and judgment, we agree that a therapeutic trial of CoQ10co along with other antioxidants should be attempted.

In their chart, of those other antioxidants, they specifically mentioned creatine at a dose of

0.1 grams, or 100 milligrams per kilogram, orally daily, up to a maximum dose of 10 milligrams -- sorry, 10 grams per day, and then they also give adult dosage along with adverse effects to watch out for and specific comments about its utilization.

The 2015 study that Dr. Johnson and the FDA noted did specifically say that there's a general lack of consensus regarding which agents should use, although most physicians prescribe CoQ10 levocarnitine, creatine, ALA, and certain B vitamins. The citation that they actually point to, that's citation number 146, simply goes back to the survey that they conducted in 2013, where again, 75 percent of respondents stated that they do utilize compounded creatine for their patients.

Here we have the physician's guide to the treatment and follow-up of metabolic disease, where again they specifically state that administration, metabolizing cofactors such as riboflavin, ubiquinone, carnitine, and creatine are utilized. And the starting dose of creatine; again, they give

you a loading dose as well as a therapeutic maintenance dose.

So in conclusion, I hope that you have seen that there is stability data about aqueous formulations of creatine monohydrate. Again, these are packaged in amber plastic prescription bottles kept in a refrigerated temperature, and they can be stable for at least 40 days.

Typically, pharmacies will utilize a 14-or a 30-day beyond-use date for those preparations. The pH in the vehicles that that is compounded in is greater than or equal to 4.9. You've seen the data from the dietary supplement manufacturers as well.

Creatine monohydrate has shown more efficacy in certain phenotypes of mitochondrial disorders, such as MELAS and KSS, than other phenotypes due to intrinsic differences such as endogenous, creatine levels. Creatine monohydrate may benefit more in high intensity activities simply due to the way that our bodies utilize different sources of ATP generation for different types of activities. Thank you very much.

Clarifying Questions from the Committee

DR. VAIDA: Thank you, Dr. Day.

We'll now have an opportunity for some clarifying questions from the committee. Dr. Carome?

DR. CAROME: Mike Carome. So I have a question both for Dr. Day and also maybe for FDA. As a nephrologist, I have a particular interest in the renal toxicity issued here.

Dr. Day, you said FDA had no safety concerns. I'm not sure that accurately reflects FDA's position. FDA raised concerns about possible kidney toxicity, noting, though, that there have been safe doses identified for healthy adults.

In the nomination, I believe the proposed dose was up to 20 grams per day. Is that correct? That's for Dr. Day. Then for FDA, when you say that safe doses have been identified for healthy adults, what doses are you talking about?

DR. DAY: Well, the nomination data is there, so I'll let FDA address the specific questions.

DR. JOHNSON: Creatine monohydrate was nominated for use in oral formulations in divided doses of up to 20 grams per day.

Your next question was have we identified a safe dose? No. In the review from Gualano, who looked back through all the renal toxicity data, starting with 3 cases in the 1990s of bodybuilders essentially, who are trying to lose weight very rapidly.

There were three cases in which these individuals died, and at least one of them was on creatine. And apparently, that's how it got started that creatine may be associated with renal toxicity. And since then, cases have propagated. It was never clear whether the original ones were real.

So this review was undertaken, and their assessment of the data was that 5 grams per day for a prolonged period of time in healthy individuals is safe. Above that, they didn't have safety recommendations. They suggested that the data may actually support use even in type 2 diabetics who

at present had no renal impairment, that again, 5 grams might be safe. But doses higher than that really hadn't been established. They didn't particularly point to creatine deficiency syndromes or mitochondrial disorders, but we note that we just don't have that sort of information.

I will say -- and this is reflective of all of the rare diseases -- these patients are monitored very, very closely. And in the one case report that I showed, they picked up on the renal dysfunction very early on in its course and then monitored it for a while. The thing that they didn't know was that the patient was also taking creatine, and they did attribute it to his underlying disorder

Did you have another question? Was there one?

DR. CAROME: Just for Dr. Day. What types of doses are actually routinely being used?

DR. DAY: Yes. Thank you for that, and Dr. Carome. It was something I wanted to expand upon.

So up to 20 grams in divided doses, that was the maximum dose that I was able to ascertain from the practitioners out in the field that I consulted with as we put together the nomination because we want it to be as transparent as possible. And the statement was, "I once had a patient getting a dose that high." That is clearly an outlier.

Typically the doses are going to be less than 10 grams per day, however, because I did receive that information, I didn't feel the need to include that in the nomination.

DR. JOHNSON: And I would just add that we talked about the reviews that were done of AGAT and GAMT on a global basis, and the dose range that they found in AGAT was 100 to 800 milligrams per kilogram per day.

DR. VAIDA: Dr. Ghany?

DR. GHANY: Thanks. Marc Ghany. Two questions, one for Dr. Day and one for Dr. Johnson.

So first, Dr. Day, in some of the nomination letters to the FDA, one of the utilities of this compound was in autism spectrum disorders, but we

haven't heard any data on the effectiveness in that population.

For Dr. Johnson, does the FDA recommendation to support this mean that you endorse a 20-milligram dose per day? And if so, how was that decision arrived at if there's no data? Twenty grams; sorry. How was that decision arrived at if there's no data to support that dose?

DR. DAY: So I guess I'll go first. In my research and in my discussions with the practitioners who specialize in both autism spectrum disorders as well as mitochondrial disorders and other inborn genetic disorders, I asked specifically if patients on the autism spectrum, or specifically with diagnosis of autism, have a need, if it's a common or well-known supplements or it's just something that is used occasionally in the autism spectrum disorders.

The information that I received is that it's not that common unless the patient who has autism spectrum disorders also has a mitochondrial component, in which case they will try creatine.

They'll monitor for progress, and they always monitor renal function.

Not to answer on behalf of the FDA, but my understanding is that no specific dosing or indication is endorsed by FDA by going through this process. They can clarify more, I'm sure.

DR. JOHNSON: So to build on that a little bit, we have a process whereby we evaluate the nominations and look at the proposed uses as well as the information that's been submitted. And our review of the nominations was such that we found that use in mitochondrial disorders was supported in the nomination and use in autism spectrum disorders was not adequately supported in literature.

We do have a process that's ongoing, a contract with an external clinical expertise group to look at autism spectrum for all of the nominated substances. They're working bit by bit on various substances, but they're going to be giving us feedback, and we'll be publishing more information about what types of non-approved substances are

useful in autism spectrum disorder.

DR. GHANY: Could you comment on the dose?

DR. JOHNSON, We didn't, for the purposes of this review, look at autism spectrum disorder.

DR. GHANY: I meant the dose of 20 grams.

DR. JOHNSON: Oh, I'm sorry. For the purposes of the creatine deficiency syndrome, doses of 100 up to 800 milligrams per kilogram per day have been used, and that's largely in infants. It may or may not total 20 milligrams or 20 grams.

DR. VAIDA: Dr. Chelimsky?

DR. CHELIMSKY: Can I make a comment or is it only clarification questions? I just want to do that anecdotally I've used creatine with many, many of my patients, hundreds. And probably about half a dozen -- I typically use 5 grams a day, and about half a dozen, I've had to lower the dose due to a rise in creatinine, which I monitor pretty closely.

DR. VAIDA: Dr. Jungman?

DR. JUNGMAN: Dr. Day, it would be helpful for me to understand how much -- your best understanding of how much component is currently

solid oral dosage forms versus aqueous solution.

DR. DAY: My understanding of the compounding need for creatine in this patient population is that it's primary oral liquids due to the dose that's required. When you're talking about even 1 gram, putting that into capsules or solid oral dosage forms for a child to swallow or for children with multiple other medications especially is not really feasible. So they do typically utilize it into an oral liquid dosage forms.

In terms of how those are prepared, being are they aqueous at the time they leave the pharmacy or are they in a powder format, a dry format that then gets reconstituted at the time of administration by the caretaker or the parents or something like that, there's a split. There's a bit of variance in there. But in terms of how the patient actually takes it, the vast majority is going to be as an oral liquid.

Open Public Hearing

DR. VAIDA: With that, I'll now move on to

the open public hearing, and we have one speaker.

DR. KORSON Thank you. My name is Mark Korson, and I'm a biochemical geneticist with VMP Genetics of Atlanta. You will notice that this is very close to the one offered earlier for coenzyme Q10.

This is not an oversight. It is due to the fact that we are dealing with a wide range of defects and complex biosynthetic pathways of ATP or cellular energy, and the nature of mitochondrial disease and what we know of them is such that good studies have not been possible that include large numbers of patients with clear or distinct phenotypes to test each new supplement and monitor for efficacy and side effects. But this presentation focuses on creatine monohydrate, and since our approach with CoQ10 proved to be helpful clinically, we followed the same approach for creatine, looking for improvement and watching for creating specific side effects.

Identifying the patient for whom creatine is appropriate is still a challenge, but comparable to

coenzyme Q10 synthesis defects as they apply to coenzyme Q10, with creatine synthesis defects, the biochemistry defines the problem, the treatment is clear, and the patients can show a response. Although, depending on the defect and the status of the patient, the response may be variable.

Remember, there are hundreds of different mitochondrial disorders. The benefit of creatine is not always clear. These patients are in need of energy from wherever they can get it. Different from other supplements, though creatine provides another source of ATP as well as acting as an antioxidant, offering a neuroprotective effect.

Are all these patients then candidates for creatine? No, but again, there are a few therapies for this cluster of diseases that address the root problem. And here, creatine provides a clear alternative source of energy. These disorders have a dramatic impact on functioning of quality of life, and there's a relatively low incidence and transient nature of the side effects, so many of these patients are offered to trial.

I support a trial of creatine in patients with disease when it is associated with fatigue or weakness that impacts functioning. Again, self care, home life, learning at school, or work, and so on. Studies have looked mostly at aerobic activities, but from a practical perspective, it is perhaps more important that one look at common even basic activities in these patients' lives that are less energy demanding, but which still may utilize creatine as an energy source.

In my practice, we have treated over 250 patients, patients with documented mitochondrial disease or who have significant evidence to support a diagnosis. But because of possible renal concerns, we have not provided creatine to patients with any history or evidence of kidney disease.

This dosing, it was obtained from consensus reports of mitochondrial disease provider practices. The patients are provided a trial of creatine for at least 3 months, given the time it's needed, to assess improvement and/or side effects. And since a cocktail usually involves more than one

supplement, it is impractical to provide a separate period of introduction of more than a few months.

Again, we try to appreciate the benefits to the patients since providing a supplement is a burden for patients and families that are already saddled with the medical, psychological, and financial burdens of the disease itself. We try to rely on uninformed observers. You see a lot of children or patients in their clinical practices from an industry perspective: physical and occupational therapists, teachers, activity leaders who can distinguish who stands out from the norm, but who have also followed the patient over time.

Again, someone who sees a patient several times a month or several times a week may be in a position to better assess a change in strength or stamina -- may be able to better assess a change in strength or stamina than a physician who sees a patient every 6 months or so, especially if highly specialized research technologies are not available.

Again, we monitor for improvement

prospectively after starting the supplement, but again, sometimes the benefit is not observed after starting the supplement, but only when it is taken away. The improvement is more apparent in retrospect.

Sometimes if an obvious benefit is unclear, we have also recommended periods of time off the supplement, again, without informing observers in the community of the switch, to determine if there has been a change this time in reverse.

GI upset, abdominal pain, and flatulence has been reported. Regarding the abdominal pain, though, the question is, again, is it due to the supplement itself or is it due to the presence of pills or powder in the stomach that doesn't empty properly since gastroparesis or slow gastric emptying is a common symptom in patients with mitochondrial disease.

Creatine is almost never prescribed as a solitary supplement. Following recommendations like the ones of Tarnopolsky, et al., the Mitochondrial Medicine Society often includes

cocktails that include supplements that impact different aspects of the energy production pathway. Thank you.

Committee Discussion and Vote

DR. VAIDA: Thank you. We will now proceed with the vote. The question is, the FDA is proposing that creatine monohydrate solid oral dosage forms be included on the 503A bulks list. Should creatine monohydrate solid oral dosage forms be placed on the list?

We'll now open up for any discussion before we vote. Any discussion from the committee?

(No response.)

DR. VAIDA: Hearing none, we'll take the vote. Please vote either yes, no, or abstain.

(Voting.)

DR. FAJICULAY: For the record, the results are 17, yes; zero, no; and zero abstain.

DR. VAIDA: Thank you. We'll go around the table from the committee and state your name, your vote, and in any comments. We'll start here on my right-hand side with Dr. Ghany.

DR. GHANY: Marc Ghany. I voted yes. I do have one comment. The reason I voted yes was, again for the disorders under question, there is no effective therapy. And while the evidence is weak that this compound does work, there is some suggestion that some patients do benefit.

The comment I have is I would strongly urge the FDA to look into the safety data for renal toxicity and perhaps consider what might be a safe upholdment [ph] of dosage that you all would approve.

DR. CHELIMSKY: Tom Chelimsky. I voted yes, and I actually echo the comments of my colleague.

DR. KHURANA: Sandeep Khurana. I voted yes for the similar comments.

DR. IKONOMIDOU: Chris Ikonomidou. I voted yes. I agree with all that has been said. And in addition, I think it's important to have access to this compound for the treatment of creatine biosynthesis disorders.

MS. SUN: Jeanne Sun, I voted yes. I would suggest or recommend that we look at this bulk drug

substance without the qualifications, similar to my recommendations for ALA. Similar to the discussion that went on, there are stability data for other dosage forms. And it seems like even the questions asked today, there's some inconsistencies on how the substances are nominated. Some say a route of administration, some say the dosage form, and some do not any at all if you look at the previous meetings.

So my recommendation would be to add the bulk substance to the list without the qualifications of the dosage form or route of administration.

DR. DESAI: Seemal Desai. I also voted yes for the reasons previously stated.

DR. JUNGMAN: Elizabeth Jungman from Pew. I voted yes. I had some hesitance about the AEs and high doses, but I thought the balance of factors was in favor of inclusion on the list given the limited options for these patients.

DR. WALL: Donna wall. I voted yes for the reasons that they've stated, but it also should be

emphasized that this is the drug in which both the prescriber and the pharmacist really need to closely monitor these patients to make sure that we do not encounter the ADEs, or if we do, we can address them.

DR. CAROME: Mike Carome. I voted yes. I think from a safety perspective, this drug substance rarely can cause some renal injury, but I think those risks are outweighed by the benefits for the patients who have these very metabolic disorders.

DR. BOGNER: Robin Bogner. Similar to Jeanne, I vote yes without any dosage form constraints. If you need further evidence, Ted Labuza's article out of his group in 2009, Drug Development in Industrial Pharmacy, has a very clear temperature pH activity of water data on the stability of creatine monohydrate in water.

DR. VAIDA: Allen Vaida. I voted yes, although I had some concerns over what is the real dose or the correct dose of the drug.

DR. PATEL: Kuldip Patel. I voted yes. I

did have some concerns about the efficacy data but also realize that there are a subset of patients that will benefit from having this available.

MR. HUMPHREY: William Humphrey, I voted yes. I felt like it met the inclusion criteria. And I also recommend that the alternative dosage form be considered.

DR. HOAG: Steve Hoag. I voted yes for the reasons considered. Also, I thought it was good that they specified the state of the monohydrate because I think you need to pay attention to that, especially in situations where there's not a monograph. Also, I think the FDA should look at other dosage forms and examine the stability issues.

DR. VAIDA: Our two committee members on the phone starting with Dr. Venitz.

DR. VENITZ: Jurgen Venitz. I voted yes, and I have nothing to add.

DR. VAIDA: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted yes. I will echo the concerns with dosage and renal

considerations, but other than that, feel like it should be useful for a small subgroup of patients.

DR. VAIDA: Okay. Thank you. Why don't we just take a 5-minute break, and we'll reconvene after 5 minutes.

(Whereupon, at 2:21 p.m., a recess was taken.)

DR. VAIDA: If committee members could get back to their seats, in just another minute, we will begin.

I'd also just like to mention that Dr. Ghany, Chelimsky, and Khurana, that were with us for the first three items will not be with us for the next two. They were just here for temporary members for that and that Dr. Ikonomidou had to leave for her flight, but she will be calling in for the next item on the agenda.

We want to begin with Dr. Johnson, talk about the next substance that's up, pyridoxal 5 phosphate monohydrate.

FDA Presentation - Susan Johnson

DR. JOHNSON: Once again, my name is Susan

Johnson, and I'm from the Office of Drug Evaluation IV in CDER'S Office of New Drugs. And the substance that we'll be discussing now is pyridoxal 5 phosphate monohydrate. And reflecting back to creatine monohydrate, we do discriminate between salts. These different crystalline forms are things that we can generally consider as the same substances. So this is a similar scenario to the last substance that we discussed.

Again, I'd like to express my thanks to the review team and to Dr. Philip Sheridan, who couldn't be here today, from OND's Division of Neurologic Products.

Pyridoxal 5 phosphate monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under 503A. It's proposed for oral and intravenous use in the treatment of epilepsy and seizure disorders. It was not associated with the dose in the nomination.

Pyridoxal 5 phosphate monohydrate and pyridoxal 5 phosphate are considered the same active pharmaceutical ingredient, as with the last

scenario. And I'll be referring to both of them as PLP. PLP has a well characterized structure and is soluble in water. I know that's a relief to everybody.

(Laughter.)

DR. JOHNSON: In aqueous formulations, PLP is most stable between a pH of 5 and 8. PLP is also stable in solid form. PLP can be synthesized in manufacturing from pyridoxamine. So in summary, PLP is well characterized and likely to be stable in the proposed oral and intravenous dosage forms.

Vitamin B6 is a term which is used to refer to any one of 6 vitamers or a mix of those vitamers. These 6 vitamers include pyridoxal and its phosphorylated ester PLP. Pyridoxine and pyridoxamine, and both of their phosphorylated esters comprise the 6 vitamers. These 6 vitamers can be inter converted in the body, and it's notable that PLP is the one metabolically active form of vitamin B6.

PLP is a essential cofactor in numerous enzymatic reactions and can be found in various

animal food sources. FDA has set a recommended tolerable upper limit of dose of 100 milligrams per day in food that does not necessarily pertain to drugs, but that's a guideline that we have.

We did not find any animal pharmacokinetic data for PLP. When humans ingest PLP or other phosphorylated, they're usually hydrolyzed by intestinal phosphatases, and the non phosphorylated forms are then rapidly absorbed. After absorption, each vitamer can be phosphorylated again and then converted to PLP.

The enzyme that converts phosphorylated pyridoxine and pyridoxamine to PLP is PNPO. At high doses, PLP is absorbed without being hydrolyzed that reduces the body's dependence on PNPO to convert PNP and PMP to PLP. To say that again, pyridoxamine and -- now I'm getting myself confused. Pyridoxine and pyridoxamine are phosphorylated once absorbed and then are ultimately converted to PLP. At high doses, PLP when taken orally can be absorbed intact and does not need to be re-phosphorylated once absorbed.

Most of the super physiologic oral dose of the vitamers will be excreted unchanged in the urine, although a small portion of the vitamers are metabolized to pyridoxic acid. Drug interactions can occur between the vitamers and drugs like isoniazid or L-dopa that react with carbonyl groups.

We found no animal toxicity data specific to PLP, so we reported on information from the study of vitamin B6. Neuronal damage and sensory and motor effects have been seen across many different species when exposed to prolonged high doses. In reproductive toxicity studies, vitamers had been shown to cross the placental barrier and reach the fetus. And although no teratogenicity was seen, high doses were associated with a decrease in body weight of pups. We found no genotoxicity or carcinogenicity studies for PLP or for vitamin B6.

In the FAERS database, there were 20 cases in which PLP use was reported. In 12 cases, the event was likely related to the underlying disease or to concomitant medication. In 8 reported cases,

including 6 deaths, there was insufficient information to determine whether there was a causal association with PLP. There were 98 reports in the CAERS database in which PLP was reported, but each was confounded by use of multi ingredients supplements. We found no clinical studies designed specifically to assess safety.

There are literature reports of neuronal damage with high-dose vitamin 6, and one could expect similar events with PLP. We do not have specific information about the cutoff of doses at which you might begin to see neuronal damage.

In addition, at high doses, PLP can interfere with platelet function. PLP has also been associated with dermatologic, gastrointestinal, and hepatic adverse events, including two reports of cirrhosis in PNPO deficient patients. And I should emphasize that those were pediatric patients. Although PLP is generally safe and well tolerated, with long-term high dosing, it may be associated with peripheral nerve injury. Other types of events, including

hepatotoxicity, have been infrequently reported.

PNP and PMP are converted, as we said, to the metabolically active form PLP via the oxidase PNPO. But a rare inborn error of metabolism can result in a deficiency of PNPO oxidase. The onset of PNPO deficiency is usually observed within the first two weeks of life and is characterized by monoclonic seizures that can progress to status epilepticus. These seizures are not controlled by anticonvulsants.

In some patients, it's theorized that there may be residual PNPO activity, and treatment with pyridoxine may be sufficient to sustain the production of PLP. Some of these patients may have onset of seizures later in life, and there is much current activity going on to identify genotypes and phenotypes where this may be the case. But patients with essentially no PNPO activity are dependent on PLP therapy.

This condition of PLP-dependent epilepsy was first observed in the early 2000S. A cessation of seizure activity with the administration in PLP in

the face of treatment failure with pyridoxine administration and anticonvulsants helps to establish the distinct condition. And as we said earlier, administration of high-dose oral PLP will allow for PLP to be absorbed with its phosphate group intact and bypass the need for PNPO activity.

We conclude that PLP is effective for treating PLP-dependent efficacy in neonates and infants. PLP has been compounded in various dosage forms since at least 2010. It's known to be compounded to treat PLP-dependent epilepsy, but there's insufficient information on which to assess the extent of use for this or other conditions.

In summary, PLP as well characterized and can be stable under normal storage conditions in oral and intravenous formulations. It is generally safe but may cause peripheral nerve damage if used at high doses for prolonged periods. There are also literature reports of rare adverse events, including hepatotoxicity.

Based on literature reports and clinical practice, PLP is effective in treating the rare

disease PLP-dependent epilepsy and has been documented to be compounded for this purpose. A balancing of these factors weighs in favor of pyridoxal 5 phosphate monohydrate being added to the list of bulk drug substances that can be used in compounding under Section 503A. Thank you, and I'm happy to take questions.

DR. VAIDA: Thank you. Are there any clarifying questions from the committee for Dr. Johnson?

(No response.)

DR. VAIDA: All right. Seeing none, we will now have a presentation by our nominator, Mr. Tom Wynn from Fagron.

Nominator Presentation - Tom Wynn

MR. WYNN: Thank you very much for having us today, and thank you to the FDA for a great discussion about pyridoxal 5 phosphate monohydrate. Pyridoxal 5 phosphate is considered the most important member of the vitamin B6 group, which was already stated. It is an active coenzyme for more than a hundred enzymes, including glutamic acid

decarboxylase, an enzyme involved in gamma aminobutyric acid synthesis.

I'll talk a little bit about glutamic acid - decarboxylase. It synthesizes GABA or gamma-aminobutyric acid. GABA's the principal inhibitory neurotransmitter in the cerebral cortex and maintains the inhibitory tone that counterbalances the neuronal excitation that goes on in the brain. P5P is needed for glutamic acid decarboxylase as the coenzyme for the synthesis of GABA.

When we talk about pyridoxine-dependent seizures, and oftentimes that's what they're going to call them, even though we're actually using a pyridoxal 5 phosphate to treat, it's a condition caused by autosomal recessive inborn error of metabolism, and affected patients are dependent upon regular pharmaceutical doses of pyridoxine or pyridoxal 5 phosphate, which the FDA has mentioned is the more potent form of pyridoxine to help treat that condition.

Untreated, the disorder results in death

from status epilepticus. In most instances, the institution of either parenteral or oral pyridoxine rapidly results in seizure control and improvement of the encephalopathy. And again, here we're using pyridoxine, but we know -- and I'll have an article to come up later in my talk -- the pyridoxal 5 phosphate is the more active and form that we're going to use in this case. But the diagnosis for this type of seizure is by clinical observation where an infant with anticonvulsant resistant seizures offered a trial of pyridoxine, or P5P, that results in often a dramatic cessation of these events.

This is just one particular case report, and in this one, it was a male infant born at 35 weeks who promptly responded to oral administration of PLP. This particular patient neurological outcome at 21 months is favorable and illustrates the importance of standardized vitamin trials in an acute setting of therapy-resistant neonatal seizures. If you look more into this, it's showing that this particular patient, again, at a very

early age was not responding to other therapies. But when the PLP was administered, it did result in cessation of those seizures.

A positive outcome, again, of the early diagnosis within 12 hours, irritability and erratic myoclonic jerks involving all 4 extremities were noted. The first EEG recorded 2 hours after the onset of symptoms showed a suppression burst pattern with synchronized bursts of bilateral, moderate amplitude spike and waves. These seizures are resistant to phenobarbital, phenytoin, and vigabatrin. And again, we're still talking about this same 35-week a child here.

Profound authority in hypertonia were noticed over the following 3 weeks. PLP was administered every 6 hours at a dose of 35 milligrams per kilogram per day, and anticonvulsant therapy withdrawn. After 5 week, the infant was discharged with mild hypertonia and adequate bottle feeding. So in this particular case study, again, the other normal, let's say, or commercially available options weren't working, so the PLP was

administered and was able to control the seizures, and the child was discharged with pretty much normal activity.

This one here does get into pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Again, it gets into more about the P5P. Among 574 children with active epilepsy, 94 were diagnosed with idiopathic intractable epilepsy for more than 6 months. And then the conclusion was that PLP could replace pyridoxine in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms, which is what we're really looking at here today, is the infantile spasms.

In that study, after the first attempt and to treat West Syndrome -- and West syndrome is another name for what they have for infantile spasms -- with high-dose vitamin B6, was recognized, the treatment dose, for that syndrome. The 574 children with active epilepsy were referred to a pediatric neurology department. After appropriate management, 219 had medically

intractable epilepsy; again, 94, age between 8 months or 15 years, were defined as having those type of infantile spasm were enrolled in this study. 11 of 94 responded dramatically to intravenous infusion, achieving seizure-free status. The 11 responded to the dose of 10 milligram per kilogram per day. The other 8 needed a dose of 50 milligrams per kilogram per day.

Our present study, PLP was effective controlling up to 46 percent of the patients with intractable infantile spasms. In conclusion, our data suggests that PLP is more effective than regular pyridoxine in some children with idiopathic intractable epilepsy, particularly children with infantile spasms. And I think those are the ones that we're really looking at here. The infantile spasms are the ones that it really helps out more.

Looking at this year, it's pyridoxine oxidase deficiency treatable cause of neonatal epilepsy with burst suppression. This is a case report. They reported on a patient with myoclonic

and tonic report on a patient with myoclonic and tonic seizures at the age of one hour. P5P was started on the first day of life and seizures stopped at the age of 3 days. The encephalopathy persisted for 4 weeks. They had normal neuro development outcome, and age 12 pyridoxal 5 monotherapy was the only therapy that they had for that child.

So looking more into that particular study, again, 41 percent of patients with pyridoxine 5 phosphate oxidase deficiency were treated with pyridoxine supplementation, 30 milligrams per kilogram per day. Of those patients, 71 percent were seizure free; 42 percent had normal neuro developmental outcome for pyridoxal monotherapy.

Pyridoxine 5 phosphate and pyridoxine supplementation therapy are the only treatments, and untreated oxidase deficiency results in early death. Dose range is from 30 milligrams per kilogram per day to 100 milligrams per kilogram per day given through a neogastric tube.

As far as stability, I know that the FDA

already talked about that they had found that pyridoxal 5 phosphate is found to be stable. This was just one -- it wasn't really a study, but they were looking at the hydrolysis that could occur with pyridoxine 5 phosphate, and looking at ways that can be minimized. Part of it was they talked about the pH temperature, and then they also found that adding metabisulfite can also help stabilize those solutions even more.

So I do feel that they can be stabilized for the length of time that we need to utilize that, whether it'd be an IV or in some type of suspension. And this was just another study, if you will, that was looking at ways to kind of combat what can happen as far as degradation with it

So in clinical safety, I know the FDA has already mentioned that they found no issues in the literature that I looked over. I too could not find any issues with safety. They did mention sometimes that there could be high doses, that they were having some issues with some possible

neuropathy or a neuro type damage could occur. Seizure breakthrough was the only thing that I saw in the studies that I looked at of the few that I presented today.

I did want to talk about one in particular. It mentioned in one of the studies, they actually went through a review, and they looked at right around 50 of the current cases that they saw where P5P was actually utilized to help with infantile spasms. And of those, 50 they were looking at did they actually do any therapy at all, did they not, and the different dosage range that they did.

The doses did vary anywhere from 10 milligram per kilogram up to 100 milligram per kilogram per day. And I think the dosing is adjusted to -- they're trying to control the seizures, so they'll start out at a lower dose and work up if they have to just to get them under control.

But the most interesting thing that I saw was that in those studies, whenever they did not do anything, it resulted in death. And when they

actually add the P5P, there was always an outcome of either mild seizures or none at all. So definitely, there is something to that in these infantile spasms, if we do not treat, I think the outcome is not good. And usually within less than a week, this was actually resulting in death.

So again, the main points is that the commercially available options have limited effect, if anything at all, in infantile spasms. Definitely, that seems to be true. Pyridoxal 5 phosphate seems to be superior to pyridoxine. There were no severe adverse effects reported, and even the ones that the FDA had mentioned becomes a risk-benefit at that point.

If we know that if the infantile spasms are not treated and the current commercially available options aren't working as far as treatment, that it results in early death, I think we need to weigh out the risk-benefit of the possible neuropathy that could occur compared to the outcome if we don't treat at all.

Clarifying Questions from the Committee

DR. VAIDA: All right. Thank you. Any clarifying questions?

DR. IKONOMIDOU: I have more of a comment. Thank you very much for the presentation. I think information you presented on the efficacy of pyridoxal 5 phosphate on infantile spasms and also the lack of other therapies for infantile spasms is misleading. That is not the case. Pyridoxal 5 phosphate is not the treatment of choice for infantile spasms. There are other therapies. ACTH is a first line therapy followed by steroids and vigabatrin.

The only scenario where pyridoxal 5 phosphate could be of use is if the infantile spasms are the expression of a mild form of pyridoxal 5 phosphate dependent epilepsy, which starts later during the first year of life. So I think this information cannot stand as was presented here.

I think that pyridoxal 5 phosphate does indeed have a place in the treatment of pyridoxal 5 phosphate dependent epilepsy, and we are definitely

dependent on this medication. Also, oftentimes in refractory neonatal seizures, we do pursue clinical or therapeutic trials with these compounds until we have the diagnosis. But I do not agree with the infantile spasm presentation. Thank you.

DR. VAIDA: Any other questions? Dr. Sun?

DR. SUN: This may be more of a question for FDA. I know one of the case reports had talked about dosing through the nasal neogastric tube. So would that still qualify under the oral dosage form?

DR. GANLEY: Yes, that would be oral.

DR. VAIDA: I have one question, too. Back in 2014, the organizations, it was only the oral capsules, and then just this year when you did the confirmation, you asked for the IV also, the IV was never mentioned in any of the original nominations from all three organizations.

So was that because there's been more IV used in the last few years? What was the change?

MR. WYNN: Sure. It's been more -- as we went to reclarify and we started looking at the

ways that it could be used to help with seizures, sometimes you're dealing with such small children that it may not be feasible to always give an oral dose.

Sometimes you want to get those seizures stopped more quickly, so doing an IV would be the better way to go. And looking at the studies that I had, they were doing IV as well as oral therapy. They were doing both, and the ones who had this deficiency be able to [indiscernible] the P5P and make that decarboxylase enzyme.

DR. VAIDA: Okay. But I'm also taking for granted that a lot of that has been made by the compounders -- I'm sorry, all of that, that the intravenous is now being made by the compounders all of a sudden.

MR. WYNN: I'm sorry?

DR. VAIDA: That the intravenous is now being made by the compounders versus the oral.

MR. WYNN: Well, this is something, yes, that has come more recently. As I mentioned, it's just been since 2000 that there's been kind of a

rise in awareness.

DR. VAIDA: I'm just thinking of the ability to produce the IV versus the oral. That's fine.

MR. WYNN: Okay.

DR. VAIDA: Any other questions?

(No response.)

DR. VAIDA: Then we'll move on to the open public hearing, and we have -- Dr. Johnson?

DR. JOHNSON: This is Sue Johnson. I just wanted to reiterate that the development of hepatotoxicity associated with the treatment of PLP-dependent epilepsy is new, and they're thinking that this might be an actual new genotype. I read recently that PNPO deficiency may in time prove to be a suitable candidate for consideration of therapeutic liver transplantation in select patients.

So I don't want us to lose track of the fact that there could be serious consequences to administering PLP, but as the nominator has said, this is life-saving therapy in this genetic disorder. But I just wanted to make sure that that

didn't get lost in the conversation.

Committee Discussion and Vote

DR. VAIDA: All right. We'll proceed to the vote, and the vote -- for the record, there are no presenters for the open public hearing, and we'll now proceed to the vote. The vote that's up is the FDA is proposing that pyridoxal 5 phosphate monohydrate, intravenous and oral dosage forms, be included on the 503A bulks list.

Should pyridoxal 5 phosphate monohydrate intravenous and oral dosage forms be placed on the list? I'll open it up for the committee for any discussion before the vote. Dr. Patel?

DR. PATEL: I just wanted a clarification. We had a panel member, Hrissanthi, who mentioned there are other treatment alternatives or standard of care has -- she listed a list of agents.

Can I get a clarification that for infantile spasms, that that is indeed the standard of care, that there are options available before going to PLP?

DR. JOHNSON: PLP-dependent epilepsy is a

very specific disorder, so we're talking about a subset within other sets. Infantile spasms is a larger set. I think at some places, it intersects with PLP dependency. And in some cases of PLP-dependent epilepsy, you may see some efficacy with other things. But she was talking about infantile spasms being a broader disorder than actual PLP-dependent epilepsy.

Did I make it worse?

(Laughter.)

DR. JOHNSON: So, yes, there are other treatments for infantile spasms, but you would go through the process of eliminating any antiepileptic therapy and pyridoxine, and then you would be able to establish whether or not this was truly PLP-dependent epilepsy.

DR. VAIDA: Any other questions?

DR. PATEL: One more follow-up question. On the study, Wang and colleagues, it appears that the investigators claimed that PLP was effective in controlling up to 46 percent of the patients, but actually they started off with 574 patients. And

toward the end, only 3 responded. In addition to that, they said 94 percent of patients responded dramatically. But then during that course of time, the patients were also on other antiepileptic medications, which were later tapered off.

Is that correct?

Is your question --

DR. PATEL: To the nominator.

DR. JOHNSON: I can take a stab at that. My understanding of these cases -- and I think our pediatric geneticist had to leave for another meeting. But my understanding is that this is a completely empirical field, and there is a protocol -- or several protocols, many -- followed by the neurologists where each sequential treatment is tried.

In the absence of genetic testing, which identifies exactly what the condition is, they work through each of these. PLP is one of the later or latest parts of this protocol. They don't try that until they've failed regular anticonvulsants and pyridoxine.

DR. VAIDA: All right. We'll now vote, either yes, no, or abstain. Please hold down the button for at least 15 seconds.

DR. FAJICULAY: For the record, the results are 14, yes; zero, no; and zero, abstain.

DR. VAIDA: I'll start to my right here with Dr. Sun. If you'll state your name, vote, and any comment.

DR. SUN: Jeanne Sun. I voted yes. I think the presentations illustrate that it's well characterized and it's well supported for efficacy and safety.

DR. DESAI: Seemal Desai, I also voted yes. I also thought that this clearly has a role in a very rare combination set of diseases. We think we have a theme today in talking about rare diseases, but this one in particular on the infantile population, it really seemed like this could be a life or death benefit for PLP-deficient epilepsy, as Susan clarified a moment ago.

DR. JUNGMAN: Elizabeth Jungman from Pew. I voted yes for the same reasons.

DR. WALL: Donna Wall. I voted yes for the same reasons.

DR. CAROME: Mike Carome. I voted yes for the exact same reason.

DR. BOGNER; Robin Bogner. Yes; same reasons.

DR. VAIDA: Allen Vaida. I voted yes, although I do have to say I'm a little concerned if the indications are going to start to wander off because back in '14, too, along with just oral, it was only indicated for the PLP dependent. Then in '18, they talked about a lot more indications. That's my only concern with that, although I voted yes.

DR. PATEL: Kuldip Patel. I also voted yes for the same reasons that are already described.

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

DR. HOAG: Steve Hoag. I voted yes, and I agree with what was said previously.

DR. VAIDA: Members o the phone? Dr. Gulur?

DR. GULUR: Dr. Gulur.

DR. VAIDA: Right.

DR. GULUR: I voted yes for the reasons already stated.

DR. VENITZ: Jurgen Venitz. I voted yes; same reasons.

DR. IKONOMIDOU: This is Chris Ikonomidou. I voted yes because pyridoxal 5 phosphate is the only available treatment for pyridoxal-dependent epilepsy.

DR. VAIDA: All right. Thank you.

Why don't we just skip this break and move on to the next topic. The next topic, we'll hear from the FDA, Dr. Ganley, on the quercetin dihydrate.

FDA Presentation - Charles Ganley

DR. GANLEY: Good afternoon. Thank you. I'm Charlie Ganley from the Office of New Drugs, and I'm just going to give a brief summary of the quercetin dihydrate nomination. This slide just shows the review staff involved in the review. I wanted to acknowledge their efforts here and also acknowledge the many people behind the scenes who

have not been acknowledged in any of these slides. There are a lot of people that go in putting these meetings together, and we appreciate their efforts.

Just to go through this quickly, quercetin dihydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A. We listed the proposed uses that we have reviewed, and these are the proposed routes of administration.

Quercetin -- and I think it's important to note that in a lot of this, I'm going to be talking about quercetin, although the nominated substance is quercetin dihydrate. And it becomes very important to understand that distinction as I go through the talk because there are very great differences between different forms of quercetin.

Quercetin is a naturally occurring flavonol found in fruits and vegetables. It is a yellow crystalline solid chemical with a well characterized structure. The structure shown here is for quercetin. If there were 2 water molecules shown, it would be the dihydrate form. And I want

you to take note of the hydroxyl side chains off of the ring structure because they are important in understanding the forms of quercetin present in foods, and they also are important in understanding how the molecule is metabolized by the body. We'll be getting to that in a few slides.

Quercetin exists in different crystalline forms based on the degree of hydration. It is stable in its solid form and protected from oxygen. Quercetin dihydrate is the most thermodynamically stable hydrate form, which may contribute to its lower bioavailability. And again, I want to make note of that because you'll see later on when I present some pharmacokinetic data, there is a difference between these different forms of quercetin.

In aqueous solutions, because of rapid oxidation and other degradations, under basic condition, it is unlikely to be stable when compounded in aqueous solutions. Now, I don't mention on this slide here the aqueous solubility, but I just want to point out an error that I've

noted in the page 4 of the memo. The memo stated that quercetin is soluble in water. Well, quercetin dihydrate is not very soluble in water. In fact, it has a very poor solubility. And in one literature article that I found, it was shown to be 2.5 milligrams per liter.

Now, other forms of quercetin may be more soluble, but we're not talking about those. We're talking about quercetin dihydrate today. The possible synthetic route is extraction from plant tissues, rapid extraction from powdered quercetin bark with dilute ammonia and boiling of the extract with sulfuric acid. Once you obtain the quercetin, it's probably recrystallized with water. Again, we don't know what the source of the bulk substance manufactured is.

In summary, quercetin is a naturally occurring, well characterized flavonol. The extraction and synthesis are well developed. It is likely to be stable in a solid form when protected from oxygen but not in aqueous formulations. And again, I noted that a dihydrate form is not very

soluble in water. Quercetin dihydrate is most thermodynamic, stable, hydrated forum, which may affect its bioavailability.

With regard to the general pharmacology, the average quercetin dietary intake from food sources for humans ranges from 25 to 205 milligrams per person per day. But in some individuals who have high intakes of fruit and vegetables, you could get up to as much as 1250 milligrams per day, and that doesn't include all the other flavonoids that are in food.

Examples of foods that contain quercetin are many, and I'll just mention a few: onions, berries, and tea. And there'll be different forms of it, not the dihydrate form. In its natural form in food, quercetin exists as a quercetin glycoside or rutinoside. And I want to highlight this point because the form of quercetin impacts on the absorption of quercetin into the body for reasons that are not entirely clear.

There are approximately 150 glycosides of quercetin that have been described and include

mono- di-, and oligosaccharides. The structure shown here is quercetin-3-glucoside. If I can show, there is the glucose hanging off of the hydroxyl group.

In the gut, quercetin glycosides are converted to quercetin aglycone and sugar moieties. It's important to note that the term "aglycone" is a general term applied to quercetin without any side chains bound to the hydroxyl groups. That would include quercetin dihydrate because there are no groups bound to the hydroxl group. This is important because quercetin is lipophilic, while glycoside forms are polar. Quercetin glycosides are more polar and were more soluble in aqueous solution.

Based on the in vitro and in vivo models, quercetin may act as an antioxidant, anti-inflammatory, antiproliferative, and anti-angiogenic agent, and many of these models are conducted with quercetin aglycone and not quercetin metabolites. And that's important to understand, and we'll get to that in a few minutes.

The bioavailability of quercetin is generally poor and variable. The solid dosage formulations -- the chemical form of quercetin makes for solid dosage forms. The form of quercetin seat makes a difference. In a study comparing absorption of quercetin from quercetin dihydrate and onionskin extract, the bioavailability of quercetin was greater with the extract.

In this study, the amount of quercetin in the onion extract was 163 milligrams and a dihydrate forum was 134 milligrams. The values in the slide were normalized to the amount of quercetin administered. And as you can see with the onionskin extract form, the AUC and Cmax is about fivefold greater for the extract form versus the dihydrate form.

Now, this is very difficult to explain because when they actually do the analysis of quercetin that is present in the onion extract, they characterize it as the aglycone, meaning that there's no side chain, but 95 percent is the

aglycone and about 5 percent have different glycosides. And again, this is the dihydrate form, so it gets back to this issue of thermal stability I think, the absorptive capacity of one form versus another one when they're both characterized as the aglycone form.

The elimination of quercetin is via conjugation reactions or ring fission to eventually produce benzoic acid, which is excreted in the kidneys. Conjugation occurs quickly in the intestinal cell. The aglycone form undergoes glucuronidation, sulfation, and methylation. And these are the primary forms of circulating quercetin.

When we're eating food and it has a quercetin glycoside, there are brush border enzymes on the luminal cells that cleave that, and that forms an aglycone. The aglycone is absorbed into the intestinal luminal cell and almost immediately undergoes conjugation.

This also raises question about the bioavailability, and it also raises question that

when you're looking at these studies of in vitro or cell studies that talk about the antioxidative or anti-inflammatory effects, they're not talking about necessarily the conjugates, which is the predominant form that circulates in the body. There have been some studies that look at conjugated forms and their activity, and it's somewhat all over the place. Many of them have little or no activity, though.

The other thing to note is the conjugated form is excreted in the bile fluid and can undergo enterohepatic circulation. And you can see it in this slide. I can't see it very well from here, but the dark value here shows a biphasic curve. It's this little dip and then increase. You can go and look at individual patients, and you can see that second peak. So what's happening is the conjugated form is being excreted in the bowel. That conjugate is cleaved, and it's reabsorbed.

Now, this is a part of a slide from your background memo. What I've done is I've taken off the -- originally there were two, the quercetin

glycoside and the quercetin rutinoside. Their side chains are cleaved, and they form an aglycone. And very quickly, this aglycone, in the luminal cell and also in the liver, is converted to the conjugated forms, a glucuronide, a sulfate, a methylated form. All these reactions occur very quickly, so most of the quercetin that circulates in our body after we eat food that contains quercetin is in the conjugated form.

Various foods and drinks can affect quercetin absorption. We've listed some of them in the background memo. There are potential drug interactions through different mechanisms. Quercetin interacts with different CYP450s that have not been fully characterized. Some of these are from different in vitro studies.

In another, I believe it was a cell study where quercetin may enhance or inhibit the transport of P-glycoprotein substrate, and the example was been vincristine depending on the concentration quercetin. That's one of the issues when you're looking at the literature of these in

vitro and cellular studies and they're defining a certain concentration. We don't know what concentration is going to be at the cellular level.

With regard to the nonclinical safety, there is limited data on the acute toxicity of quercetin. Observational studies were limited to animal symptoms without histopathology. For repeat dose toxicity, there were no toxicity seen in rabbits for orally-fed quercetin at 1 percent for 410 days.

In a 2-year rat carcinogenicity study, there was increased severity of chronic nephropathy, slight increase in focal hyperplasia of the renal tubule epithelium, an increased incidence of parathyroid hyperplasia seen in males at 10,000 parts per million, which is essentially a 1 percent feed. A 6-month interim report for 2-year study showed reduction in body weight among females at 40,000 parts per million or 4 percent feed and increases in relative kidney and liver weights in both sexes at 4 percent feed.

With regard to genotoxicity, there have been positive genotoxic toxic signals for in vitro

studies, including Ames chromosome aberrations and sister chromosome aberrations. There were negative genotoxic signals for in vivo studies, specifically micronuclei and sister chromatid genes. The developmental and reproductive toxicity, there were no adverse effects reported in the literature. With regard to carcinogenicity, oral administration of quercetin 0.1 percent in a diet for 540 days in rats did not increase the incidence of tumor formation when compared to concurrent controls.

With regard to clinical safety for the FDA adverse reporting system, there were 7 reports submitted to FDA for an FDA-approved drug that included the concomitant use of quercetin. These were reports for other drugs, which quercetin just happened to be being used by the individual. The attribution to quercetin is not possible because of multiple concomitant drugs or limited information, but there was one report of a possible interaction with apremilast, which is Otezla. The brand name was Otezla.

Now, apremilast is metabolized by cytochrome

P450s, and subsequently glucuronide. If you read the package insert, there's a drug interaction with rifampin, and this is because rifampin induces CYP3A. What happened in this individual is that the adverse event was related to a lack of effectiveness. In the next slide, I'm going to show that there is at least one study that shows that quercetin can induce a CYP3A. So there is a possible drug interaction here.

With regard to CFSAN adverse event reporting system, there were 20 reports; 7 were hospitalizations but none appeared directly related to quercetin. The majority of cases were confounded by multiple medications and their underlying disease, and there was insufficient information for assessment.

There were no adverse events reported in clinical trials for orally administered, and also there were no specific case reports for orally administered. Serious adverse events occurred after the administration of high-dose intravenous quercetin to patients with cancer, including pain

at the site of injection at greater than 60 milligrams per meter squared, dyspnea at greater than 1400 milligrams per meter squared, and vomiting greater than 1700 milligrams per meter squared. There was significant renal toxicity noted at greater than 630 milligrams per meter squared, and in some patients, they had residual renal injury after the treatment was stopped.

There were some drug-drug interaction studies. As I noted and I mentioned earlier with apremilast, quercetin significantly induced CYP3A activity to the substrate midazolam, and this was partly related to CYP3A5 genotype. Quercetin is also present in St. John's wort and has been shown to inhibit activities of cytochrome 1A2, 2C19, and 2D6.

With regard to clinical effectiveness for cancer prevention and treatment, there are mechanistic in vitro studies in the literature, there are sporadic small clinical studies, and extensive literature on purported mechanisms for treating a wide variety of cancers, but no

compelling clinical studies evaluating effectiveness. For prevention, there are no clinical studies, and most information is based on dietary intervention with multiple dietary ingredients, none of which is supportive abuse to prevent cancer.

With regard to allergy, most clinical studies conducted to date have evaluated combinations or mixtures of ingredients either in the form of an herbal product or in a food substance. There is insufficient data from clinical studies to support the effectiveness of quercetin in the treatment of allergy.

With regard to hypertension, there was a meta-analysis published I think in 2016 that looked at the available randomized control trials evaluating the impact of quercetin on blood pressure. The author suggested a statistically significant effect of quercetin supplement in the reduction in blood pressure when used at doses greater than 500 milligrams per day. However, I will add that the authors noted in their summary

that further studies are necessary to investigate the clinical relevance of these results, and the possibility of quercetin application as an add-on to in anti-hypertensive therapy.

Now, in these 7 studies, several of them were the dihydrate, several were just characterized as the aglycone form, and one of them had an anhydride form. We looked at all 7 studies, and in evaluating each study in the meta-analysis, we did not find a single study that showed a significant effect on blood pressure compared to placebo, and placebo was present in many of these studies.

I should note here -- and I should have pointed out earlier -- that this was an effect on blood pressure, so not all these individuals in these studies had high blood pressure. There were some studies where individuals had high blood pressure.

If you read just the abstracts of these studies, some of them report a statistically significant effect s on blood pressure, but the authors really conducted a within-treatment

comparison, which was baseline minus the in-study visit and not a between-treatment comparison, even though there was a placebo group available. And the change in blood pressure for quercetin versus placebo did not show a significant difference. So we disagree with any suggestion that it does improve hypertension.

With regard to asthma, there are no clinical studies where quercetin was administered and evaluated for the treatment for asthma. Clinical effectiveness, our conclusion is there is insufficient data to support the effectiveness of quercetin dihydrate in the treatment of cancer, allergy, hypertension, or asthma.

With regard to the historical use in compounding, quercetin dihydrate is available as a dietary supplement, but its historical use in compounding is unclear. There is insufficient information available to determine how long quercetin dihydrate has been used in pharmacy compounding. Insufficient data are available from which to draw conclusions about the extent of use

of quercetin dihydrate in compounded drug products. Quercetin dihydrate is not listed in the British, European, or Japanese pharmacopeia.

So with regard to our recommendation, with regard to chemistry, quercetin dihydrate is well characterized and stable in a solid dosage form if protected from oxygen. It is likely to be unstable in aqueous solutions and rarely undergoes oxidation, but also add that the dihydrate form is insoluble in aqueous solutions.

With regard to safety with the oral administration, there appear to be no serious adverse events. For intravenous administration, serious adverse events include dyspnea, vomiting, and kidney toxicity. Oral absorption is poor and variable. There is rapid metabolism to glucuronide and sulfates, which raise questions about the bioavailability of quercetin dihydrate.

There are potential interactions with cytochrome enzymes that have not been fully explored, which raise concerns about potential drug interactions if used with approved drug products

that are metabolized by cytochrome enzymes, and there also may be some interaction with transporters.

With regard to effectiveness, there is insufficient data to support the effectiveness of quercetin dihydrate in the treatment of cancer, allergy, hypertension, or asthma. With regard to the historical use in compounding, insufficient data are available from which to draw conclusions about the extent of use of quercetin dihydrate in compounded drug products.

So overall, our recommendation after balancing the 4 evaluation criteria, it weighs against quercetin dihydrate being added to the list of bulk drug substances that can be used in compounding under Section 503A. Thank you.

Clarifying Questions from the Committee

DR. VAIDA: Thank you. We'll now entertain any clarifying questions from the committee. Dr. Desai?

DR. DESAI: I was curious about your comment with the drug-drug interaction with apremilast. I

haven't seen -- and apremilast is a fairly new drug. It's FDA approved for moderate to severe plaque psoriasis, so obviously I use that frequently in my practice as a dermatologist. I haven't heard of many CYP interactions with apremilast. Can you comment a little bit more about that?

DR. GANLEY: The only one that I saw listed in the package insert had to do with rifampin induction.

DR. DESAI: Right.

DR. GANLEY: That was the only one. I pointed that out. I'm not here to review apremilast. I pointed it out because there was evidence of a clinical study where they looked at cytochrome 3A and suggested that quercetin could induce that. So the adverse event was limited in the amount of information. I didn't see information on what the specific details are regarding to the dose of quercetin or things like that, or how it was administered, or what form it was and things like that.

DR. DESAI: And that was just one report that you found?

DR. GANLEY: We hardly had any -- again, that was from 7 reports for quercetin in the drug adverse event, so we're not going to expect a lot from there.

DR. VAIDA: Any other questions? Hearing none, we'll now hear from --

DR. GANLEY: She has a question over here.

DR. SUN: Thank you. I just have a quick question about the safety and efficacy data. Was that based on compounded preparations or the dietary supplements?

DR. GANLEY: Well, we don't know. I'm not sure what specific safety data you're referring. When we look at safety data that comes into -- presumably if it's coming into the CAERS, the CFSAN database, that was a dietary supplement. If it's coming into the FAERS, which is the drug adverse event reporting system, that could be a dietary supplement also. We don't get granular information on these things.

DR. SUN: Yes. I was referring to those two databases.

DR. GANLEY: Right.

DR. VAIDA: All right. We're now hear from Dr. Paul Anderson.

DR. LOUVEN: [Inaudible - off mic]. My name is Bob Louven from the Division of Pharmacovigilance. I think the case of the reported drug interaction, if I'm not mistaken, if it's the same case we're discussing, there's one report we found in FAERS that the patient taking apremilast with a dermatologic condition reported lack of effect, they suspected a lack of effect.

There's really no other information. It was just sort of a very brief comment that the patient had expected a better result, did not have efficacy, and mentioned that they were suspecting, just theoretically, there might be an interaction, but there's no objective data.

In general, it's important to know that lack of effect type of AE is the most commonly reported in FAERS, so it's really very hard to interpret

that case.

DR. GANLEY: No. I don't disagree. I'm just pointing out that we already have data that this drug can induce CYP3A just like rifampin. In most drug interactions, we're speculating. I'm just raising that there is a connection of the dots here, and there's a lot of interactions, potential interactions, through cytochromes that we don't fully understand related to this specific ingredient.

DR. VAIDA: All right. Now we're hear from Dr. Paul Anderson from Anderson Medical Specialty Associates with the nominator presentation.

Nominator Presentation - Paul Anderson

DR. ANDERSON: Thank you. I know we're at the end, so a few things is based on the prior testimony by the FDA. All of the primary concepts and many of the data I was going to present our similar, so what I will do is just spend the little time I have on the differences and a little bit of preliminary data and information around modern uses other than oral that are currently going on and

some related to an ongoing trial.

So, obviously we've already gone through the nominated indications. And what I would say is that -- of course there's over 16,000 references. So having a short time, I'd just like to mostly review just to show what was, what was being done, whether through a meta or a regular review.

So in asthma and allergy, as was mentioned prior, what you really have as opposed to really hardcore, good single agent studies are a lot of mechanistic studies, a lot of mechanistic studies that speak to changes in cytokines, et cetera.

Many of these mention traditional use. Traditional use is hard to tease out with quercetin. In the 30 years I've been around people, physicians who have used quercetin, it is commonly used really in the asthma-allergy setting and for a few other purposes that I will mention.

I think one thing that's really important and in almost every study mentioned, and certainly just about every study that I'm going to briefly go through, one of the points always made is it's

generally an add-on therapy. It's never really a monotherapy. Now, there may be exceptions to that, but generally it is as an add-on therapy as either a synergist or some other type of add-on effect.

So I think that's important to mention.

The other problem in looking at the particular nominated substance, which is likely the very best for compounding, as was just brought up, is it's not always the substance that was used in the trials that are mentioned. And then when you get either the metas or the reviews, you've got this mixture of that going on. So in that respect, I would also completely agree with the data you've already been given, so I won't go deeply into that because it's going to be the same information.

But I think when you look at the totality of the asthma-allergy, it is not being certainly promoted and the traditional use is not as a replacement for most standard asthma or allergy medications. It is usually used as a synergist in either children or adults to either lower their dependence on some of their background medications

or to decrease their antigenicity, allergenicity.

Most of these have been gone through, and most of the reviews have statements in them, if you read through the whole paper, that are very hopeful and promising with respect to quercetin, but again, as a agent that we need to study more to figure out the mechanisms more deeply. Then the other things which were already brought up, which revolve around absorption, et cetera, are kind of common themes in almost every paper that you look at.

This is one that did get a little bit more deeply into activities, so talking about alteration of IL-8 and that it's comparable or better than cromolyn, then IL-6 and calcium level changes shifting as well. So there are some studies looking into actual cytokine shifts and changes.

In oncology, again, I've not ever seen anything, either in traditional use or published, where quercetin itself was purported to be a monotherapy, but in a trial that's currently going on -- and I apologize it didn't get in the slide, but I'll read it into the record, so it's there.

Clinical trial NCT02494037, which is a prospective human trial on 4 types of cancer. The question is, being used in a very multimodal, multifactoral treatment protocol that is individualized for the patient. So that is ongoing right now. It's 2 years its 5 years, and a fair amount of quercetin has been used in that, and I'll be talking about that in a little bit.

Again, as was discussed earlier, I'm going to just move this phase 1 trial forward because FDA used that to speak specifically about parenteral use quercetin, so I'll move that to the parenteral safety coming up later. This was, again, I believe a 1996 trial. It was a phase 1 trial where they were doing the best that they could to solubilized quercetin so it could be infused, which, as was mentioned, it's not a water soluble component. So as a phase 1 trial, they learned a lot of things the hard way, so we'll talk about that coming up.

This is a low-dose in vitro mechanism, and something interesting in the oncology data as you read through it. And it's the same as with

asthma-allergy, et cetera. You have certainly in vitro studies. You've got a lot of animal, proof-of-concept, and mechanism studies. And then you've got some observational studies with human. You find statements -- and I believe this is a little hard to see from the side here, but you find statements like this. And one study will say, well, we had to get to very large oral doses to achieve an effect, and then other studies will say we were able to achieve effect at smaller doses.

One of the other things that I think is confounding to the discussion is that the delivery mechanisms for oral, especially use, have been quite varied as was brought up in the FDA presentation. What we have seen over time is as delivery mechanisms are more stable and better absorbed, meaning it's not just plain quercetin or even the quercetin being mentioned here, but normally it's complex with something to either get past the brush border enzymes or enhance absorption, you get very different treatment effects.

So as was brought up earlier by FDA, you cannot homogeneously extract from every study that quercetin in one is at all like quercetin in another. So we want to be up front about that as well.

There are a lot of mechanistic studies and reviews that show, essentially, if you look at all of these -- and you've already had them. But if you look at all of them together, what most of those papers around oncology say is this obviously is not going to be a monotherapy, but it may be a therapy that would help in either chemosensitization or potentially in improving quality of life, et cetera.

Similar to the way that the drug, LipoCure, which is a version of a curcuminide [ph] molecule, which is in final trials right now as being used as a chemosensitizing and improving of certain aspects of quality of life, that's kind of the theme of all of those particular studies.

When it comes to hypertension, both FDA and myself have comment on the same review, of the

papers that were already mentioned because my colleague went into good depth on that one. I won't go into a whole lot of depth there. What I can say is from particular -- if you take, as I said, the 30 years I've been watching the clinical use of quercetin, I do not see hypertension as an extremely common use for it unless it's used as a synergist or an add-on. I see quercetin used in asthma-allergy, and I see it used in oncology, primarily.

I want to mention a few things just about administration and safety because this is another thing that's highly, highly variable over time. If we go back to that first paper that was mentioned with respect to parenteral administration and all of those side effects that came out, which is in the briefing document, et cetera, that goes back to 1996. And the ability to even get quercetin of any form into a suspension that could be parenterally administered was very, very, very difficult at that time. And I would argue it's difficult at this time, too, but we know more than we did.

So this is a quote from the briefing document from FDA, and it's exactly the same as what was given already. This is the Ferry paper from '96, and they were looking at dose ranges that were fairly robust in intravenous administration. If you look at that paper and you look at the pharmacology of what's going on with it, there's probably some issues in taking a 1996 approach and extrapolating that to what pharmacies are doing right now. And I will circle back around to current compounding pharmacy activity with respect to parenteral use of quercetin coming up.

The first thing is -- and this is something probably we would have done in 1996 not knowing, and even the authors, if you read the Ferry paper, talk about, well, this is a phase 1 trial and we're supposed to be learning what works and what doesn't work, essentially. They took the quercetin, and the only way that they could get it to stay in suspension was with a very, very concentrated dose of DMSO. So 50 mLs of RIMSO, or DMSO, and they diluted it, the RIMSO, 50 percent water, and then

they put the quercetin in that solution to keep it in suspension.

The thing that they did that created most of the trouble -- and they discussed at length in the paper -- is that they then took that -- and hard to imagine now doing this, but they gave it by intravenous push. So you're taking essentially a solution that's 50 percent DMSO on its own, which would not be recommended to be given by IV push, and you put quercetin in it, and then you give it by IV push.

Well, there are a couple of things that happen. One is, of course, you have no dilution effect, which actually the authors of the paper in their conclusion come around and say we should have done that. But the other thing is this is an extremely fibrogenic, so the pain at the injection site you would expect actually, as opposed to that being a surprise side effect.

This is not at all what would be being done now, which I will describe in a little bit, and it's also certainly nowhere in standard practice

for parental administration of, really, anything that I can think of at this point.

With regard to the renal issues, one of the things that's potentially possible is that this bolus of 50 percent DMSO that was holding the quercetin on its own could cause some renal issues. And then if you take that potential and then you add this molecule that you saw earlier of quercetin, you're getting a very large, fast bolus of two potentially nephrotoxic agents hitting the kidneys very, very rapidly.

Now, one of the things that they said -- and it's the second bullet point here -- being clear that simple IV prehydration could at least partially aggregate the nephrotoxicity, et cetera. And if you look through the paper as they're discussing what happened well and did not go well, essentially what they came to was we need to do this if we do another trial in some sort of dilution. That is something I'll be getting to that we have found more in modern times.

Recent use, there is intravenous use of

quercetin, but there is quite a different way of both producing it and administering it. In the last six years, there have been 5 different compounding pharmacies that made parenteral quercetin available. Much of it is for this particular trial that I had mentioned, and in the preparation, it's either prepared as an emulsion or it is prepared in cyclodextrin, which was mentioned for another drug earlier today. There is no preparation using DMSO currently in modern times.

The dose escalation that has been used most commonly -- and this again would be germane to the oncology prospective study that's going on -- 1 milligram per kilogram is the test dose, and they have escalated up to 50 milligrams per kilogram.

The other thing that's very different from the 1996 paper, which is what they foreshadowed in forecasted in their advice to future drug studiers, was that it is very highly dilute. What has been found over the time, over these six years -- so it goes between a half and 1 and a half liters given

over a fairly slow amount of time. It's given on a dose-per-time basis. So unlike 1996, it's never pushed. It is highly diluted. And what has been found and reported back to me is that most of those side effects, there's not been a single event where either the creatinine or the eGFR has risen. There's not been a single high-grade side effect since changing, based essentially on the recommendations of Ferry in '96.

From those 5 pharmacies that we're producing it over the 6 years that we have been monitoring currently, I believe there's 2 or 3 that are still making either an emulsion or a cyclodextrin based parenteral product. And this essentially goes to both current use and historical use, so I want to make sure that you knew that it was out in the compounding world.

No high grade; transient nausea and flushing, which were self-limited in 10 percent of the cases, and essentially that was relieved by slowing the infusion rate or diluting the infusion to a higher degree. he level of adverse events at

this point, none high grade and most are very, very transient and self-limited. But because this type of parenteral use is not anything that is currently published but is ongoing, I want to make sure, at least for historical use, you know that that has happened or is happening.

The other thing that I found of interest in looking because of our experience -- so when I say "our," I gave you the trial number, I was a founding member of the first center. There are 8 centers where it's going. And since, I have moved on to other work, but I'm still in contact with the centers, and I keep track of the experimental things that they're doing. So that's where I got that information.

But in looking, what I found also curious was quercetin, again, in either animal models or very early research, there is a lot of research going on that is looking at parenteral forms, whether for interarticular or subcutaneous mostly for intravenous use. And most of these are from either this year or 2012 essentially. So it's not

something that is not being looked into and not being researched because of at least the mechanistic papers that have gone on proof of concept, but it's not something that is in large, wide-scale human trials either. So it is still at that stage.

The one comment from the study group that I was asked to share was, if quercetin is unable to be compounded in the future, then they would have to go back and do an IND, et cetera, and by the time that was done, this particular trial would be over.

In summary, a few things. Modern use from my own personal but also monitoring other groups, whether parenteral in the modern sense, in the modern way that it's done or oral in very stable systems has been very safe. We have looked -- really, the CAERS and the FAERS data was looked through. And we've already gone over that a few times, so I don't need to go over it. It's exactly the same story. You can't really trace much back to quercetin as a problem in the CAERS or

FAERS data.

This is a summary paper or a review paper looking just at the safety. Most of them, really, when you look at them -- and I will admit that this is limited by the fact that they may be reviewing numbers of different types of oral quercetin, for example, that were used. So it may not exactly be the type that we're talking about completely. But generally, there's very little concern, at least, around safety.

This comes directly from the nomination statement, "intend to preserve for nomination all routes until adequate time to prepare a response, but intravenous, intramuscular, oral, sublingual uses."

Clarifying Questions from the Committee

DR. VAIDA: Thank you.

Any clarifying questions? We'll start with that. Dr. Carome?

DR. CAROME: Mike Carome. In your presentation -- I just want to make sure I'm fairly interpreting what you said -- I didn't hear you say

anything that refuted FDA's assessment that there is no good data on the effectiveness for any of the diseases for which this drug was nominated. Am I understanding correctly?

DR. ANDERSON: I would say, based on the fact that all of the data that FDA presented and the summary data that I presented come from the same place, if the standard is large-scale human trials of this particular molecule, then we are in agreement.

DR. VAIDA: Dr. Wall?

DR. WALL: I may be in a little bit of an afternoon fog, but just to clarify, are there any patients or type of situations currently in which you would go to this agent and say, yes, I believe it can help somebody in this situation? Or is it mostly we still need to do studies and keep going with figuring out where it's going to fit into the various processes?

DR. ANDERSON: That's a good question. And if I missed the first couple of words and I answer this wrong, let me know, and I'll re-answer it, but

I believe I got what you said. Based on traditional use, as far as it being generally safe in its oral form, especially, the types of patients most commonly, where quercetin is an additive therapy, are in asthma-allergy, allergic phenomena, especially digestive tract, either eosinophilic digestive problems or that sort of allergy.

So those are areas where it is very commonly, in its oral form, used very early in therapy. Because there are no papers looking at it head to head with other things because it's normally used as an additive therapy, clinically what we see -- and this is an anecdotal statement. But clinically what I have seen and observed in others is that the escalation in an atopic allergic patient to other medications can often be truncated at the addition of quercetin. So the atopic conditions are a very common use for it.

This also is based on the second part of the question in respect to the cancer research that's going on. There are not enough cases where it has been used parenterally to string together a

particular benefit scenario, et cetera, but based on the first two years where it's been used parenterally, there are about -- I believe among the 8 centers, there's probably about 8 to 10 cases where as a single agent additive, it made a difference in either disease progression or particular side effect profiles from other therapies that were being given.

Those would be, I would say, the two areas. One is very research oriented; one is traditional use, and the atopic oral use is the most common reason.

DR. VAIDA: Any other questions?

DR. BOGNER: I guess this is to the FDA since it was your presentation. I thought I might hear it, but I did not. You note that it's stable in its solid form when protected from oxygen. How are we imagining this will be protected from oxygen when it's distributed?

DR. ZHANG: This is Ben Zhang from FDA. When you start oral dosage forms, you can formulate it with antioxidants to prevent it from oxidation.

DR. BOGNER: The other thing that I was looking at in the literature trying to find quercetin and what purity you could get it. And even in the research realm, they're able to get maybe 96, 97 percent quercetin. Some of the solid state characterization was extraordinarily difficult because of different forms.

How well characterized is this stuff? There are so many different oxidation states to it and different hydration, and solvates are in there. So I'm not feeling comfortable that it's well characterized.

DR. ZHANG: For traditional analytical methods, it's easy to characterize whether this is in the proposed structure or it is in the proposed hydrous form. It's not that difficult.

DR. BOGNER: Okay.

DR. ZHANG: As for the impurities, you probably want to know the impurity profiles, what is left, 3 percent. That thing, we don't have that information to make judgment.

DR. VAIDA: One question. You had mentioned

that there were 500 compounding pharmacies, compounding the parenteral.

DR. ANDERSON: Five.

DR. VAIDA: Five?

DR. ANDERSON: Not 500. Sorry.

DR. DAY: And there was about 2500 doses.

DR. ANDERSON: Yes.

DR. VAIDA: This information is from --

DR. ANDERSON: That information is from my monitoring of the 8 sites that are doing that current trial, who are the primary users of parenteral quercetin.

DR. VAIDA: One more question, Dr. Humphrey?

DR. HUMPHREY William Humphrey. The sites where they're doing the clinical trials, I don't understand why there's not an IND.

DR. ANDERSON: I'm just thinking back to the beginning. So the trial was begun in Seattle and the IRB was through the University of Washington. And then it was set up as a multisite trial because at the time that it was set up, under this particular process, there had been no hearing about

the substance. And it's not the only substance that they use. And because it was a generally available from compounding pharmacies, the IRB passed on the use of it as a generally available substance.

What I don't know because I'm not on the UDUB [ph] board, whether they looked at it and characterized it as a dietary supplement in that respect or how they did that. But that's how that happened.

DR. VAIDA: Dr. Ganley?

DR. GANLEY: A study that you mentioned, is that an oral or parenteral?

DR. ANDERSON: It's both actually. It's not a single-agent study. It's a multi-agent study.

Open Public Hearing

DR. VAIDA: Okay. Thank you.

We'll now proceed to hear the open public hearing speakers, and we have two of them. Our first speaker?

MR. DUMOFF: Good afternoon. My name is Alan Dumoff. I'm an attorney. I represent the

American Association of Naturopathic Physicians and the Integrative Medicine Consortium, which is a group that's composed of a professional association and practice, functional and integrative medicine.

The topics I want to discuss today I think go directly to the important exchange that occurred between Dr. Carome and Dr. Anderson about the standards of evidence and review of these kinds of uses. I want to approach the idea of functional medicine and functional uses very quickly through three different topics. The first is the definition of a drug and whether a functional use is a sufficient use rather than requiring a disease indication.

Secondly, I want to talk about the [inaudible - audio break] in the way that drugs are considered.

We got a different mic? Thank you.

So I want to discuss some of the particular, what I would say are some tunnel-vision decisions that have come out of the committee, and discussing quercetin as an example. I want to discuss the way

FDA has characterized one of those studies with regard to hypertension.

We are discussing professional differences of viewpoints. These are the organizations that I represent, and I want to note that, for example, integrative medicine, which is not really represented before the committee, is board certified, recognized by the American Board of Physician Specialties, and naturopathic naturopathic medicine is licensed in 20 states.

Before I proceed, I want to just say that the AANP and IMC very much appreciate the decisions being made today and the discussion that are getting into the functional issues, but we've been raising with FDA that a drug that's claim is a functional use is by law a drug. If I market something just for functional use, unless it's under DSHEA, I am violating drug law.

Nothing in DQSA or in the Modernization Act, which governs 503A, excludes functional uses as an adequate and sufficient basis for use. And the requirement that we demonstrate disease indications

is taking valuable components out of physicians' hands who are well trained and using these functional approaches by requiring these disease standards.

We've been hearing at our course center [indiscernible], for example, that antioxidant was insufficient. A physician may want to use anti-inflammatory or antioxidants for a number of reasons, maybe targeting a physiologic or functional cause.

I'm hearing today discussion of adjunctive uses and some of the interactions. That's positive, but in the past, we've not really heard that a physician may want to use an approved drug and have a functional adjunctive part of their armamentarium to use as well, as well as compounding for nutritional purposes, which has not been discussed.

So we're reducing as a head to head, and the evidence of risk on the approved drug is not really being considered. So I want to give two quick examples. MSM we were told could not be approved

because there were 4 cases of bleeding or elevated INR. But instead, physicians should prescribe Celebrex, which has a black box warning for stroke. So physicians are being told that the choice is so clear, because of those few bleeding episodes, that they should instead use a Cox-2 inhibitor. That is to us not a sensible outcome.

With 5-HTP, we were told that because it's used for the indication of depression that we have to be able to prove that 5-HTP doesn't have the same side effects. So the outcome of that was, we were told, we have to use a synthetic pharmaceutical, known have these side effects, because the physiologic ingredient might have those effects. That's not a sensible outcome.

Now finally, I want to talk about the quercetin presentation. We heard from Dr. Ganley, and in the report, it said that the data in the meta-studies did not align with the result. But if you look at what they said, they said that only one genotype was efficiently demonstrated, but that genotype was 70 percent of the population. There

were only 3 genotypes -- one was underpowered with three. So it's not a fair assessment to say that the significant swing of up to 12 points in systolic blood pressure was not a significant outcome.

In fact, as Dr. Ganley mentioned, there was skewed because in the case of many of the physiologic and functional items, they only work where there's a problem. So the normotensive patients, there was no effect, and this cohort had a number of normotensive patients.

So if you look at the actual result, it was actually more significant than the study authors showed. So we'd ask you to consider those things as you review quercetin and their other nominations. Thank you for your time.

DR. VAIDA: Second speaker?

DR. OSBORNE: Good afternoon. I'm Dr. Virginia Osborne, and I'm also with the Integrative Medicine Consortium and the AANP. I have 23 years of experience as a practitioner, a [inaudible - mic fades] -- Portland, Oregon, and

also now an international lecturer on many of the topics that you cover in these [inaudible - mic fades].

This is a critical applications aspect. [Inaudible - mic fades] -- a number of doctors, I'd say tens of thousands of patients, in what we experience in our offices. And we are looking at a number of these agents and integrating many of them. What we're seeing here is that we have all taken the oath of first do no harm, so the proven scientific applications for safe and effective treatments are what we have our guidelines on. Our treatment plans are for the patient, resulting in quality-of-life outcomes.

Quercetin was one of these, and we've gone over a number of these discussions here already, which provides a safe option. We have the benefit of improving the vasodilation, and [indiscernible] flavonoids, and the muscle contraction, and improvement of cardiac and pulmonary diseases or prevention.

Really, what we're trying to do here is

prevention, to get this before it gets to the point of a disease process. We have these things available to us that we can have options when our patients walk through the door.

Talking about the alpha lipoic earlier with Dr. Berkson and demonstrating the clinical applications, thank you so much. The benefits that my patients receive from this is the same as he has explained today. So we are thankful for that, that I don't have to go back and tell those patients, "Sorry. It's not available anymore."

We're looking at an anti-inflammatory and antioxidants through the reduction of inflammation, through the nutrients that we are able to provide, both infusibly through peripheral and parenteral, oral, and the biochemical and physiological responses that they receive.

When they have been ill and they finally are starting to feel better, the improvement of oxygenation through alpha lipoic, the quercetin, CoQ10, improving mitochondrial function, this is the thing that can turn around their lives and

improve immensely; and the P5P we find with those who have impaired liver function and now able to bypass that antiemetic action that is required with pyridoxine and certainly has been shown in the research for autism.

I'm just reiterating that, what was just proved here, I have used this for the last couple of decades. And certainly thanks to Dr. Stanley Jacobs, where I first met him in Oregon, where I practiced and lectured. He had multiple research papers on that. There are hundreds of them online and books that he has written.

I've seen now, since that, many researchers who have come after him to reiterate what he has found. Yes, there is platelet aggregation. It's knowing your patient, knowing them well, knowing what you're choosing to give them. And maybe that was what they needed. So we're looking at the benefits of this through several metabolic disorders that can be the anti-inflammatory action of MSM.

This is just a case, and this is leading up

to all of this. This is a 57-year-old woman who was in bed for 10 years due to the tick-borne infections, ehrlichia, babesia, and bartonella. She went through the many pharmaceuticals and the visits to the well-known clinics and hospitals in our area. She was referred to me in 2016. At this point, we reviewed her labs and her nutrients and gave her MSM.

I look back on this because I just saw her 2 weeks ago for a post follow-up of -- we've been working together for 2 years. And in that time, and the improvements and with changes that we've been able to make as we've gone through this, she now has the ability to get out of bed and have dinner with her husband, g get out in her garden [inaudible - mic fades] -- and her grandsons now know her as their well grandmother instead of the ill one in the bedroom.

The last case -- and this is a case of a 40-year-old male who has now been out of the military. But he had viral illnesses and certainly heavy chemical exposures while in Iraq and

Afghanistan. I just threw in there, there are multiple pharmaceuticals, hospitalizations, pre- and post-discharge from military service. This is ongoing for him. He was exposed to deep-well contamination fluids, which he had to be in up to his chest, which lead to cardiac issues.

So he was referred to me, so we went again to [inaudible - mic fades] some of his biochemical pathways through these nutrients we have been talking about today -- were all a part of this, and of course the MSM, the quercetin, the CoQ10, were all a part of that, and the P5P; alpha lipoic acid for reoxygenation of the cells and, of course, reducing of his neuropathies.

We were going to continue on, but these things became less and less available, and he could see what was going to happen, and he left the country for his health care. And that's what I'm starting to see now. I'm starting to hear from patients, like, "You know what? This is getting too expensive for me. Things are no longer available. I need to leave the country to get my

health care."

I just want you to be aware of what we are dealing with out there. And with that, I just want you to know that we have done our best to educate and to make available information for many physicians to know. Because that was a question that came up earlier. "How do they know about this? Are they relying just on the pharmacies when they call them?"

No, we are trying to be out there to educate practitioners on the [inaudible - mic fades] -- what's efficacy on all of these nutrients. Thank you.

DR. VAIDA: Thank you.

DR. FAJICULAY: Jay Fajiculay, designated federal officer for the PCAC. Just a quick announcement. I received notice that our voting system detected an additional vote for the first 4 voting sessions. So for the record, I would like to correct this to say there were 16 voting members, not 17.

The first 3 sessions for alpha lipoic acid,

coenzyme Q10, and creatine monohydrate, the vote results for each of these 3 voting sessions should be corrected to 16, yes; zero, no; and zero, abstain. Additionally, for the pyridoxal 5 phosphate session, there were 13 voting members, not 14, and the vote results should be corrected to 13, yes; zero, no; and zero, abstain.

Now we will proceed with the final voting question.

Committee Discussion and Vote

DR. VAIDA: Thank you. That concludes our open session, our public session, and now we'll go onto the vote. Any discussion? The vote is that FDA is proposing that quercetin dihydrate not be included on the 503A bulk list. Should quercetin dihydrate be placed on the list?

Any discussion? Dr. Bogner?

DR. BOGNER: Can we split the question? Many of the other candidates that we're talking about have gone on the list with a route of administration, and I was wondering if we can split the route of administration here.

DR. VAIDA: I'm taking for granted, FDA, that it doesn't matter what route, right?

DR. GANLEY: Yes. Our recommendation was not for any route. That's what you're voting on. So if you think there is a route of administration, then you would say that you don't agree with our recommendation, and then just clarify that in your comments.

DR. VAIDA: So you're saying you would put that in the comment, for the route?

DR. GANLEY: No. When she does --

DR. VAIDA: Oral or IV, right?

DR. BORMEL: The vote is on the question, should quercetin dihydrate be placed on the list? You either will vote, yes, it should be placed on the list, or no, it shouldn't be placed on the list. And then whatever your vote is, when it comes time to explain it, you can put a comment to that.

DR. VAIDA: Dr. Wall?

DR. WALL: I wanted to thank the last couple of speakers from the audience because they're

providing a different view of medicine that I really don't have a lot of exposure to. And I would like to know a little bit more on some of those things. That's all.

DR. VAIDA: Dr. Johnson [sic]?

DR. JUNGMAN: So this is for FDA, I think, and I may not be a fair question. But as we think about the oral formulation, one issue that comes to mind is this is available as a dietary supplement. It's been proposed here as a drug for the treatment of several conditions, including cancer. So as I understand it, if FDA it on the list, it could be marketed and advertised for those conditions.

That raises for me questions about how it is currently marketed and advertised in the dietary supplement context. I'm just trying to wrap my head around, as an oral formulation that's available as a dietary supplement as opposed to as available as a drug for this particular substance, what are the kinds of differences you would expect to see in the claims that folks who are trying to sell the substance could make about the product?

DR. VAIDA: Mr. Mixon?

MR. MIXON: I just want to mention that it's widely available; it's an over-the-counter supplement. There's no need to compound it. I mean, it's regulated as a dietary supplement, it'[s widely available, and, no, that's not available -- I mean, that's not appropriate use for intravenous use, but for oral use, it's not a problem.

DR. JUNGMAN: That's helpful.

DR. VAIDA: Yes, Dr. Bogner?

DR. BOGNER: What's the difference between compounding with a bulk substance of quercetin versus compounding with a commercially available dietary supplement in a bottle, opening it up and compounding with it? Does one fall into 503A and the other doesn't? How does this all work?

DR. BORMEL: I think we spoke about this. Sara Rothman, during our presentation, spoke about this, this morning. If you take a dietary supplement that's marketed, and you manipulate it, and you're making another dietary supplement,

you're not doing anything other than repackaging or mixing it with other dietary ingredients and complying with all of the FDA laws and regulations pertaining to dietary supplements, it does not belong in what we're considering here, 503A, compounding by a 503A facility in compliance with the conditions of 503A.

What we're talking about here is taking bulk quercetin and making it into a drug pursuant to a patient's specific prescription.

DR. BOGNER: Thank you.

DR. VAIDA: Dr. Ganley?

DR. GANLEY: I think it's important also to understand -- and I think this ingredient in particular -- there are real issues about how much you actually can absorb from the dihydrate, whether it's a dietary supplement or a drug. Under the dietary supplement regulations, there's no requirement for them to provide data to the agency that show these to get absorbed.

When we look at things from a drug perspective, though, we have an expectation that if

you're going to get a compounded drug, there are going to be absorptions of it. There's no point in taking it if you can't get it to the site of action, if it is an effective therapy. And you have to, I think look at it in the context of that.

The other thing on the drug side are these issues with drug interactions. You have a situation here where there's clearly suggestions that this ingredient causes or is associated with some interaction with cytochrome P450. And now you're going to say, I'm going to throw this on top as a drug, where that's what we're thinking of here.

A dietary supplement is completely different, but as a drug, I have a lot of confidence that I can take an antihypertensive agent and then just throw this as a drug in there and not be concerned about drug interactions. Well, that's not how we think about drugs. We're on a different playing field here, and that's how you have to think about it for these things when you're putting them on the 503 list.

DR. VAIDA: Dr. Hoag?

DR. HOAG: Steve Hoag. Two points of clarification. Am I correct in saying that dietary supplements have to be taken orally? Right? You could have an IV dietary supplement. And then also, that's got a negative or a not. So if I vote yes, I'm voting not?

DR. BORMEL: At first with number 5, we're telling what the FDA proposal is. Our proposal is that quercetin dihydrate not be included on the 503A bulk list. The question that you're voting on, though, is should quercetin dihydrate be placed on the list. If you vote yes, you're voting to place it on the list. If you vote no, you're voting not to place it on the 503A bulks list.

DR. HOAG: Well, I shouldn't read that [inaudible - off mic].

DR. BORMEL: You should read the question and respond to the question, which is the second statement on number 5.

DR. VAIDA: Correct. If you vote no, you're recommending FDA not place the bulk drug on the

list, on the 503 list.

Everybody understand? Are we ready to vote? Please vote yes, no, or abstain.

(Voting.)

DR. FAJICULAY: For the record, the results are zero, yes; 11, no; zero, abstain; and 1, no voting.

DR. VAIDA: Okay. If we want to go around the room and state your name, your vote, and any comment. Dr. Sun?

DR. SUN: Jeanne Sun. I voted no. I want to note that USP does have dietary supplement monograph, but as per the comments around the table, it seems like it is widely available over the counter. And if it needs to be available in other dosage forms, there are other routes like an investigational new drug application that might be available.

DR. DESAI: Seemal Desai. This one, personally, was difficult for me because I felt that the research that I had done prior to coming, based on the materials provided in the docket, from

what I heard from the FDA, and what I heard from the nominator, there were some similarities but a good amount of conflicting information.

Ultimately, I did vote no, however, I will make a comment that we do have a USP monograph, as Jeanne mentioned, so potentially, the oral formulation is something that I think could be still looked at it, particularly if you're talking about a few of the indications that were discussed from the nominator's presentation.

DR. JUNGMAN: Elizabeth Jungman from Pew. I voted no. Glad to see that there is an ongoing study in the substance, but at this point, the effectiveness data just doesn't seem to be there.

DR. WALL: Donna Wall. I voted no. I appreciated the comments from some of our naturopaths and different uses of it, but I would like to see more substantial information before I could actually go forward with it.

DR. CAROME: Mike Carome. I voted no because there's a lack of reasonable data on effectiveness for any of the proposed uses. And

for the proposed uses, there are numerous FDA-approved products that have been proven to be safe and effective, and there are plausible concerns about drug-drug interactions with this and other drugs.

DR. BOGNER: Robin Bogner. I voted no because all of the work that I know that's being done in formulation involves complex dosage forms, which give highly variable bioavailability. I look forward to the 2500 patients or subjects in that study, the parenteral study. And if that pans out, I think you should come back.

DR. VAIDA: Allen Vaida. I voted no, mostly for the reason that was just mentioned by Dr. Carome. I think, for today, this was one of the products that there are a lot of different products that are available for these conditions.

DR. PATEL: Kuldip Patel. I voted no for some of the reasons that have already been stated.

MR. HUMPHREY: William Humphrey. I voted no for similar reasons. I do think that the use of the intravenous product needs to be within the

context of a clinical trial.

DR. HOAG: Steve Hoag. I voted no for all the reasons mentioned. And just to emphasize, this is available orally, and it can be manipulated orally, but this does affect the IV use of this. And I wasn't quite sure of the IV use. And certainly as more data and things become available, then that's something we should perhaps reconsider.

DR. VAIDA: Committee members who are on the phone? Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no for the reasons that have been stated by Dr. Vaida and Dr. Carome. And if the IV formulation data should be stronger in the future, it's definitely worth a second look at that point. Thank you.

DR. VAIDA: Dr. Venitz? Oh, I'm sorry He's off.

All right. This convenes the meeting. I want to thank everyone for bearing with us, and we almost got back on time.

Adjournment

DR. VAIDA: I just have to read one more

line. We will now adjourn the meeting. Panel members, please leave your name badges here on the table so they may be recycled, and please take all your personal belongings with you, as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 4:36 p.m., the afternoon session was adjourned.)