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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

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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

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

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

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

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

1 rulemaking.

2 The synthesis of creatine as a bulk
3 substance is illustrated here. In summary, we find
4 creatine is well characterized and likely to be
5 stable in solid oral dosage forms. In healthy
6 humans, creatine is endogenously synthesized from
7 other amino acids at a rate of up to approximately
8 2 grams per day. The synthesis process involves
9 the kidney, pancreas, and liver. Once synthesized,
10 creatine is transported to other tissues in the
11 body that use energy, including the brain.

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

22 Pharmacokinetics from rodent models of oral

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

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

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

1 creatine deficiency syndromes.

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

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

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

1 for creatine.

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

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

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

1 those were most likely causal.

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

8 Moving on to slide 11, we found no reports
9 of serious adverse events from studies of patients
10 with mitochondrial disorders, and there were no
11 studies in patients with creatine deficiency
12 syndromes. We identified one case report of a
13 patient with creatine deficiency syndrome who
14 experienced urinary crystals at a dose of 800
15 milligrams per kilogram per day -- I'm sorry,
16 800 milligrams per day. I was correct the first
17 time; 800 milligrams per kilogram per day. The
18 condition resolved with a dose reduction.

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

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

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

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

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

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

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

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

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

8 We found 3 placebo controlled trials that
9 were crossover studies of creatine's use in
10 mitochondrial disorders. One of these studies
11 showed minor improvement on a subset of endpoints
12 only under conditions of intense exercise. The
13 2015 guidelines from the Mitochondrial Medicine
14 Society do not provide a recommendation on the use
15 of creatine.

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

22 Having said that, we are aware that creatine

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

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

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

1 mitochondrial disorders.

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

7 **Clarifying Questions from the Committee**

8 DR. VAIDA: Thank you, Dr. Johnson.

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

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

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

22 So we can't say what the optimal dose would

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

2 DR. VAIDA: Dr. Sun?

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

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

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

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

3 Does that answer your question?

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

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

13 DR. VAIDA: Dr. Chelimsky?

14 DR. CHELIMSKY: Just a dose clarification.
15 So that was truly 800 milligrams per kilogram per
16 day, which translated for a 70-kilogram person
17 would be somewhere around 50 grams per day? That's
18 10 times more than -- that's a good thing. If the
19 only thing that happened was urine crystals, that
20 means even at that dose, it seems reasonably safe.

21 DR. VAIDA: Dr. Khurana?

22 DR. JOHNSON: Let me make sure I have that

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

3 DR. VAIDA: Dr. Khurana?

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

11 DR. JOHNSON: These are extremely rare.
12 There were surveys done globally to assess the
13 number of patients, and they identified families.
14 In AGAT deficiency, a review was done in 2015
15 looking globally at the number of patients, and
16 they found 16 patients in 8 families. If there can
17 be a rare-rare disease, that's the one. GMAT is
18 slightly more common. There were 48 patients from
19 38 families in a review done in 2014.

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

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

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

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

19 DR. KHURANA: Great. Thank you.

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

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

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

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

13 DR. JOHNSON: Correct, yes.

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

21 DR. VAIDA: All right. Thank you.

22 We'll now move on to the presentation by the

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

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

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

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

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

1 so when we get to the efficacy component, we'll
2 remember this stuff right before lunch, hopefully.
3 When we talk about the stability component of it,
4 FDA cited three studies. Two of them, which were
5 just shown on that slide, were from the 1920's,
6 1925 and 1928. They were looking at not the
7 stability of creatine or creatine monohydrate.
8 These studies were designed to find an equilibrium
9 point between creatine monohydrate and creatinine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 18-year-old male patient with MELAS had two
2 previous episodes of cerebral stroke.

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

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

22 From the discussion part of the study, they

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

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

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

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

5 Komura had a follow-up article in
6 2006 -- sorry. This case study was the follow-up
7 article from 2006, and again, the conclusion of
8 this article is that creatine monohydrate
9 supplementation improved gross and fine motor
10 skills and respiratory and cardiac function in the
11 present Leigh syndrome patients.

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

16 When we look at the conclusion and the
17 discussion of these articles from Klopstock in
18 2000, creatine supplementation is most effective in
19 subjects with low endogenous muscle creatine
20 concentrations. As these concentrations are normal
21 in CPEO patients, these patients may benefit less
22 than patients with other mitochondrial diseases.

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

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

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

1 outcome.

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

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

14 Another article that the FDA addressed in
15 their briefing information is Rodriguez trial from
16 2007, and they talk about how difficult this study
17 is to assess the specific therapy or outcomes of
18 the utilization of creatine. It's an article to
19 utilize a combination of creatine, CoQ10, and alpha
20 lipoic acid. I would like to point out that this
21 is one of the most clinically relevant studies
22 because this is more realistic to how patients are

1 treated in the real world.

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

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

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

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

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

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

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

1 0.1 grams, or 100 milligrams per kilogram, orally
2 daily, up to a maximum dose of 10
3 milligrams -- sorry, 10 grams per day, and then
4 they also give adult dosage along with adverse
5 effects to watch out for and specific comments
6 about its utilization.

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

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

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

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

9 Typically, pharmacies will utilize a 14-or a
10 30-day beyond-use date for those preparations. The
11 pH in the vehicles that that is compounded in is
12 greater than or equal to 4.9. You've seen the data
13 from the dietary supplement manufacturers as well.

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

1 **Clarifying Questions from the Committee**

2 DR. VAIDA: Thank you, Dr. Day.

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

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

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

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

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

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

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

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

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

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

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

16 Did you have another question? Was there
17 one?

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

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

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

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

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

17 DR. VAIDA: Dr. Ghany?

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

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

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

3 For Dr. Johnson, does the FDA recommendation
4 to support this mean that you endorse a
5 20-milligram dose per day? And if so, how was that
6 decision arrived at if there's no data? Twenty
7 grams; sorry. How was that decision arrived at if
8 there's no data to support that dose?

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

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

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

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

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

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

1 useful in autism spectrum disorder.

2 DR. GHANY: Could you comment on the dose?

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

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

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

11 DR. VAIDA: Dr. Chelimsky?

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

19 DR. VAIDA: Dr. Jungman?

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

1 solid oral dosage forms versus aqueous solution.

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

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

21 **Open Public Hearing**

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

1 the open public hearing, and we have one speaker.

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

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

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

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

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

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

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

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

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

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

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

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

22 Again, we monitor for improvement

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

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

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

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

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

4 **Committee Discussion and Vote**

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

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

13 (No response.)

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

16 (Voting.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. VAIDA: Dr. Gulur?

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

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

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

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

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

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

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

21 **FDA Presentation - Susan Johnson**

22 DR. JOHNSON: Once again, my name is Susan

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

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

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

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

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

5 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

1 hepatotoxicity, have been infrequently reported.

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

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

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

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

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

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

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

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

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

11 (No response.)

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

15 **Nominator Presentation - Tom Wynn**

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

1 decarboxylase, an enzyme involved in gamma
2 aminobutyric acid synthesis.

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

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

22 Untreated, the disorder results in death

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

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

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

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

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

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

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

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

1 intractable epilepsy; again, 94, age between
2 8 months or 15 years, were defined as having those
3 type of infantile spasm were enrolled in this
4 study. 11 of 94 responded dramatically to
5 intravenous infusion, achieving seizure-free
6 status. The 11 responded to the dose of
7 10 milligram per kilogram per day. The other 8
8 needed a dose of 50 milligrams per kilogram per
9 day.

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

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

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

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

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

22 As far as stability, I know that the FDA

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

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

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

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

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

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

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

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

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

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

22 **Clarifying Questions from the Committee**

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

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

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

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

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

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

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

12 DR. GANLEY: Yes, that would be oral.

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

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

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

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

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

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

17 MR. WYNN: I'm sorry?

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

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

1 rise in awareness.

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

4 MR. WYNN: Okay.

5 DR. VAIDA: Any other questions?

6 (No response.)

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

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

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

1 didn't get lost in the conversation.

2 **Committee Discussion and Vote**

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

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

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

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

22 DR. JOHNSON: PLP-dependent epilepsy is a

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

9 Did I make it worse?

10 (Laughter.)

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

17 DR. VAIDA: Any other questions?

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

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

6 Is that correct?

7 Is your question --

8 DR. PATEL: To the nominator.

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

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

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

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

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

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

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

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

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

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

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

7 DR. VAIDA: Allen Vaida. I voted yes,
8 although I do have to say I'm a little concerned if
9 the indications are going to start to wander off
10 because back in '14, too, along with just oral, it
11 was only indicated for the PLP dependent. Then in
12 '18, they talked about a lot more indications.
13 That's my only concern with that, although I voted
14 yes.

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

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

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

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

22 DR. GULUR: Dr. Gulur.

1 DR. VAIDA: Right.

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

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

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

10 DR. VAIDA: All right. Thank you.

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

15 **FDA Presentation - Charles Ganley**

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

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

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

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

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

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

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

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

1 noted in the page 4 of the memo. The memo stated
2 that quercetin is soluble in water. Well,
3 quercetin dihydrate is not very soluble in water.
4 In fact, it has a very poor solubility. And in one
5 literature article that I found, it was shown to be
6 2.5 milligrams per liter.

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

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

1 soluble in water. Quercetin dihydrate is most
2 thermodynamic, stable, hydrated form, which may
3 affect its bioavailability.

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

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

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

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

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

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

1 The bioavailability of quercetin is
2 generally poor and variable. The solid dosage
3 formulations -- the chemical form of quercetin
4 makes for solid dosage forms. The form of
5 quercetin salt makes a difference. In a study
6 comparing absorption of quercetin from quercetin
7 dihydrate and onionskin extract, the
8 bioavailability of quercetin was greater with the
9 extract.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 In a 2-year rat carcinogenicity study, there
11 was increased severity of chronic nephropathy,
12 slight increase in focal hyperplasia of the renal
13 tubule epithelium, an increased incidence of
14 parathyroid hyperplasia seen in males at 10,000
15 parts per million, which is essentially a 1 percent
16 feed. A 6-month interim report for 2-year study
17 showed reduction in body weight among females at
18 40,000 parts per million or 4 percent feed and
19 increases in relative kidney and liver weights in
20 both sexes at 4 percent feed.

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

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

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

22 Now, apremilast is metabolized by cytochrome

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

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

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

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

9 There were some drug-drug interaction
10 studies. As I noted and I mentioned earlier with
11 apremilast, quercetin significantly induced CYP3A
12 activity to the substrate midazolam, and this was
13 partly related to CYP3A5 genotype. Quercetin is
14 also present in St. John's wort and has been shown
15 to inhibit activities of cytochrome 1A2, 2C19, and
16 2D6.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 **Clarifying Questions from the Committee**

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

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

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

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

11 DR. DESAI: Right.

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

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

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

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

9 DR. GANLEY: She has a question over here.

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

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

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

3 DR. GANLEY: Right.

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

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

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

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

1 that case.

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

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

14 **Nominator Presentation - Paul Anderson**

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

1 some related to an ongoing trial.

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

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

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

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

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

5 So I think that's important to mention.

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

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

1 or to decrease their antigenicity, allergenicity.

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

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

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

1 Clinical trial NCT02494037, which is a prospective
2 human trial on 4 types of cancer. The question is,
3 being used in a very multimodal, multifactoral
4 treatment protocol that is individualized for the
5 patient. So that is ongoing right now. It's
6 2 years its 5 years, and a fair amount of quercetin
7 has been used in that, and I'll be talking about
8 that in a little bit.

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

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

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

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

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

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

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

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

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

11 I want to mention a few things just about
12 administration and safety because this is another
13 thing that's highly, highly variable over time. If
14 we go back to that first paper that was mentioned
15 with respect to parenteral administration and all
16 of those side effects that came out, which is in
17 the briefing document, et cetera, that goes back to
18 1996. And the ability to even get quercetin of any
19 form into a suspension that could be parenterally
20 administered was very, very, very difficult at that
21 time. And I would argue it's difficult at this
22 time, too, but we know more than we did.

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

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

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

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

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

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

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

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

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

22 Recent use, there is intravenous use of

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

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

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

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

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

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

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

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

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

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

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

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

1 FAERS data.

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

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

16 **Clarifying Questions from the Committee**

17 DR. VAIDA: Thank you.

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

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

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

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

11 DR. VAIDA: Dr. Wall?

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

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

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

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

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

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

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

13 DR. VAIDA: Any other questions?

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

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

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

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

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

17 DR. BOGNER: Okay.

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

22 DR. VAIDA: One question. You had mentioned

1 that there were 500 compounding pharmacies,
2 compounding the parenteral.

3 DR. ANDERSON: Five.

4 DR. VAIDA: Five?

5 DR. ANDERSON: Not 500. Sorry.

6 DR. DAY: And there was about 2500 doses.

7 DR. ANDERSON: Yes.

8 DR. VAIDA: This information is from --

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

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

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

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

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

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

11 DR. VAIDA: Dr. Ganley?

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

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

16 **Open Public Hearing**

17 DR. VAIDA: Okay. Thank you.

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

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

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

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

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

18 We got a different mic? Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 DR. VAIDA: Second speaker?

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

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

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

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

22 Really, what we're trying to do here is

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

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

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

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

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

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

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

22 This is just a case, and this is leading up

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

9 I look back on this because I just saw her
10 2 weeks ago for a post follow-up of -- we've been
11 working together for 2 years. And in that time,
12 and the improvements and with changes that we've
13 been able to make as we've gone through this, she
14 now has the ability to get out of bed and have
15 dinner with her husband, g get out in her garden
16 [inaudible - mic fades] -- and her grandsons now
17 know her as their well grandmother instead of the
18 ill one in the bedroom.

19 The last case -- and this is a case of a
20 40-year-old male who has now been out of the
21 military. But he had viral illnesses and certainly
22 heavy chemical exposures while in Iraq and

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

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

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

1 health care."

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

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

14 DR. VAIDA: Thank you.

15 DR. FAJICULAY: Jay Fajiculay, designated
16 federal officer for the PCAC. Just a quick
17 announcement. I received notice that our voting
18 system detected an additional vote for the first
19 4 voting sessions. So for the record, I would like
20 to correct this to say there were 16 voting
21 members, not 17.

22 The first 3 sessions for alpha lipoic acid,

1 coenzyme Q10, and creatine monohydrate, the vote
2 results for each of these 3 voting sessions should
3 be corrected to 16, yes; zero, no; and zero,
4 abstain. Additionally, for the pyridoxal 5
5 phosphate session, there were 13 voting members,
6 not 14, and the vote results should be corrected to
7 13, yes; zero, no; and zero, abstain.

8 Now we will proceed with the final voting
9 question.

10 **Committee Discussion and Vote**

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

17 Any discussion? Dr. Bogner?

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

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

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

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

11 DR. GANLEY: No. When she does --

12 DR. VAIDA: Oral or IV, right?

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

20 DR. VAIDA: Dr. Wall?

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

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

5 DR. VAIDA: Dr. Johnson [sic]?

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

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

1 DR. VAIDA: Mr. Mixon?

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

10 DR. JUNGMAN: That's helpful.

11 DR. VAIDA: Yes, Dr. Bogner?

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

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

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

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

11 DR. BOGNER: Thank you.

12 DR. VAIDA: Dr. Ganley?

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

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

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

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

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

1 DR. VAIDA: Dr. Hoag?

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

8 DR. BORMEL: At first with number 5, we're
9 telling what the FDA proposal is. Our proposal is
10 that quercetin dihydrate not be included on the
11 503A bulk list. The question that you're voting
12 on, though, is should quercetin dihydrate be placed
13 on the list. If you vote yes, you're voting to
14 place it on the list. If you vote no, you're
15 voting not to place it on the 503A bulks list.

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

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

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

1 list, on the 503 list.

2 Everybody understand? Are we ready to vote?

3 Please vote yes, no, or abstain.

4 (Voting.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 context of a clinical trial.

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

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

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

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

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

21 **Adjournment**

22 DR. VAIDA: I just have to read one more

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

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