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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Thursday, June 23, 2016

8:29 a.m. to 11:17 a.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center
The Great Room (Rm. 1503)
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Cindy Hong, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Michael A. Carome, MD, FASHP**

11 *(Consumer Representative)*

12 Director of Health Research Group

13 Public Citizen

14 Washington, District of Columbia

15

16 **Gigi S. Davidson, BSPH, DICVP**

17 *(U.S. Pharmacopeial Convention Representative)*

18 Director of Clinical Pharmacy Services

19 North Carolina State University

20 College of Veterinary Medicine

21 Raleigh, North Carolina

22

1 **John J. DiGiovanna, MD**

2 Senior Research Physician

3 DNA Repair Section

4 Dermatology Branch

5 Center for Cancer Research

6 National Cancer Institute

7 Bethesda, Maryland

8

9 **Padma Gulur, MD**

10 Professor, Department of Anesthesiology and

11 Perioperative Care

12 University of California, Irvine

13 Orange, California

14

15 **Stephen W. Hoag, PhD**

16 Professor

17 Department of Pharmaceutical Science

18 University of Maryland, Baltimore

19 Baltimore, Maryland

20

21

22

1 **William A. Humphrey, BSPHarm, MBA, MS**

2 Director of Pharmacy Operations

3 St. Jude's Children's Research Hospital

4 Memphis, Tennessee

5

6 **Elizabeth Jungman, JD**

7 Director, Public Health Programs

8 The Pew Charitable Trusts

9 Washington, District of Columbia

10

11 **Katherine Pham, PharmD**

12 Neonatal Intensive Care Unit Pharmacy Specialist

13 Children's National Medical Center

14 Washington, District of Columbia

15

16 **Allen J. Vaida, BSc, PharmD, FASHP**

17 Executive Vice President

18 Institute for Safe Medication Practices

19 Horsham, Pennsylvania

20

21

22

1 **Jurgen Venitz, MD, PhD**

2 *(Chairperson)*

3 Associate Professor, Virginia Commonwealth

4 University

5 School of Pharmacy, Department of Pharmaceutics

6 Richmond, Virginia

7

8 **PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Donna Wall, PharmD**

11 *(National Association of Boards of Pharmacy*

12 *Representative)*

13 Clinical Pharmacist

14 Indiana University Hospital

15 Indianapolis, Indiana

16

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1 **PHARMACY COMPOUNDING DRUGS ADVISORY COMMITTEE**

2 **INDUSTRY REPRESENTATIVE MEMBERS (Non-Voting)**

3 **Ned S. Braunstein, MD**

4 *(Industry Representative)*

5 Senior Vice President and Head of Regulatory
6 Affairs

7 Regeneron Pharmaceuticals, Inc.

8 Tarrytown, New York

9
10 **William Nixon, RPh, MS, FIACP**

11 *(Industry Representative)*

12 Former Owner

13 The Compounding Pharmacy

14 Hickory, North Carolina

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P R O C E E D I N G S

(8:29 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning. I would first like to remind everyone present to please silence your cell phones, Blackberrys, and other devices if you have not already done so.

I would also like to identify the FDA press contacts for this open session meeting, Mr. Chris Kelly and Ms. Lindsay Meyer. If you're present, please stand so everybody can see you. Over there. Thank you.

Good morning. My name is Jurgen Venitz. I'm the chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee into order.

We will now ask those at the table, including FDA staff and committee members, to introduce themselves starting with the FDA to my left and moving along to the right side ending with one of the industry representatives,

1 Dr. Ned Braunstein.

2 So let's start to my left, please.

3 DR. BRAVE: I'm Michael Brave, a medical
4 officer in the Office of Oncology Drug Products, in
5 the Hematology and Oncology Drug Products.

6 MS. GEBBIA: Emily Gebbia, CDER, Compliance.

7 DR. GANLEY: Charlie Ganley, from the Office
8 of New Drugs.

9 MR. FLAHIVE: Jim Flahive, CDER, Compliance,
10 Office of Unapproved Drugs and Labeling Compliance.

11 DR. DOHM: Julie Dohm, agency lead on
12 compounding.

13 MS. BORMEL: Gail Bormel, Center for Drugs,
14 Office of Unapproved Drugs and Labeling Compliance.

15 DR. DiGIOVANNA: John DiGiovanna. I'm a
16 dermatologist at the National Cancer Institute.

17 DR. GULUR: Padma Gulur. I'm a professor of
18 anesthesiology at the University of California,
19 Irvine.

20 DR. HONG: Cindy Hong. I'm DFO for Pharmacy
21 Compounding Advisory Committee.

22 DR. VENITZ: Jurgen Venitz, clinical

1 pharmacologist and professor at the VC School of
2 Pharmacy.

3 MS. DAVIDSON: Gigi Davidson. I represent
4 the United States Pharmacopeia.

5 MR. HUMPHREY: William Humphrey, director of
6 pharmacy, St. Jude Children's Research Hospital.

7 DR. HOAG: Steve Hoag, professor of
8 pharmaceutical sciences at the University of
9 Maryland, Baltimore.

10 MS. JUNGMAN: Elizabeth Jungman, director of
11 public health programs at the Pew Charitable
12 Trusts.

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

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

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

20 DR. WALL: Donna Wall. I represent NABP,
21 and I'm a pharmacist at Indiana University Hospital
22 in Indiana.

1 MR. MIXON: My name is Bill Mixon from
2 Hickory, North Carolina. I'm the non-voting
3 industry member.

4 DR. BRAUNSTEIN: Ned Braunstein from
5 Regeneron Pharmaceuticals. I'm the non-voting
6 pharmaceutical and biotech industry rep.

7 DR. VENITZ: Thank you, everyone. Let me
8 then read for the official record.

9 For topics such as those being discussed at
10 today's meeting, there are often a variety of
11 opinions, some of which are quite strongly held.

12 Our goal is that today's meeting will be a
13 fair and open forum for discussion of these issues
14 and that individuals can express their views
15 without interruption.

16 Thus, as a reminder, individuals will be
17 allowed to speak into the record only if recognized
18 by the chair. We look forward to a productive
19 meeting.

20 In the spirit of the Federal Advisory
21 Committee Act and the Government in the Sunshine
22 Act, we ask that the advisory committee members

1 take care that their conversations about the topic
2 at hand take place in the open forum of the meeting
3 only. We are aware that the members of the media
4 may be anxious to speak with the FDA about these
5 proceedings.

6 However, FDA will refrain from discussing
7 the details of this meeting with the media until
8 its conclusion. Also, the committee is reminded to
9 please refrain from discussing the meeting topic
10 during lunch breaks or other breaks.

11 Today, we will cover six bulk drug
12 substances nominated for inclusion on the list of
13 bulk drug substances that may be use to compound
14 drugs in accordance with Section 503A of the Food,
15 Drug, and Cosmetic Act: chrysin, cesium chloride,
16 sodium dichloroacetate, pyruvic acid, tea tree oil,
17 and 2,3-DMPS.

18 For each of these six substances, we will
19 hear presentations from FDA, ask clarifying
20 questions, hear nominators' presentations, ask
21 clarifying questions, hold an open public hearing,
22 and have committee discussion and voting.

1 This afternoon, we will also hear
2 presentations from FDA on expanded access to
3 investigational new drugs and ask clarifying
4 questions.

5 Let us begin. We will now have
6 Dr. Cindy Hong read the conflict of interest
7 statement.

8 **Conflict of Interest Statement**

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

13 With the exception of the National
14 Association of Boards of Pharmacy, the United
15 States Pharmacopeia, and the industry
16 representatives, all members and temporary voting
17 members of the committee are special government
18 employees or regular federal employees from other
19 agencies and are subject to federal conflict of
20 interest laws and regulations.

21 The following information on the status of
22 this committee's compliance with the federal ethics

1 and conflict of interest laws covered by but not
2 limited to those found at 18 U.S.C. Section 208 is
3 being provided to participants in today's meeting
4 and to the public.

5 FDA has determined that members and
6 temporary voting members of this committee are in
7 compliance with federal ethics and conflict of
8 interest laws.

9 Under 18 U.S.C. Section 208, Congress has
10 authorized FDA to grant waivers to special
11 government employees and regular federal employees
12 who have potential financial conflicts when it is
13 determined that the agency's need for a special
14 government employee's services outweighs his or her
15 potential financial conflict of interest when the
16 interest of the regular federal employee is not so
17 substantial as to be deemed likely to affect the
18 integrity of the services which the government may
19 expect from the employee.

20 Related to the discussions of today's
21 meeting, members and temporary voting members of
22 this committee have been screened for potential

1 financial conflicts of interest of their own, as
2 well as those imputed to them, including those of
3 their spouses or minor children and, for the
4 purposes of 18 U.S.C. Section 208, their employers.

5 These interests may include investments;
6 consulting; expert witness testimony;
7 contracts/grants/CRADAs; speaking/teaching/writing;
8 patents and royalties, and primary employment.

9 During the morning, the committee will
10 discuss six bulk drug substances nominated for
11 inclusion under Section 503A bulk drug substances
12 list.

13 FDA will discuss the following nominated
14 bulk drug substances: cesium chloride, chrysin,
15 sodium dichloroacetate, pyruvic acid, tea tree oil,
16 and 2,3-dimercapto-1-propanesulfonic acid, DMPS.

17 The nominators of these substances will be
18 invited to make a short presentation supporting the
19 nomination. In addition, during the afternoon, the
20 committee will receive updates on certain issues to
21 follow up on discussions from previous meetings
22 including the option for obtaining access to

1 investigational new drugs under expanded access.

2 This is a particular matters meeting during
3 which specific matters related to the six bulk drug
4 substances will be discussed.

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

10 To ensure transparency, we encourage all
11 standing committee members and temporary voting
12 members to disclose any public statements that they
13 have made concerning the bulk drug substances.

14 We would like to note that Dr. Donna Wall is
15 a representative member from the National
16 Association of Board of Pharmacy and that
17 Ms. Gigi Davidson is a representative member from
18 United States Pharmacopeia.

19 Section 102 of the Drug Quality and Security
20 Act amended the Federal Food, Drug, and Cosmetic
21 Act with respect to the advisory committee on
22 compounding to include representatives from the

1 NABP and USP.

2 Their role is to provide the committee with
3 the points of view of the NABP and USP. Unlike the
4 other members of the committee, representative
5 members are not appointed to the committee to
6 provide their own individual judgment on the
7 particular matters at issue.

8 Instead, they serve as the voice of the NABP
9 and USP, entities with the financial or other
10 stakes in the particular matters before the
11 advisory committee.

12 With respect to the FDA's invited industry
13 representatives, we would like to disclose that
14 Dr. Ned Braunstein and Mr. William Mixon are
15 participating in this meeting as non-voting
16 industry representatives acting on behalf of
17 regulated industry.

18 Their role at this meeting is to represent
19 industry in general and not any particular company.
20 Dr. Braunstein is employed by Regeneron
21 Pharmaceuticals, and Mr. Mixon is employed by The
22 Compounding Pharmacy.

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

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

13 DR. VENITZ: Thank you.

14 Dr. Carome, would you please make a
15 disclosure statement for the record?

16 DR. CAROME: Mike Carome. I am the director
17 of Health Research Group of Public Citizen and I
18 would like to disclose that in 1999, Public Citizen
19 submitted comments to an FDA docket and presented
20 testimony at an FDA advisory committee regarding
21 products nominated for inclusion on the 503A bulk
22 drug substances list.

1 As part of the comments, Public Citizen
2 urged the FDA not to include
3 2,3-dimercapto-1-propanesulfonic acid or DMPS and
4 also characterized DMPS as an example of the abuse
5 of pharmacy compounding.

6 In today's session, the committee will
7 consider six bulk drug substances nominated for
8 inclusion under Section 503A bulk drug substances
9 list as they relate to the issue of whether they
10 are appropriate for inclusion on the list of bulk
11 drug substances that may be compounded in
12 accordance with 503A of the FDCA.

13 These discussions will include the bulk drug
14 substance DMPS. I will be participating following
15 in the deliberations of this session of the meeting
16 and will vote on all but the one question posed to
17 the committee regarding DMPS.

18 I'd like to note for the record, as I've
19 noted before, that Public Citizen disagrees with
20 the FDA's policy on so-called non-financial
21 conflict of interest both in terms of its concept
22 and implementation. Thank you.

1 DR. VENITZ: Thank you, Dr. Carome.

2 That will be the start of our presentations.
3 Our first presentation will be from Dr. Julie Dohm
4 at FDA. But before she gets started, I would like
5 to remind to public observers at this meeting that
6 while this meeting is open for public observation,
7 public attendees may not participate except at the
8 specific request of the committee.

9 Dr. Dohm, please?

10 **FDA Introductory Remarks - Julie Dohm**

11 DR. DOHM: Good morning. I would like to
12 welcome you to the fifth meeting of the Pharmacy
13 Compounding Advisory Committee. Again, I am
14 Julie Dohm, senior science advisor for compounding
15 at CDER and the agency lead on compounding issues.

16 As you may be aware, after 25 years of
17 dedicated service at FDA and 41 years in
18 government, Jane Axelrad, associate director for
19 policy at FDA CDER, retired from federal service on
20 April 29th.

21 Jane was a driving force behind many high
22 profile activities, including the many legislative,

1 policy, surveillance, and high profile activities
2 related to drug compounding oversight.

3 As the audience well knows, she set the
4 stage for the continued work that must be done on
5 the compounding program, including that for the
6 advisory committee. It goes without saying that
7 Jane is and will continue to be missed.

8 I look forward to continuing this important
9 work with all of you. I feel fortunate to have
10 been given the opportunity to become an integral
11 part of the compounding program.

12 Already, I've had the pleasure of working on
13 fascinating and complex issues at the intersection
14 of law, science, and policy, and I feel that my
15 background has prepared me for this work.

16 I have bachelor's degrees in biochemistry
17 and chemistry from the University of Chicago and a
18 PhD in biology from Johns Hopkins University where
19 I studied the effect of a drug on the interactions
20 between a transcription factor and its cognate DNA
21 binding site.

22 After graduate school, I became a

1 post-doctoral fellow at Northwestern University,
2 researching the role of DNA mechanics in
3 transcription regulation.

4 During my post-doc, I decided that I wanted
5 to go law school. I earned my J.D. from the
6 University of Pennsylvania Law School, and then I
7 clerked for federal judges in the U.S. Court of
8 Appeals for the federal circuit and the U.S.
9 District Court for the District of Maryland.

10 Following my clerkships, I joined FDA's
11 Office of Chief Counsel as a civil litigator,
12 representing FDA with the Department of Justice in
13 enforcement, defensive, and third-party
14 litigations, both at the trial and appellate
15 levels. I also served a detail as drugs counselor
16 in FDA's Office of Chief Counsel, advising CDER on
17 legal issues relating to generics and biosimilars.

18 Enough about me and turning back to the
19 meeting today, we will discuss the six bulk drug
20 substances nominated for inclusion on the list of
21 bulk drug substances that can be used in
22 compounding by entities seeking to qualify for the

1 exemptions under Section 503A.

2 As others have mentioned, those are going to
3 be chrysin, cesium chloride, sodium
4 dichloroacetate, pyruvic acid, tea tree oil, and
5 DMPS.

6 At today's meeting, we are trying a slightly
7 different approach in the presentation of
8 information. Previously, we had scheduled a few
9 bulk drug substances to be addressed at each open
10 public hearing.

11 Now, we have scheduled time after each bulk
12 drug substance presentation for the nominators to
13 speak and then we will hold an open public hearing
14 on that drug substance before going on to consider
15 the next substance.

16 This allows the committee to focus on one
17 bulk drug substance at a time just prior to the
18 vote on that substance. In addition, during the
19 afternoon, we will review FDA's expanded access
20 investigational new drug program.

21 Our intent is to provide you with more of
22 the nuts and bolts of that program than we have

1 during prior Pharmacy Compounding Advisory
2 Committee meetings.

3 Dr. Jarow, senior medical advisor for CDER,
4 will be giving that presentation, and he will be
5 available to answer questions after he completes
6 it.

7 I would also like to provide you with an
8 update on policy documents issued by the agency
9 since the committee last met in March. In April,
10 FDA issued three draft guidance documents that
11 describe FDA's proposed policies concerning,
12 one, the prescription requirement in Section 503A,
13 two, how the agency intends to apply the
14 prescription requirement in Section 503A to
15 compounding in a hospital or health system
16 pharmacy, and, three, the definition of the term
17 facility in Section 503B of the Act.

18 Each draft guidance document is available
19 for public comment for 90 days. The comment
20 periods for each of those draft guidances will
21 close on July 11th.

22 The first draft guidance is entitled Draft

1 Guidance Prescription Requirement under Section 503
2 of the FDCA. It describes FDA's proposed policies
3 concerning certain prescription requirements for
4 compounding human drug products for identified
5 individual patients under Section 503A.

6 It addresses compounding after the receipt
7 of a prescription for an identified individual
8 patient, what is called anticipatory compounding,
9 and compounding for office use, also known as
10 office stock.

11 The draft guidance states, among other
12 things, that a compounder can fill a prescription
13 for compounded drugs under Section 503A only
14 pursuant to a patient-specific prescription.

15 Hospitals, clinics, and healthcare
16 practitioners can obtain non-patient-specific
17 compounded drug products or office stock from
18 compounders registered as outsourcing facilities
19 under Section 503B.

20 The second guidance is entitled Draft
21 Guidance Hospital and Health System Compounding
22 Under the FD&C Act. Pharmacies located within a

1 hospital or standalone pharmacies that are part of
2 a health system frequently provide compounded drug
3 products for administration within the hospital or
4 health system.

5 This draft guidance describes FDA's proposed
6 policies regarding the application of Section 503A
7 to drugs compounded in state-licensed hospital or
8 health system pharmacies for use within that
9 hospital or health system.

10 Specifically, the draft guidance states that
11 drug products compounded by a licensed pharmacist
12 or licensed physician that are not compounded in
13 accordance with all of the provisions of
14 Section 503A may be subject to regulatory action
15 for violations of the new drug approval, adequate
16 directions for use, and current good manufacturing
17 practice requirements of the Act.

18 However, FDA does not intend to take action
19 if a hospital pharmacy distributes compounded drug
20 products without first receiving a patient-specific
21 prescription or order provided that three things
22 happen.

1 First, the drug products are distributed
2 only to healthcare facilities that are owned and
3 controlled by the same entity, that owns and
4 controls the hospital pharmacy, and that are
5 located within a one-mile radius of the compounding
6 pharmacy;

7 Two, the drug products are only administered
8 within the healthcare facilities to patients within
9 the healthcare facilities pursuant to a
10 patient-specific prescription or order.

11 Three, the drug products are compounded in
12 accordance with all other provisions of
13 Section 503A and any other applicable requirements
14 of the FD&C Act and the FDA regulations. For
15 example, the drug products are not made under
16 unsanitary conditions or being misbranded.

17 The third draft guidance is entitled Draft
18 Guidance Facility Definition Under Section 503B of
19 the FD&CA. Section 503B defines an outsourcing
20 facility, in part, as a facility at one geographic
21 location or address.

22 This draft guidance seeks to answer

1 questions received from outsourcing facilities and
2 other stakeholders about the meaning of the term
3 facility, such as whether multiple suites used for
4 compounding human drugs at a single street address
5 constitute one or more multiple facilities, or
6 whether a single location where human drugs are
7 compounded can be subdivided into separate
8 operations that compound under different standards.

9 In the draft guidance, FDA has proposed to
10 interpret facility at one geographic location or
11 street address to mean a business or other entity
12 under one management, direct or indirect, engaged
13 in human drug compounding at a geographic location
14 or street address.

15 The agency considers all activities,
16 equipment, and materials part of such facility if
17 they are related to human drug compounding under
18 the supervision of the facility's management at the
19 same street address, or in the same building, or in
20 buildings located in close proximity to one
21 another.

22 As noted above, all drug products compounded

1 in an outsourcing facility are regulated under
2 Section 503B and subject to CGMP requirements.
3 These conditions cannot be avoided by segregating
4 or subdividing compounding within an outsourcing
5 facility.

6 Last, on June 9th, the agency issued two
7 final guidances, one on the interim policy in
8 compounding using bulk drug substances under
9 Section 503A and the other on the interim policy in
10 compounding using bulk drug substances under
11 Section 503B.

12 These final guidances set forth the agency's
13 interim regulatory policy concerning compounding
14 using bulk drug substances under Sections 503A and
15 503B respectively while FDA is developing the lists
16 of bulk drug substances that can be used in
17 compounding under each of those sections.

18 With respect to the bulk drug substances
19 nominated for use in compounding under
20 Section 503A, until a substance has been evaluated
21 and is identified in a final rule as being included
22 or not included on the 503A bulks list, FDA does

1 not intend to take action against a state-licensed
2 pharmacy, federal facility, or licensed physician
3 compounding a drug product using a bulk drug
4 substance that is not a component of an
5 FDA-approved drug product and is not the subject of
6 an applicable USP or NF monograph, provided that
7 the following conditions are met.

8 First, the bulk drug substance appears in
9 503A, Category 1, on FDA's website. A bulk drug
10 substance in Category 1 may be eligible for
11 inclusion on the 503A bulks list, was nominated
12 with sufficient supporting information for FDA to
13 evaluate it, and has not been identified by FDA as
14 a substance that presents a significant safety risk
15 in compounding prior to the publication of the
16 final rule.

17 The substances that FDA has identified to
18 present a significant safety risk and that are not
19 eligible for this interim policy are included in
20 Category 2 listed on the same webpage.

21 In addition, substances that were nominated
22 with insufficient supporting information for FDA to

1 evaluate them appear on the webpage in Category 3.

2 If such substances are renominated with
3 adequate supporting information for FDA to evaluate
4 them, FDA will consider which category these
5 substances should be placed after it completes its
6 evaluations of the substances that currently appear
7 in Category 1.

8 Renominated and newly nominated substances
9 are not eligible for the policy until they've been
10 placed affirmatively in Category 1.

11 The second condition is that the original
12 manufacturer and all subsequent manufacturers of
13 the bulk drug substance are establishments that are
14 registered under Section 510, including foreign
15 establishments that are registered under
16 Section 510(i) of the Act.

17 The third condition is that the bulk drug
18 substance is accompanied by a valid certificate of
19 analysis. And fourth, the drug product compounded
20 using the bulk drug substance is compounded in
21 compliance with all of the other conditions of
22 Section 503A.

1 With respect to the 503b bulks list, until a
2 substance has been evaluated and a final Federal
3 Register notice is published identifying the
4 substance as being included or not included on the
5 503B bulks list, FDA does not intend to take action
6 against an outsourcing facility for compounding a
7 drug using a bulk drug substance that does not
8 appear on the 503B bulks list and that is not used
9 to compound a drug that appears on the FDA drug
10 shortage list at the time of compounding,
11 distribution, and dispensing, provided that the
12 following conditions are met.

13 First, the bulk drug substance appears on
14 503B, Category 1 on FDA's website. Like 503A, a
15 Category 1 substance may be eligible for inclusion
16 on the 503B bulks list, was nominated for inclusion
17 on that list with adequate supporting information
18 for FDA to evaluate it, and has not been identified
19 by FDA as a substance that appears to present a
20 significant safety risk in compounding prior to the
21 publication of a final notice in the final Federal
22 Register.

1 FDA has also posted Categories 2 and 3 on
2 its website of bulk drug substances that are not
3 eligible for this policy because they appear to
4 present significant safety risks or were not
5 nominated with adequate supporting information for
6 FDA to evaluate them.

7 If substances currently in Category 3 are
8 renominated with adequate supporting information
9 for FDA to evaluate them, FDA will consider which
10 category these substances should be placed in after
11 it completes its evaluation of the substances that
12 currently appear in Category 1.

13 Renominated and newly nominated substances
14 are not eligible for the policy until they have
15 been placed in Category 1.

16 The second condition, like 503A, is that the
17 original manufacturer and all subsequent
18 manufacturers of the bulk drug substance are
19 establishments that are registered under
20 Section 510 and, again, including foreign
21 establishments that are registered under 510I.

22 Third condition is that the bulk drug

1 substance is, again, accompanied by a valid
2 certificate of analysis.

3 The fourth condition is that if the bulk
4 drug substance is the subject of an applicable USP
5 or NF monograph, the bulk drug substance complies
6 with that monograph.

7 Fifth, the drug product compounded using the
8 bulk drug substance is compounded in compliance
9 with all the provisions of Section 503B.

10 In addition, FDA does not intend to take
11 action against an outsourcing facility for
12 compounding of a drug product using a bulk drug
13 substance that is not on the 503B bulks list if the
14 drug compounded from the bulk drug substance,
15 one, appeared on the FDA's shortage list within
16 60 days of distributions and dispensing and,
17 two, was to fill an order that the outsourcing
18 facility received for the drug while it was on
19 FDA's drug shortage list.

20 These guidances appear on the FDA's
21 compounding website under the section titled
22 Regulatory Policy.

1 I would like to thank you for your
2 participation on the Pharmacy Compounding Advisory
3 Committee, and I look forward to a productive
4 meeting and to our continued work with you.

5 Thank you.

6 DR. VENITZ: Thank you, Dr. Dohm. Speaking
7 on behalf of the committee, let me welcome you and
8 we're all looking forward to working with you as
9 our agency lead.

10 Let me also take the personal privilege of
11 thanking your predecessor, Dr. Axelrad, for her
12 tireless work for getting us all started, and I
13 hope she enjoys her retirement.

14 Now, we're proceeding to our first order of
15 business, which is the review of chrysin. The FDA
16 presenter is Dr. Michael Brave. He is a medical
17 officer in the Division of Oncology Products and
18 will introduce FDA's review.

19 **Presentation - Michael Brave**

20 DR. BRAVE: Good morning. I'm Dr. Brave
21 from the Office of Hematology and Oncology
22 Products, and I reviewed the nomination for

1 chrysin. I'd like to thank my colleagues listed
2 here for also reviewing this nomination.

3 Chrysin has been nominated for compounding
4 as an aromatase inhibitor, which prevents the
5 conversion of testosterone to estrogen for the
6 treatment of quote, "high estrogen and low
7 testosterone."

8 The proposed route of administration is
9 topical. The references provided in the nomination
10 contain only nonclinical information. Chrysin is
11 currently available as a dietary ingredient in
12 dietary supplements.

13 Chrysin is a flavone found in plants such as
14 the blue passion flower and in propolis or bee
15 glue. Epidemiologic studies suggest that chrysin
16 may have anticancer and chemopreventive properties.

17 Chemically, chrysin is a small molecule that
18 can be easily characterized, and it is stable under
19 ordinary storage conditions for topical dosage
20 forms.

21 Chrysin reportedly has activity against
22 cancer cell lines in vitro. In addition, xenograft

1 studies suggest several potential mechanisms of
2 action, including carcinogen biotransformation,
3 free radical scavenging, and modulation of cellular
4 pathways linked to inflammation, proliferation,
5 differentiation, and metastases.

6 Systemic exposure to ingested chrysin in
7 humans is low due to poor oral bioavailability, and
8 rapid metabolism, and elimination.

9 In healthy male volunteers, after a single
10 oral dose of 400 milligrams, mean plasma
11 concentration of chrysin remained less than
12 0.1 millimolar due to pre-systemic intestinal, and
13 hepatic glucuronidation, and sulfation, and efflux
14 of metabolites back into the intestine for
15 hydrolysis, and fecal elimination.

16 It is therefore not surprising that in a
17 study published by Gambelunghe and colleagues, oral
18 chrysin had no observable effect on testosterone
19 metabolism in healthy male volunteers.

20 In summary, we considered the following
21 factors in evaluating the effectiveness for chrysin
22 for the proposed indication. Nonclinical data

1 suggests that chrysin has biological effects, which
2 could support a rationale for its development as a
3 chemopreventive agent or as an adjunct to
4 chemotherapy.

5 Chrysin is sold and is readily available as
6 a nutritional supplement, and we found no published
7 reports of chrysin toxicity. Thus, chrysin may be
8 relatively safe at usual dietary doses.

9 Nonetheless, no clinical trial has, to our
10 knowledge, ever been conducted with an objective to
11 demonstrate clinical anticancer activity. We are
12 also unaware of any preclinical or clinical data
13 regarding chrysin administered topically. Finally,
14 FDA-approved testosterone replacement products are
15 available.

16 Clinical trials with chrysin have not, to
17 our knowledge, been done. However, we found no
18 reports of toxicity attributable to chrysin in the
19 FAERS database or in published literature.

20 We found insufficient information to
21 determine how long chrysin has been used in
22 pharmacy compounding. Currently, oral and topical

1 compounded formulations of chrysin are advertised
2 on the internet.

3 In summary, chrysin is chemically
4 well-characterized and expected to be stable in
5 topical formulations. Although nonclinical data
6 suggests that chrysin has biological effects, which
7 could support a rationale for its development as a
8 chemopreventive agent or as an adjunct to
9 chemotherapy, no clinical trial has been conducted,
10 to our knowledge, with an objective to demonstrate
11 clinical anticancer activity.

12 We also found no clinical studies that
13 demonstrate the efficacy of topical or oral chrysin
14 as an aromatase inhibitor for treatment of quote,
15 "low testosterone or high estrogen."

16 Several FDA-approved testosterone
17 replacement formulations are already marketed, as
18 are several aromatase inhibitors for the treatment
19 of breast cancer in postmenopausal women.

20 Clinical safety information is scant and is
21 mostly derived from the use of orally ingested
22 chrysin as a nutritional supplement. No

1 information was found to assess the safety of
2 topically applied chrysin.

3 There is insufficient information to
4 evaluate the historical use of chrysin in pharmacy
5 compounding. Chrysin does appear to be compounded
6 currently and is promoted for use primarily with
7 regard to bodybuilding and men's health.

8 Based on a balancing of the four evaluation
9 criteria articulated in the Federal Register, we
10 find that chrysin is not a suitable substance for
11 the bulk drug substance list under Section 503A of
12 the Food, Drug and Cosmetic Act. Therefore, we
13 recommend that it not be included on the list.

14 **Clarifying Questions from the Committee**

15 DR. VENITZ: Thank you, Dr. Brave.

16 Any clarifying questions by any of the
17 committee members?

18 Go ahead, Dr. DiGiovanna.

19 DR. DiGIOVANNA: Yes. Dr. DiGiovanna. You
20 have in the materials that chrysin is sold as
21 cosmetics. Is it widely sold? And if it's not on
22 the bulk drug substances list, will it still be

1 available under those ways that it's sold now?

2 MS. BORMEL: This is Gail Bormel. I'll
3 answer that. We're only addressing the chrysin
4 nomination for the 503A bulks list. It's used as a
5 drug for that. So if it's sold in other forms, for
6 cosmetics, et cetera, this would not affect that.

7 DR. VENITZ: You mentioned it has
8 insufficient safety information. What about
9 potential expected toxicity based on the structure
10 and the suspected biologic activities? Are there
11 any theoretical risks since we --

12 DR. BRAVE: I don't know.

13 DR. VENITZ: I'm sorry. You said --

14 DR. BRAVE: I don't know.

15 DR. VENITZ: You don't know. Okay.

16 Any other questions?

17 (No response).

18 DR. VENITZ: Thank you, Dr. Brave.

19 Then we have our nominator's presentation.
20 The nominator for chrysin is Mr. Wynn from Fagron.

21 **Presentation - Tom Wynn**

22 MR. WYNN: Thank you very much for having me

1 today. My name is Tom Wynn, and I'm from Fagron.
2 We really appreciate you giving this chance to
3 speak about our nomination for chrysin.

4 So chrysin, as was mentioned, is a
5 naturally-occurring bioflavonoid. It is found in
6 passion flower, Indian trumpet flower, honeycomb,
7 chamomile, oyster mushrooms, as well as in tomato
8 skin, fruit skin, and other foods as well. So we
9 do ingest quite a bit of chrysin through our normal
10 diets probably every day.

11 Bioflavonoids, like chrysin in the plant,
12 their purpose, they would act as chemical
13 messengers. They're necessary in the production of
14 pigmentations involved in -- excuse me -- UV
15 filtration and influence symbiotic relationships
16 and nitrogen fixation.

17 They also have been found to have
18 bioflavonoids, such as chrysin -- they have
19 antibacterial properties as well.

20 So the FDA has stated in their evaluation of
21 chrysin that it is easily characterized, relatively
22 stable, and it's a small molecule. It's true.

1 Chrysin actually has, as far as being small, a
2 molecular size of only 254 grams per mole, and that
3 molecular weight is consistent with that of steroid
4 hormones. And actually, it's a bit smaller than
5 most of them that are currently available that are
6 used topically.

7 Then they also mentioned that oral
8 supplementation, that the bioavailability is
9 relatively low, also true. Same study here that he
10 mentioned before is that 400 milligrams of chrysin
11 did not really get very much absorbed through the
12 gut.

13 There is some talk of it having some
14 activity in the gut as well, but the actual
15 systemic absorption was low.

16 Keeping that in mind, the first thing we're
17 going to think of when we have something that has
18 low bioavailability is, does it have topical
19 administration feasibility?

20 We did mention that it has a very low
21 molecular weight. That being said, we know, based
22 on this study here on transdermal routes, that if

1 something has a molecular weight less than
2 500 Daltons, that's a very good candidate for
3 transdermal absorption.

4 It also mentions that unionized entities
5 have better absorption and chrysin is non-polar, so
6 it has some capabilities of being able to be
7 utilized topically based on just its normal
8 structure and its ionization.

9 Efficacy potential; if we get away from just
10 the transdermal part and just talk about can there
11 be efficacy to actually use chrysin? And in this
12 study here, they looked at its ability to inhibit
13 human aromatase. Besides chrysin, they looked at
14 others.

15 What they found was that these
16 bioflavonoids, such as chrysin, did actually have
17 the ability to bind to the active site of aromatase
18 and then actually cause activity.

19 Also, another study where they actually
20 looked at chrysin again, and this one was done in
21 Leydig cells. They were looking at, does it have
22 potential to enhance steroidogenesis?

1 What they found with these results that
2 chrysin did actually show the potential to
3 induce -- they didn't really induce the gene
4 expression, but they were able to actually increase
5 the functionality of the Leydig cells based on
6 cyclic AMP stimulation.

7 They're allowing that process to continue
8 easier and thereby increasing the aromatase
9 activity in kind of a roundabout way, maybe not
10 exactly hitting the enzyme but actually affecting
11 the cyclic AMP, which then goes ahead and affects
12 the aromatase.

13 Another one here -- this one talks about the
14 beneficial effects of chrysin and again in animals.
15 This one, we looked at recently isolated from
16 passion flower, administered to two-year-old male
17 rats for a period of 30 days.

18 They saw a significant improvement in
19 overall sexual function in the rats compared to the
20 control rats. Both had increased sperm count,
21 greater fertilization potential, greater litter
22 size, and they definitely showed a change by adding

1 the chrysin to this rat's diet.

2 The next one, we also look here at
3 beneficial effects of chrysin on the reproductive
4 system again in rats. In this one, we were divided
5 in two groups. Rats were given a control corn oil.

6 Chrysin was administered at a dose of
7 50 milligrams per kilogram per day. And the
8 results indicated that chrysin significantly
9 increased both GSH, CAT, GSH-Px, and copper-zinc-
10 SOD levels, but it did not change the formation of
11 the TBARS which is the tissue thiobarbituric acid
12 reactive.

13 In addition, sperm motility, sperm
14 concentrations, and serum testosterone levels were
15 significantly increased. So here, we're actually
16 showing that the testosterone levels were increased
17 by the addition of chrysin.

18 Now, if we look at mutagenicity, the FDA
19 points to studies in bacteria strains using the
20 Ames test. Within the study that they actually
21 presented, the study looked at all bioflavonoids
22 and actually found that chrysin was the only one

1 that showed negative mutagenicity across every
2 strain tested.

3 This was done using the Ames test
4 which -- and the study listed below is actually
5 proven to be a very sensitive test. It has greater
6 specificity and predictability over all forms of
7 mutagenic testing. Within the test that they
8 actually provided, it actually showed that chrysin
9 had negative mutagenicity.

10 This is that actual test here. This was the
11 article that was submitted, and it said, finally,
12 chrysin, which has only two hydroxyl groups, did
13 not induce mutagenicity activity in any of the
14 bacterial strains used.

15 Then they also mentioned in their evaluation
16 about neurotoxic effects. Chrysin has been shown,
17 in this study, that it actually had neuroprotective
18 effects.

19 Here, polyphenolic compounds, especially
20 flavonoids, are known to be the most common chemical
21 class of phytochemicals which possess a multiple
22 range of health-promoting effects.

1 Chrysin, belonging to the flavone class, is
2 one of the more important bioactive constituents of
3 fruits, vegetables -- we went over that -- but
4 chrysin possesses potent neuroprotective effects
5 and suppresses neuroinflammation.

6 Here, in this study, we're actually showing
7 that instead of having negative effects, it
8 actually does have positive effects and is actually
9 neuroprotective.

10 Now, another study, one that they also
11 submitted in their actual review of chrysin, was
12 neuroprotective efficacy of chrysin against
13 cisplatin-induced toxicity via attenuation of
14 oxidative stress. This came out of the Journal of
15 Pharmacy and Pharmacology.

16 In that study, they actually found that
17 chrysin suppressed the cisplatin-induced renal
18 injury. Actually, having chrysin along can
19 actually suppress any kind of ill effects that
20 cisplatin can cause while we're actually trying to
21 treat the tumors in that that we use cisplatin for.

22 Chrysin also has hepatoprotective effects.

1 In this study here, we looked at the antioxidant
2 status in hepatitis in rats. The treatment with
3 chrysin was 25, 50, and 100 milligrams per kilogram
4 of body weight.

5 Within that, these findings demonstrate that
6 chrysin acts as hepatoprotective, antioxidant agent
7 against D-galactosamine-induced hepatotoxicity.
8 This is just another example where it's actually
9 causing positive and not negative effects.

10 We also have another study here where the
11 influence of chrysin on hepatic markers and lipid
12 profile, rats again are treated with different
13 concentrations, 20, 50, and 100.

14 It also decreased the level of cholesterol,
15 phospholipids, triglycerides, free fatty acids in
16 plasma and tissues of liver and kidney. Chrysin
17 exhibits hepatoprotective and antihyperlipidemic
18 activity. This is another study again showing the
19 positive effects of chrysin on those parameters.

20 Chemoprotective effects, this is something
21 that the committee did talk about and possibly said
22 that they do see potential for it there. This is a

1 study here that talked about findings that might
2 suggest that possible chemopreventive activity of
3 chrysin in early step of colon tumorigenesis. So
4 this is just another study again showing positive
5 effects in looking at the chemoprotective effects.

6 The next one here, this study, chrysin
7 promotes tumor necrosis factor-related
8 apoptosis-inducing ligand-induced apoptosis in
9 human cancer cell lines. In this study, we find
10 that pre-treatment with chrysin could promote the
11 cell death induced by TRAIL according to
12 morphological changes and appearance in four human
13 cancer cell lines.

14 All data indicate that chrysin can enhance
15 apoptosis in induced trials. This is actually a
16 trial that they did, and they found that chrysin
17 did have chemoprotective effects.

18 In conclusion, there are reference studies
19 that do look at the aromatase inhibition of
20 flavonoids, as well as chrysin. Chrysin is a good
21 candidate for topical and transdermal delivery.

22 Historically, it's been effective used at

1 much lower doses when it's commonly used orally
2 because of low bioavailability. So again, it has
3 the potential there to be done transdermally.

4 Animal studies suggest that chrysin
5 supplementation will improve sperm count,
6 fertility, suggesting that it improves free
7 testosterone levels. In the Ames test referenced
8 by the committee, chrysin did not induce any
9 mutagenic activity. Studies have shown that
10 chrysin is neuroprotective, chemoprotective, and
11 has hepatoprotective properties.

12 That's all I have.

13 **Clarifying Questions from the Committee**

14 DR. VENITZ: Thank you, Mr. Wynn.

15 Any clarifying questions by the committee?
16 Dr. Jungman?

17 MS. JUNGMAN: I was wondering if you could
18 talk a little bit about if there's a clinical need
19 here that chrysin fills that's not being filled by
20 FDA-approved products.

21 MR. WYNN: Sure. With chrysin, one of the
22 things we can look at is -- we talked about is the

1 safety profile. In long-term use, with a lot of
2 the commercially available products that are out
3 there that are used for aromatase inhibition, I
4 mean, a lot of the complaints that they get;
5 they're skeletal complications, musculoskeletal
6 pain, visual disturbances, neurological
7 disturbances, and a lot of -- that's just a few of
8 the things that have been documented that can be an
9 issue with the current available aromatase
10 inhibitors that are out there in long-term use.

11 Chrysin is a way to have a more natural
12 product out there that, to this date and from what
13 we've seen in the studies that are out there now,
14 has not really shown to have any of those issues in
15 longer-term use.

16 Most of the time now, what you're seeing is
17 true. We may not necessarily -- most of those
18 studies have been done in women and breast cancer
19 because they're the ones that are going to use
20 aromatase inhibitors the longest.

21 But again now, more and more, we're seeing
22 that they are used in men, not really for the

1 bodybuilding, but for areas of actually increasing
2 testosterone levels with maybe not having to use as
3 high of a dose because dose-related incidences of
4 long-term use of high hormones can actually be an
5 issue.

6 If we can lower the dose by allowing the
7 dose to be more effective and decrease the
8 potential for increased estrogen or other things
9 that we might get from the hormone replacement that
10 having an option that's an aromatase inhibitor that
11 could be used long-term would be better than maybe
12 having a lot of these side effects that we have
13 from the ones that are currently out there.

14 DR. VENITZ: Dr. Vaida?

15 DR. VAIDA: Yes. It seems that a lot of the
16 studies that you were showing, although they were
17 in rats and animals, that was all with, what, oral
18 therapy?

19 MR. WYNN: Those were all with oral therapy
20 where they were actually utilizing, showing that if
21 they were coming with the contact -- but yes, they
22 were all oral. Let's just say yes.

1 DR. VAIDA: Thank you.

2 DR. VENITZ: Dr. Gulur?

3 MR. WYNN: But I think that, to answer more
4 of that question, is what they're also stating in
5 the findings that they did in the preliminary look
6 at our nomination -- they said there was no safety
7 or efficacy for oral or topical.

8 So they're actually stating that there's
9 none out there at all, and actually, what we have
10 shown is there is information out there on its
11 safety and efficacy.

12 DR. VENITZ: Dr. Gulur?

13 DR. GULUR: The studies that you brought up
14 are all on animals, rats and mice. Do we have
15 studies, clinical trials on human beings,
16 especially considering that you made the statement
17 regarding the long-term side effects of existing
18 FDA supplements? Are there further studies showing
19 that chrysin, in long-term therapy, is safe in
20 humans?

21 MR. WYNN: Currently, right now, there
22 aren't any trials of chrysin that are available out

1 there. As far as historically, I know the
2 presenter said that he doesn't really have any data
3 on how long chrysin has been used.

4 I can tell you just from personal
5 experience. I've been a pharmacist since '94 and
6 I've seen it used since then. At the very least,
7 it's been out there that long, probably longer than
8 that and haven't really had any issues that I know
9 of come up that have been submitted to the FDA or
10 presented to me as a provider at the time. But
11 currently right now, there are no clinical trials
12 on chrysin that I know of.

13 DR. VENITZ: Go ahead.

14 DR. GULUR: Just one clarifying -- is there
15 a formal mechanism for where you collect this data
16 in patients that you compound on and do you collect
17 whether there are adverse effects on these patients
18 anywhere?

19 MR. WYNN: When I actually had my pharmacy,
20 which I do not now, we actually did have a program
21 that I had set up that basically we were calling
22 and checking on patients.

1 It was a way for us to keep in contact to
2 make sure that the patients were utilizing what we
3 were making and compounding properly and at the
4 same time gathering this kind of information.

5 If there was an issue, we wanted to know. I
6 had my own program set up in my pharmacy that we
7 did that with, and it was just part of our SOPs,
8 and we actually called and checked.

9 DR. GULUR: All right. Thank you.

10 DR. VENITZ: Dr. Braunstein?

11 DR. BRAUNSTEIN: Yes, hi. I mean, do you
12 have any data on either in humans or even in
13 animals on levels achieved of this compound, any
14 evidence that the levels you're achieving are able
15 to inhibit aromatase, any evidence that the drug is
16 actually producing a pharmacologic effect in
17 animals or in humans? I mean, it's one thing to
18 establish safety of something if it doesn't do
19 anything.

20 MR. WYNN: Good point. Definitely, right
21 now, I don't know -- I did not find a study on
22 transdermal.

1 The only one that was submitted by the
2 reviewer of our nomination was actually one where
3 they actually used plant extract, which I didn't
4 feel was maybe the proper way to look at how
5 transdermal penetration would occur. Because if
6 that's true, then the commercially available
7 estrogen products we have, why don't we just use
8 yen powder? I mean, we definitely use the
9 constituent itself.

10 Currently, there's not information out there
11 that's going to promote or dismiss its transdermal
12 capabilities. I can say again, as personal
13 experience, that the doctors were checking
14 testosterone levels and looking at changes that
15 were occurring while they were utilizing chrysin.
16 But I would not have a true study.

17 DR. VENITZ: Let me ask you a follow-up
18 question then. In your compounding experience, was
19 it exclusively transdermal or did you also compound
20 oral formulation?

21 MR. WYNN: Sure. It was exclusively
22 transdermal. I had some physicians that would use

1 chrysin alone, and they would do that sometimes as
2 patients get older when they didn't want to give a
3 whole bunch of testosterone, their idea being that
4 if they could get what we're already making, what
5 little they're making to stay around a bit longer,
6 they could get some additive effects of what they
7 needed for those patients.

8 So I did see mostly all transdermal, and I
9 did see it with some other steroid hormones and by
10 itself.

11 DR. VENITZ: So it was all transdermal even
12 though you had no evidence that it actually
13 achieves levels that are better than the
14 400-milligram oral study that was reviewed that
15 didn't show any effects on the --

16 MR. WYNN: These patients are actually under
17 the care of a physician who was actively checking
18 levels at the time. And if they weren't actually
19 being effective to his needs, he would have stopped
20 the therapy. So he was actually controlling -- he
21 or she was looking at the levels and then assessing
22 what they wanted to do at that point.

1 So I was not actively doing it, but the
2 physician was in control, and watching levels, and
3 making sure that they were getting a positive
4 response.

5 DR. VENITZ: Okay. Thank you. Yes,
6 Dr. Davidson?

7 MS. DAVIDSON: Dr. Wynn, can you
8 characterize, either from your personal experience
9 or as a supplier of the API, the number of patients
10 that are receiving transdermal chrysin or the
11 prescribers that are prescribing transdermal
12 chrysin?

13 MR. WYNN: Sure. Hard to tell that. I
14 honestly don't know. I'm not sure how many
15 patients are actually currently actively being
16 utilized. Like in my practice, let's say -- and
17 this has been -- I've been out for a number of
18 years, but at that time, maybe we had 15 percent
19 that were actually utilizing chrysin. Not all
20 physicians were doing that, but I had several that
21 were utilizing its aspects for what they wanted.

22 MS. DAVIDSON: And can you help me

1 understand what 15 percent means in terms of
2 numbers?

3 MR. WYNN: Sure. All right. So we were
4 doing probably 300 a month; so 15 percent of that.

5 **Committee Discussion and Vote**

6 DR. VENITZ: Any other clarifying questions
7 by the committee?

8 (No response.)

9 DR. VENITZ: Then thank you for your
10 presentation.

11 We now have supposedly an open public
12 hearing, but we have nobody signed up. We're going
13 to continue our discussion and vote. We're now
14 starting the official discussion on the topic of
15 chrysin that we're going to vote on in a few
16 minutes.

17 Any discussion? Dr. Davidson?

18 MS. DAVIDSON: I have an overarching
19 question for FDA. It seems like there may be some
20 potentially promising use for chrysin in terms of
21 neuroprotection and maybe chemoprotection. I'm not
22 sure I understand what that means other than

1 promoting apoptosis.

2 But my question is, could substances not
3 placed on this list potentially be used in an
4 investigational situation? Could they still be
5 prepared for investigations under an IACUC, IRB,
6 whatever?

7 MS. BORMEL: You're suggesting something
8 could be looked at like chrysin under an IND? Yes,
9 it could be looked up under an IND separate from
10 consideration of the 503A bulks nomination process.

11 MS. DAVIDSON: I wasn't specifically
12 thinking of an IND as we know it, which we'll learn
13 a lot more about this afternoon, but an individual
14 institutional researcher that may want to use it in
15 a small human population for a prospective
16 head-to-head comparison.

17 MS. BORMEL: Right. Usually, if a
18 researcher is going to look at a particular drug,
19 they would get an IND. We're talking about the IND
20 process in order to do a research project. So yes,
21 the researcher still could look at this particular
22 drug under an IND.

1 DR. VENITZ: Any other questions? Yes,
2 Dr. Pham?

3 DR. PHAM: I think I'm starting to get
4 confused. If everyone else is clear on this, help
5 me out here. But it seems like a lot of data
6 that's being presented is speaking to the oral
7 product, but the oral absorption is poor.

8 Yet at the same time, it seems that from a
9 public access perspective, it seems most people
10 will want the transdermal product, but we're not
11 seeing a lot of data on transdermal.

12 I feel like there's a big disconnect, so I'm
13 kind of getting a sense that what we want to
14 potentially say is maybe there's a place for
15 topical. Dr. DiGiovanna, help me out if you have
16 some thoughts.

17 Maybe there's a place for topical, but the
18 data doesn't support that. The data shows oral,
19 but then there's not great information that oral
20 gets absorbed, and it's potentially already
21 accessible through dietary supplements and other
22 things.

1 What is the sense then for -- is it even
2 worth talking about just topical, knowing that oral
3 is available through other mechanisms? But do we
4 want something that doesn't actually have data
5 supporting topical, even though it's actually
6 potentially the way that it's used?

7 DR. DiGIOVANNA: I'm not sure if you're
8 addressing that to me, but I'll take it on. So my
9 perception of this is there's not a great deal of
10 information, that it's poorly absorbed orally, and
11 there's no information about the pharmacology of it
12 when it's applied topically.

13 We don't know if it's absorbed well or at
14 all. And without a clinical study to suggest that
15 it does something, if you don't know that it's
16 absorbed and you have no clinical evidence that it
17 works, it makes it really difficult to make an
18 assessment of its utility.

19 DR. VENITZ: And I would add to that, if you
20 look at the doses that were used in those rat
21 studies, if you scale them up to humans, they were
22 like 2 to 7 grams per day.

1 To translate that into a dermal, the
2 transdermal absorption would have to be very high,
3 presumably at the doses that they're using because
4 it is intended for the systemic effect.

5 On the other hand, I didn't hear in the FDA
6 presentation nor in the nominator presentations any
7 significant concerns about safety. We can argue
8 whether the drug works or not or whether there's
9 evidence to support that it might work after
10 transdermal administration or not. But I haven't
11 really heard anything related to safety issues. It
12 could be a compounded placebo.

13 Yes, Dr. Vaida? I thought you raised your
14 hand.

15 Okay. Any other comments?

16 (No response.)

17 DR. VENITZ: Do we want to proceed with the
18 vote? Okay. Then let me go through my spiel.

19 The panel will be using an electronic voting
20 system for this meeting. Each voting member has
21 three voting buttons on your microphone: yes, no,
22 and abstain.

1 Please vote by pressing your selection
2 firmly three times. After everyone has voted, the
3 vote will be complete. Voting will be on the one
4 product that just was presented.

5 All vote questions relate to whether the
6 product should be included on the 503A bulk list.
7 As always, after the completion of each vote, we
8 will read the vote from the screen into the record
9 and then hear individual comments from each member.

10 Ready to vote then? Can you put up the
11 question?

12 So the voting question is FDA is proposing
13 that chrysin not be placed on the list. Please
14 vote yes, no, or abstain.

15 (Vote taken.)

16 DR. HONG: Question 1 on chrysin, we have
17 2 yeses, 9 nos, and zero abstain.

18 DR. VENITZ: Okay. Let's go around the
19 table then, starting to my right.

20 Yes, Donna?

21 DR. WALL: I voted no because I just didn't
22 really see a purpose in it. There's just so many

1 unanswerd questions.

2 DR. CAROME: Mike Carome. I voted no.
3 There's no evidence that, topically or orally
4 taken, this has any pharmacological effect, no
5 evidence clinically that it offers any benefits.
6 We have no safety data, and there are FDA-approved
7 products for treating cancer and for treating
8 testosterone deficiency.

9 DR. VAIDA: Allen Vaida. I voted no
10 basically for the same reasons. I don't see any
11 clinical evidence for this drug.

12 DR. PHAM: Katherine Pham. I voted no. I
13 think that the lack of adverse effects could
14 potentially allude to safety, but I don't think
15 that there's a consistent mechanism in place to
16 catch that data in the community.

17 So balancing that with the fact that we have
18 question on absorption, either orally or
19 transdermally, I voted no.

20 MS. JUNGMAN: Elizabeth Jungman. I also
21 voted no. The lack of efficacy and poor
22 bioavailability were kind of the primary issues

1 there, coupled with the lack of safety information
2 for long-term use.

3 Understanding that there are complaints
4 about some of the FDA-approved alternatives, at
5 least we have robust data about those.

6 DR. HOAG: I'm Steve Hoag. I voted on the
7 question, which was "not," so I'm not sure if
8 I -- because at the end, it was a little ambiguous.

9 But anyway, I would suggest that it not be
10 on the list. In the future, I may consider that
11 because if there's more data, it could be
12 promising. But at the moment, it hasn't risen to
13 that level for my evaluation.

14 MR. HUMPHREY: William Humphrey. I voted no
15 for many of the same reasons already expressed. I
16 didn't hear any evidence that it is absorbed
17 topically and has any efficacy from that.

18 MS. DAVIDSON: Gigi Davidson. I struggled
19 with this one. I was stricken by the 45 patients
20 just in Dr. Wynn's practice that are still
21 receiving this. And even though it is commercially
22 available as a dietary supplement, that would not

1 be a form that could be used to prepare a
2 transdermal dosage form.

3 I think that there's fairly confident
4 knowledge that it doesn't cause the adverse effects
5 that some of the FDA-approved alternatives are, so
6 I voted yes for it to continue to be on the list
7 and be used clinically to gather more data.

8 DR. VENITZ: I'm with Dr. Davidson. I had a
9 struggle on this one, too, but ended up on the
10 other side of the coin. I think the safety to me
11 was reasonable to keep it or put it back on the
12 list.

13 On the other hand, the total lack of any
14 transdermal absorption data doesn't convince me
15 that you're avoiding the first-pass effect that
16 prevents its oral absorption in humans at very high
17 doses.

18 If there had been any even tentative data
19 suggesting that transdermal absorption actually
20 occurs and it does avoid the first-pass effect,
21 then it would be much more favorable because I
22 think the compounding history that was outlined, to

1 me, sounded pretty impressive.

2 DR. GULUR: Padma Gulur. I voted no to
3 placing this for similar reasons, which is a lack
4 of data on how much is getting absorbed, if this
5 drug is actually effective. It's true that perhaps
6 there aren't any adverse event data, but that might
7 be because the drug just isn't being absorbed. And
8 while there appears to be some utilization in the
9 population, again, lack of effectiveness or
10 absorption data makes it hard to understand.

11 DR. DiGIOVANNA: John DiGiovanna. I voted
12 no for the reasons stated.

13 DR. VENITZ: Okay. Thank you. We are ahead
14 of the schedule, so we're going to juggle a little
15 bit. I think what we might have to is take a break
16 now.

17 MS. BORMEL: Dr. Venitz, I just have a quick
18 question.

19 DR. VENITZ: Yes. Go ahead.

20 MS. BORMEL: Is the vote going to be -- what
21 is the official record of the vote?

22 DR. VENITZ: It is 9 to 2 -- with the

1 correction that Dr. Hoag made that he basically
2 would be in the no category.

3 MS. BORMEL: Okay.

4 DR. VENITZ: So the official vote is 9 to 2,
5 but it's --

6 MS. BORMEL: 10 to 1.

7 DR. VENITZ: -- supposed to be reflected
8 10 to 1, yes, for the record.

9 MS. BORMEL: Thank you.

10 DR. VENITZ: Any other comments or concerns
11 about the vote?

12 (No response.)

13 DR. VENITZ: We have a scheduling issue now
14 because we are ahead of the curve, and we have to
15 keep our open public hearing at 10:35. What I
16 would suggest is that we take a 10-minute break
17 now, reconvene, and then we work our way through
18 the lunch break, if that's acceptable?

19 (No response.)

20 DR. VENITZ: Okay. Then let's take a
21 10-minute break. It's now 9:37, so let's reconvene
22 at 9:47, please.

1 (Whereupon, at 9:36 a.m., a recess was
2 taken.)

3 DR. VENITZ: Welcome back. We are now
4 moving to our second substance to review and that
5 is cesium chloride. And as always, we are starting
6 off with the FDA presentation, which Dr. Brave is
7 going to provide us with again.

8 Dr. Brave?

9 **Presentation - Michael Brave**

10 DR. BRAVE: Good morning, again. I'd like
11 to thank and acknowledge my colleagues listed here
12 who helped me review this nomination. Cesium has
13 been nominated for compounding as an alternate
14 treatment to cancer.

15 It's unclear exactly what the nominator
16 means in this case by the term "an alternate
17 treatment to cancer." The proposed route of
18 administration is intravenously. The references
19 provided in the nomination contain only nonclinical
20 information.

21 Cesium, an alkaline metal with chemical
22 properties similar to lithium, potassium, and

1 sodium, is a trace element in human metabolism.
2 The substance nominated for compounding should not
3 be confused with radioisotopes of cesium that may
4 be used for imaging studies or for radiation
5 therapy.

6 Cesium is obtained by extraction from sea
7 water. It can be easily characterized chemically.
8 It is water soluble and stable in aqueous solution.

9 Nonclinical animal studies showed total
10 body cesium under normal conditions to be
11 approximately 1.5 milligrams. Normal plasma levels
12 of cesium range from 0.00045 to 0.26 grams per gram
13 wet weight.

14 Cesium chloride ingested by mouth is nearly
15 a hundred percent absorbed in the small intestine.
16 Cesium distribution is extensive with higher
17 concentrations in the kidneys, skeletal muscle,
18 liver, red blood cells, and brain.

19 The serum half-life of cesium is
20 approximately 70 hours in men and 96 hours in
21 women. Elimination is 85 percent urinary,
22 13 percent fecal, and 2 percent through sweat. The

1 renal mechanisms for excretion of cesium are
2 thought to be similar to those with potassium.

3 A rationale for the use of cesium in the
4 treatment of cancer was proposed in 1984 by Brewer
5 who hypothesized that cesium-established alkaline
6 conditions inside neoplastic cells leading to
7 apoptosis.

8 However, the presence of cesium in a cell
9 does not guarantee high intracellular pH, and there
10 is no theoretical or clinical evidence to suggest
11 that cancer cells are selectively vulnerable to
12 cesium.

13 Evidence of clinical benefit from cesium in
14 human cancer is limited to one case series
15 published in 1984 by Sartori. That case series had
16 major flaws, including its uncontrolled nature,
17 retrospective design, and probable case selection
18 bias.

19 Studies in animals identified the central
20 nervous system and cardiovascular system as targets
21 of toxicity. Nonclinical studies also show the
22 potential for genotoxicity and embryo toxicity.

1 Cesium blocks potassium rectifier channels
2 on atrial and ventricular myocytes resulting in
3 prolongation of the QT interval, which can lead to
4 fatal arrhythmias.

5 Numerous case reports describe serious
6 toxicities resulting from cesium chloride ingested
7 as an alternative treatment for cancer, including
8 hypokalemia, seizures, ventricular arrhythmias,
9 syncope, and death.

10 Often arrhythmias occur after weeks to
11 months of therapy with cesium, which is not
12 surprising given the long half-life of cesium. It
13 takes approximately 200 days of daily dosing to
14 reach steady state.

15 Published literature indicates that cesium
16 chloride used in the treatment of cancer has been
17 taking place since at least the 1980s. Currently,
18 oral cesium chloride is advertised by a number of
19 compounding pharmacies.

20 In summary, while cesium chloride can be
21 characterized using standard chemical techniques
22 and is stable in aqueous solution, there are

1 serious safety concerns related to its use.

2 Studies in mice showed cardiac and central
3 nervous system toxicity, as well as reproductive
4 effects. Clinically, reports of serious toxicity
5 following cesium chloride use for the treatment of
6 cancer have included hypokalemia, seizures,
7 ventricular arrhythmias, syncope, and death.

8 Cesium chloride has not been shown to be
9 efficacious for the prevention or treatment of any
10 form of cancer, whereas many FDA-approved
11 treatments for cancer do have established records
12 of safety and efficacy.

13 Finally, we found insufficient information
14 to evaluate the historical use of cesium chloride
15 in pharmacy compounding. A search of the internet
16 indicates compounding with cesium chloride takes
17 place; although the extent and indications for
18 which this compounding is done are unclear.

19 Based on a balancing of the four evaluation
20 criteria articulated in the Federal Register, we
21 find that cesium chloride is not a suitable
22 substance for compounding under 503A of the Food,

1 Drug, and Cosmetic Act.

2 **Clarifying Questions from the Committee**

3 DR. VENITZ: Thank you, Dr. Brave.

4 Any clarifying questions by the committee?

5 Dr. Carome?

6 DR. CAROME: I just want to ask, would it be
7 fair to say that FDA has concluded that cesium
8 chloride raises significant safety concerns?

9 DR. BRAVE: Would it be -- could you repeat
10 the question?

11 DR. CAROME: Would it be fair to say that
12 FDA has concluded that this drug substance raises
13 serious safety risk concerns?

14 DR. BRAVE: Yes.

15 DR. VENITZ: Dr. Hoag?

16 DR. HOAG: Just a point of clarification, is
17 this oral cesium chloride, IV, or all?

18 DR. BRAVE: It's IV. The proposed route of
19 administration is IV.

20 DR. VENITZ: Do we know any more about the
21 compounding history, about its use?

22 DR. BRAVE: That information is not

1 submitted with the nomination, so we have no way to
2 know that.

3 DR. VENITZ: Okay.

4 Any other clarifying questions?

5 (No response.)

6 DR. VENITZ: Thank you, Dr. Brave.

7 That brings us to the nominator. We have
8 one presentation on cesium chloride, Dr. Anderson
9 from the American Association of Naturopathic
10 Physicians, AANP.

11 **Presentation - Paul Anderson**

12 DR. ANDERSON: Good morning, and thank you.
13 Of the three that I am testifying on today, cesium
14 was not one I was involved in the nomination
15 process for. So I'm giving background information,
16 and I'll try and answer questions the best I can.

17 I do want to make a note, because in all of
18 my presentations, I will reference research that I
19 am involved in and in an ongoing basis, which some
20 of these of substances have been used.

21 Some of the data is published in case
22 reports, some is not, and I will speak to that as

1 we go through.

2 The first was an NIH-funded study, '09 to
3 '14, in collaboration with the Seattle Cancer Care
4 Alliance essentially and the BIORC clinics, and
5 then the current ongoing multicenter trials, the
6 CUSIOS trial.

7 To give background to where my testimony
8 will come from in the first two drugs that we're
9 going to talk about, but cesium specifically, it is
10 in specifically advanced cancer in patients who
11 have failed all other therapy. That will be what I
12 will be speaking to.

13 As far as efficacy, the Sartori paper was
14 very well-characterized earlier by our colleagues
15 so I will not go into that, except to say that this
16 is where the idea to use cesium chloride appears to
17 have arisen. It, I believe, had some use in Europe
18 prior to the 1980s which also dates back.

19 As far as the compounding history, I don't
20 have a slide specifically for that, but that is of
21 note. I am aware of cesium chloride being
22 compounded by registered compounding pharmacies,

1 both orally and for parenteral use at least to
2 1997, possibly before that, probably before that.

3 The safety, in my mind, having to review
4 protocols and look at protocols, is probably the
5 most paramount issue with cesium chloride. In
6 looking at one of the studies that was brought up
7 and then a couple of others that were not, the
8 first is just a statement from Melnikov, et al. in
9 2010 about the safety of cesium in its relatively
10 mild toxicity.

11 Like most all substances, including
12 minerals, the toxicity is highly dose-based, and
13 administration-based, and also based in monitoring,
14 appropriate monitoring. The three primary modern
15 sources for the adverse events associated with
16 cesium chloride in four. And all four of them that
17 are stated in these three have one critical factor
18 in common.

19 These two essentially were patients from '03
20 and '08 that were reported, and this is a total of
21 three cases where they had cardiac anomalies. This
22 was mentioned earlier by our colleague. And they

1 were due to dose irregularities or overdosing with
2 cesium chloride.

3 Then the more recent event, which was a
4 fatality published in 2013, and just an excerpt
5 from the abstract showing that this was actually
6 upon advice from a nutritionist, the husband took
7 an oral solution and injected 9 mLs into the tumor.

8 So this particular patient then went into
9 complete cardiac shock and passed away at the
10 emergency department. Those are the four.

11 When I read the papers on the safety issues,
12 at least these more modern ones, the most glaring
13 issue that came up to me -- because I have
14 experienced, as you'll see, at least supervising
15 and referring the use of cesium chloride
16 parenterally and orally in a large number of cases
17 and we have not seen these sort of effects as that
18 none of these people were under the care of a
19 qualified physician during the use of the cesium
20 chloride.

21 They were obtaining it as a dietary
22 supplement, and they were using it with either no

1 guidance or very poor guidance. I think that that
2 is of note.

3 Alternatives, when you are looking at -- if
4 we limit, as I said in the beginning, the
5 discussion to advanced cancers that have failed
6 therapy, alternatives is a relative term.

7 There are many, many therapies for various
8 cancers that have various levels of safety,
9 efficacy, et cetera. We all know that.

10 When we get to the point of palliative
11 oncology and/or stabilizing unstable disease, we
12 get to less and less options, and sometimes, as
13 you'll see later, we have no options.

14 In the sense that we're looking at trying to
15 palliate in advanced cancer where there is no more
16 opportunity for therapy, what we have seen and are
17 doing ongoing investigation is that cesium does
18 appear to hold a place in the palliative setting.

19 We do see stabilization of advancement of
20 disease and palliation of things such as pain and
21 other quality of life measurements.

22 We'll wrap up. My personal experience with

1 cesium chloride has been in the research setting
2 and has been in these two trials. In the setting,
3 the physician collaborators that have worked either
4 with or under me have used many, many doses,
5 thousands of doses actually without any high-grade
6 adverse events, no hypokalemia, no cardiac
7 irregularities, et cetera.

8 I believe that that is because that they are
9 monitoring the patients very closely, and they are
10 also taking prophylactic measures against such
11 things.

12 A point I would like to make is that because
13 the safety profile, in my mind, at least from what
14 I have seen from all of these doses, is based on
15 the administration, and monitoring, and management
16 by a qualified physician, it would be my opinion
17 that keeping the drug available through registered
18 compounding pharmacies would limit its use to
19 prescribing physicians only because the adverse
20 events that we've talked about happened under the
21 care of non-licensed or unqualified physicians. I
22 believe that this would be a way to regulate and

1 monitor those events. Thank you.

2 **Clarifying Questions from the Committee**

3 DR. VENITZ: Thank you, Dr. Anderson.

4 Any clarifying questions by the committee?

5 Dr. DiGiovanna?

6 DR. DiGIOVANNA: John DiGiovanna. You
7 showed some data from a study that indicated the
8 term of 50 percent recovery of patients with
9 untreatable cancers.

10 Recovery isn't a usual term I'm familiar
11 with in oncology studies. Usually, they talk about
12 objective measurements somehow. Do you have any
13 information on how that was measured?

14 DR. ANDERSON: Yes. I believe -- is it
15 Dr. Brave who gave the first presentation, and
16 brought that same study up, and mention that that
17 was one of the issues with the study?

18 So I was not really using it to justify the
19 use discretely. I was just saying that that is the
20 one that we have as flawed as it is, yes.

21 DR. VENITZ: What doses do you typically
22 use? You mentioned that the toxicities, as far as

1 you're concerned, are very much dose-dependent.
2 What doses -- how many milliequivalents do you use?

3 DR. ANDERSON: The groups that are using the
4 cesium orally and/or in parenteral use are in our
5 off-sites. Because I do not directly manage their
6 patients, I would not want to make a guess at what
7 doses they're using. We have it in monographs
8 though.

9 DR. VENITZ: Thank you.

10 Dr. Gulur?

11 DR. GULUR: Thank you for your presentation.
12 My question is with regards to your use of this
13 currently for research. Did you not have to do an
14 IND in order to conduct the research with this
15 substance?

16 DR. ANDERSON: Very good question. The way
17 that the IRB was convened and the language that
18 they used was that, as long as the substance was
19 within the scope of practice of the practitioners
20 employing it, and that there was proper informed
21 consent, and that it was compounded within the
22 guidelines of the FDA, it could be employed in

1 advanced cancer.

2 DR. VENITZ: Dr. Jungman?

3 MS. JUNGMAN: Given that you're involved in
4 these studies, and that this is a substance that
5 presents at least some significant safety concerns,
6 and is used in very sick patients, I was wondering
7 if you could help me understand the argument for
8 using it in a one-off basis obtained from
9 compounding pharmacists as opposed to as part of a
10 clinical trial protocol where you would at least
11 have review of that protocol and you'd be
12 collecting the results for use potentially for
13 future patients.

14 DR. ANDERSON: Yes. Good question. Part of
15 the purpose behind the first trial that we did in
16 cooperation with NIH was to essentially have a more
17 open source to therapies that may or may not work
18 over the time of the study but that we could
19 demonstrate that they could be administered safely.

20 The point at the end of that study was then
21 to move forward any of the substances that did show
22 reasonable safety and purported efficacy and then

1 move them to just what you were talking about.

2 One of the real rubber-meets-the-road issues
3 is certainly finding a funding source to do a
4 single-agent trial such as what you were talking
5 about without any data to back it up.

6 Our purpose in doing that -- and as you'll
7 see with dichloroacetate, et cetera, our purpose in
8 doing these was to see, A, if anything actually did
9 happen that we could measure, B, if we had some
10 level of safety and we could come up with protocols
11 that made sense. Then we could move on to
12 proposing a study.

13 DR. VENITZ: Dr. Carome?

14 DR. CAROME: Can you describe in more detail
15 the clinical trial you're talking about? Is this a
16 clinical trial that is testing only cesium chloride
17 or multiple different agents?

18 Are there control groups? Are there
19 objective criteria for enrollment, objective
20 criteria for measuring outcomes? Is NIH funding
21 all of this research? Are the trials registered on
22 ClinicalTrials.gov?

1 I'd like to know from FDA whether this is a
2 type of research that would require an IND.

3 DR. ANDERSON: Good questions. Yes. Well,
4 there's two different trials that were mentioned.
5 The first, which is closed but is in statistical
6 analysis, was a prospective study.

7 The outcomes were -- initially in that first
8 study, the outcomes were survival, and the
9 survivals were matched with our cohort within the
10 Seattle Cancer Care Alliance who were the same
11 demographic, same cancer but not enrolled in the
12 alternative therapies portion.

13 At the end, the survival of group A versus
14 group B was the final clinical measurement. The
15 use of therapies within the integrative oncology
16 arm was what I described earlier, which is it was
17 not one particular agent. It was a multiple menu
18 of agents, and they were chosen by the supervising
19 physicians as to potential for efficacy.

20 All of these had some or maybe very little
21 data to support their use in the front end, so this
22 was trying to establish that as they went through.

1 The endpoint, in that particular study, was
2 survival.

3 In the second one, the CUSIOS one that's
4 mentioned, half of the centers are actually in
5 Canada, and the other half are in the U.S. The
6 endpoints there are both survival of the particular
7 cancers, as well as quality of life measurements.

8 DR. VENITZ: Any further questions?

9 (No response.)

10 DR. VENITZ: Okay, Dr. Anderson. Thank you.

11 DR. ANDERSON: Thank you.

12 DR. VENITZ: That gets us into --

13 DR. DOHM: Can I just interject? I think
14 there was -- also part of the question that was
15 posed to FDA about whether or not an IND would be
16 required in this scenario.

17 I'd just like to say that it certainly
18 sounds like the IND requirements would be
19 applicable here, although there are certain
20 exceptions. So we would need to have a full kind
21 of suite of information about it in order to better
22 assess whether or not it would be appropriate to

1 have an IND in this scenario.

2 **Open Public Hearing**

3 DR. VENITZ: Okay. Thank you, Dr. Dohm.

4 That gets us into the first open public
5 hearing session. So let me read the official
6 announcement.

7 We will now proceed to the open public
8 hearing speakers. I will read the following OPH
9 statement into the record.

10 Both the Food and Drug Administration and
11 the public believe in a transparent process for
12 information-gathering and decision-making. To
13 ensure such transparency at the open public hearing
14 session of the advisory committee meeting, FDA
15 believes that it is important to understand the
16 context of an individual's presentation.

17 For this reason, FDA encourages you, the
18 open public hearing speaker, at the beginning of
19 your written or oral statements to advise the
20 committee of any financial relationship that you
21 may have with the product and, if known, its direct
22 competitors.

1 For example, this financial information may
2 include the payment by a bulk drug supplier or a
3 compounding pharmacy of your travel, lodging or
4 other expenses in connection with your attendance
5 at this meeting.

6 Likewise, the FDA encourages you, at the
7 beginning of your statement, to advise the
8 committee if you do not have any such financial
9 relationships. If you choose not to address this
10 issue of financial relationships at the beginning
11 of your statement, it will not preclude you from
12 speaking.

13 The FDA and this committee place great
14 importance in the open public hearing process. The
15 insights and comments provided can help the agency
16 and this committee in their consideration of the
17 issues before them. With that said, in many
18 instances and for many topics, there will be a
19 variety of opinions.

20 One of our goals today is for this open
21 public hearing to be conducted in a fair and open
22 way where every participant is listened to

1 carefully and treated with dignity, courtesy, and
2 respect. Therefore, please speak only when
3 recognized by the chair.

4 Thank you for your cooperation.

5 I'm asking now our first OPH speaker,
6 Dr. Hauser, to step forward and present.

7 DR. HAUSER: Good morning. Thank you for
8 allowing me this opportunity to share Community
9 Pharmacy's perspective regarding the work of the
10 Pharmacy Compounding Advisory Committee.

11 I'm Ronna Hauser, vice-president of pharmacy
12 affairs at the National Community Pharmacists
13 Association, and I have no financial relationships
14 to disclose.

15 NCPA represents America's community
16 pharmacists, including the owners of nearly 23,000
17 independent community pharmacies. According to a
18 member survey, approximately 88 percent of our
19 members provide some type of compounding service,
20 but over 95 percent of respondents stated they do
21 not plan to register as a 503B outsourcing
22 facility.

1 Therefore, the vast majority of our members
2 will be held to the laws and regulations of
3 Section 503A of the Food, Drug, and Cosmetic Act.

4 As the FDA and PCAC members continue to
5 consider which drugs nominated will be considered
6 for inclusion on the 503A positive list, among
7 other responsibilities, NCPA is committed to
8 working with the FDA and stakeholders on these
9 critical issues.

10 However, we do have concerns with the
11 creation, oversight, and operation of the PCAC and
12 associated processes. Among these concerns are the
13 following:

14 Number 1, inadequate member selection and
15 renewal processes. NCPA remains concerned that
16 none of our nominees to the PCAC were ever
17 contacted. Unfortunately, there is currently not
18 one voting member of the PCAC who compounds for
19 human use on a daily basis.

20 NCPA finds this fact astounding considering
21 the community is making recommendations that can
22 vastly impact the practice of compounding. The

1 previous PCAC had at least three pharmacists with
2 current experience and expertise in compounding,
3 one of which specialized in sterile compounding.

4 The FDA should reopen the nomination process
5 for committee members in order to have at least one
6 practicing human compounder on the committee as a
7 voting member.

8 Number 2, FDA's insistence that any bulk
9 drug substance not voted under the positive list
10 can easily be obtained via the investigational new
11 drug process. In reality, this is a cumbersome,
12 timely, and expensive process especially for
13 community healthcare practitioners who have
14 previously presented their real-life concerns with
15 the IND process to the committee.

16 Number 3, unequal time allotted for
17 nominators to defend substances and respond to
18 committee questions. Throughout this entire
19 process, each nominated substance is given a total
20 of 10 minutes to be defended by the nominating
21 organizations.

22 Oftentimes, nominators will have to split

1 this time up. All the while, the FDA has unlimited
2 to present their review and opinions related to the
3 nominated substances.

4 In addition, nominators have a limited
5 timeframe to organize their presentations, normally
6 less than three weeks where FDA has more time,
7 likely months, to prepare.

8 Number 4, FDA's indication that it does not
9 consider USP monographs for dietary supplements to
10 be applicable USP or NF monographs, therefore
11 limiting compounding to only USP drug monographs
12 when no basis exists for FDA to exclude USP or NF
13 monographs for dietary supplements.

14 This is a great trouble to NCPA as it defies
15 logic that these substances can be easily obtained
16 by the public at any Costco, Walmart, or CVS, for
17 example, but in the hands of healthcare
18 practitioners are not to be trusted.

19 The practice of compounding is built on the
20 patient/physician/pharmacist triad, and there's no
21 better way to oversee the use of these preparations
22 than through this relationship.

1 Number 5, a confusing nominating and review
2 process that leads many unanswered questions for
3 healthcare practitioners and patients who rely on
4 compounds, NCPA contends that it was premature for
5 the FDA to have solicited nominations for the 503A
6 list, as well as selected six products to consider
7 at the first PCAC meeting before developing and
8 agreeing on criteria used to develop the list.

9 In addition, when nominating, we were asked
10 for all possible uses, not the most likely. We are
11 also concerned that the FDA has separated
12 substances in the recently released 503A bulk drug
13 substances interim policy based on nothing more
14 than if the agency considers that adequate
15 information to evaluate the substance was included
16 as part of the nomination process.

17 Not being able to compound with these
18 substances included on FDA's 503A List 3 will cause
19 impaired patient access and is causing confusion,
20 not to mention that many of the substances included
21 on List 3 are by FDA's own definition, not active
22 pharmaceutical ingredients that should even be

1 under discussion.

2 I would also like to address a comment that
3 has been made on multiple occasions during previous
4 PCAC meetings. That is the notion that if the FDA
5 places a nominated substance on the 503A list, then
6 it can be marketed with drug claims for any use.

7 Marketing unsubstantiated claims such as
8 this are illegal, and if FDA or PCAC members have
9 concerns about claims, then appropriate action and
10 education should be undertaken.

11 Lastly, I would like to voice NCPA's support
12 for the nominated bulk drug substances that the
13 committee is discussing at this meeting. NCPA
14 nominated two of the substances under discussion,
15 chrysin and tea tree oil. And I fully support my
16 colleagues here today speaking to their merits.

17 The intent of the committee was to increase
18 appropriate access to bulk drug substances without
19 a USP/NF monograph or from an FDA-approved product.
20 Unfortunately, quite the opposite is occurring.

21 In summary, NCPA is committed to working
22 with the FDA, the committee, and other stakeholders

1 regarding these important matters. We appreciate
2 your consideration of our remarks today, and thank
3 you for allowing me the time to present.

4 DR. VENITZ: Thank you, Dr. Hauser.

5 Any questions by any of the committee
6 members for Dr. Hauser?

7 (No response.)

8 DR. VENITZ: Okay. Thank you again.

9 DR. HAUSER: Okay. Thank you.

10 **Committee Discussion and Vote**

11 DR. VENITZ: That concludes our open public
12 hearing portion, and we won't take any more
13 comments for right now.

14 We're now proceeding with our discussion and
15 ultimate vote on our second product, cesium
16 chloride. Any comments, any discussion items?

17 Mr. Mixon?

18 MR. MIXON: I just wanted to make a comment.
19 I serve pharmacies who are seeking accreditation or
20 reaccreditation for the PCAB designation, and I
21 have yet to come across any pharmacy, nor do I know
22 of any pharmacy that -- other than what are listed

1 in some of the supporting materials that compound
2 with this drug.

3 I just want the committee to know that this
4 is not something that every compounding pharmacist
5 does.

6 DR. VENITZ: Dr. DiGiovanna?

7 DR. DiGIOVANNA: John DiGiovanna. This
8 substance is a little bit different than the
9 others, I think, that we've discussed in that its
10 indication seems to be for patients who are at
11 end-of-life scenarios because of malignancy.

12 It occurs to me that these patients are a
13 very vulnerable group that are easily manipulated
14 by anything that offers them hope. I think in that
15 scenario, my perception is that potentially toxic
16 compounds really need to be studied in a controlled
17 environment under an IND to determine if there's
18 any evidence that they offer benefit comparable to
19 the toxicity that they offer. This particular
20 compound raises some concerns to me that the others
21 didn't.

22 DR. VENITZ: Any other comments?

1 The only thing to follow-up that I'd like to
2 contribute, the dose-dependence or the dose-related
3 side effects, especially the Torsades de pointes,
4 is pretty obvious.

5 Unless there are clinical studies or a study
6 like interventions that allow us to really assess
7 at what doses you can avoid, even if there were no
8 benefit, there is no way that a drug that can be
9 given safely -- not a drug; a product that can be
10 given safely and effectively.

11 So even if you state the point that the
12 efficacy is not demonstrated, it has a major safety
13 issue, and safe doses have not been established,
14 forget the fact that we know nothing about
15 effective doses.

16 No more comments? Yes, Dr. Hoag?

17 DR. HOAG: This is a comment. I also worry
18 a little bit about where you get this material.
19 The FDA said that it's easily assayed, but that's
20 only if you're set up to do those types of assays.
21 It requires often like specialized equipment and
22 things which I bet a lot of people don't have. So

1 the impurity and the impurity profiles in there
2 would be something to consider. Where would you
3 source this material from?

4 DR. VENITZ: Okay. Let's proceed with our
5 vote. Let me go through the preliminaries again.

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

14 Then the process itself, please press the
15 button firmly on your microphone that corresponds
16 to your vote. You will have approximately
17 15 seconds to vote. After you have made your
18 selection, the light will continue to flash.

19 Please go ahead and proceed with the vote.
20 No means you are not putting it on the 503A bulk
21 list.

22 (Vote taken.)

1 DR. HONG: Question 2, we have zero yeses,
2 11 nos, and zero abstain.

3 DR. VENITZ: Okay. Let's go through the
4 individual comments starting with Dr. DiGiovanna.

5 DR. DiGIOVANNA: I voted no because I think
6 there's a great concern about the toxicity, the
7 length of the half-life of excretion of the
8 compounded, the lack of any efficacy, and the
9 potential vulnerability of the population where
10 it's intended.

11 DR. HONG: Could you state your name for the
12 record, please?

13 DR. DiGIOVANNA: John DiGiovanna.

14 DR. VENITZ: Dr. Gulur?

15 DR. GULUR: Padma Gulur. I voted no for
16 similar reasons as stated by Dr. DiGiovanna. I
17 think this is definitely a drug that should go
18 through the IND process. It should be registered.
19 We should know what the adverse events are so that
20 the population can be appropriately informed.

21 DR. VENITZ: Jurgen Venitz. Ditto.

22 MS. DAVIDSON: Gigi Davidson. I voted no

1 because it has a very strong safety signal, and I
2 was also impressed by Dr. DiGiovanna's comments
3 about this vulnerable population. And I think it
4 should be used within an IND situation for that
5 reason.

6 MR. HUMPHREY: William Humphrey. I voted no
7 for many of the same reasons. The supporting
8 information that we heard this morning was it
9 sounded like either phase 1 or phase 2 clinical
10 trial for a non-approved drug, and in which case
11 would require an IND, I think.

12 DR. HOAG: Steve Hoag. I voted no for all
13 the reasons previously stated.

14 MS. JUNGMAN: Elizabeth Jungman. I also
15 voted no given the safety profile of the drug and
16 the vulnerability of the patient population. I
17 think it should be used in a more controlled
18 environment.

19 DR. PHAM: Katherine Pham. I voted no due
20 to the major dose-dependent toxicity concerns,
21 especially Torsades.

22 DR. VAIDA: Allen Vaida. I voted no for all

1 the reasons that have already been said. Also, I
2 had the real concern with the four cases that were
3 not under qualified practitioners, and I don't
4 really agree that putting it on the list would
5 actually help that.

6 DR. CAROME: Mike Carome. I voted no for
7 many of the reasons stated. I mean, the drug
8 clearly has significant toxicity, particularly
9 cardiac toxicity that has biologic mechanism for
10 that toxicity. There's no reasonable evidence that
11 offers any clinical benefit.

12 I actually would urge the FDA to immediately
13 place this drug substance on the interim 503A
14 Category 2 list of bulk drug substances that raise
15 significant safety risks that may not be
16 compounded, pending final rulemaking.

17 DR. WALL: This is Donna Wall. I voted no
18 for all of the reasons stated.

19 DR. VENITZ: Thank you. Moving right along
20 to our third bulk substance, sodium
21 dichloroacetate, and we will have Dr. Brave again
22 present the FDA's summary.

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Presentation - Michael Brave

DR. BRAVE: Hello. I also reviewed the nomination for sodium dichloroacetate, and I'd like to thank the colleagues who helped me review this application and the same colleagues that helped me review the other two applications.

Dichloroacetate has been nominated for the list of substances that can be compounded. The proposed indication is for the quote, "adjunct treatment of cancer." We are uncertain what the adjunct treatment of cancer would mean, whether it would mean in combination with other chemotherapeutic agents, for example, or as a single agent.

The proposed routes of administration are orally and intravenously. The references provided in the nomination include only nonclinical information. Dichloroacetate is available as a dietary ingredient in dietary supplements.

Chemically, dichloroacetate is a small molecule synthesized from acetic acid, and it can be easily characterized. It is stable in oral

1 dosage forms at low temperatures but is unlikely to
2 be stable as an injectable solution.

3 This slide and the next two slides discuss
4 the theoretical rationale for the use of
5 dichloroacetate as anticancer therapy.

6 Cancer cells exhibit a metabolic shift from
7 glucose oxidation to glycolysis compared with
8 nonmalignant cells. This phenomenon, known as the
9 Warburg effect, is thought to reflect mitochondrial
10 injury and alternate isoforms of glycolytic enzymes
11 in cancer cells.

12 Glycolytic enzymes in the cytosol of cell
13 metabolize glucose to pyruvate, which then enters
14 the mitochondrion, where pyruvate dehydrogenase
15 catalyzes its oxidative phosphorylation to
16 acetyl-CoA.

17 Pyruvate dehydrogenase kinase inactivates
18 pyruvate dehydrogenase by phosphorylation. By
19 downregulating the activity of pyruvate
20 dehydrogenase, pyruvate dehydrogenase kinase
21 decreases the oxidation of pyruvate in mitochondria
22 and increases the conversion of pyruvate to lactate

1 in the cytosol.

2 The opposite action of pyruvate
3 dehydrogenase kinase, namely the dephosphorylation
4 and activation of pyruvate dehydrogenase, is
5 catalyzed by pyruvate dehydrogenase phosphatase.

6 Dichloroacetate is a pyruvate analogue which
7 inhibits pyruvate dehydrogenase kinase and thus
8 facilitates entry of pyruvate into the
9 mitochondrial tricarboxylic acid cycle. This
10 inhibition is hypothesized to translate into
11 anticancer activity.

12 The information on this slide pertains to
13 the sodium salt of dichloroacetate but is likely
14 relevant to other salts as well. Dichloroacetate
15 bioavailability in healthy human volunteers varied
16 widely, from 27 to 100 percent.

17 Dichloroacetate is dehalogenated by an
18 enzyme abbreviated as GSTz1 MAAI in the liver to
19 monochloroacetate and glyoxylate. There are four
20 human polymorphisms of GSTz1 MAAI, one of which has
21 a 10-fold higher binding affinity for
22 dichloroacetate than the others.

1 After single infusions in healthy
2 volunteers, peak serum concentrations of
3 dichloroacetate were dose proportional up to
4 30 milligrams per kilogram after which clearance
5 decreased, likely due to inhibition of GSTz1 MAAI
6 by dichloroacetate leading to drug accumulation.
7 Plasma dichloroacetate clearance is markedly
8 decreased in patients with cirrhosis.

9 Dichloroacetate is a byproduct of water that
10 has been disinfected with chlorine.

11 Dichloroacetate is also a metabolite of the
12 environmental contaminant, trichloroethylene.

13 Because of its presence in the environment,
14 the U.S. Environmental Protection Agency conducted
15 carcinogenicity studies in mice, and these showed
16 dichloroacetate to be a hepatic carcinogen.

17 The safety of dichloroacetate, based on both
18 nonclinical and clinical studies, is of concern.
19 Nonclinical studies showed dichloroacetate to be
20 potentially toxic to multiple organs, as well as
21 carcinogenic. It also decreased fertility in rats.

22 In clinical studies, toxicity primarily

1 involved the central nervous system. A final
2 safety concern is that dichloroacetate exhibits
3 significant interindividual variation in absorption
4 and excretion and thus accumulates over time,
5 complicating both dosing and the management of any
6 toxic effects. FDA is aware of one study being
7 closed due to safety concerns and patient deaths.

8 Three phase 1 clinical trials evaluating
9 dichloroacetate have been published and are
10 summarized on this slide. Kaufmann randomized
11 30 patients with mitochondrial encephalopathy
12 lactic acid and stroke-like episodes, a condition
13 known as MELAS to dichloroacetate 25 milligrams per
14 day versus placebo.

15 The trial had a crossover design and the
16 primary outcome measure was an assessment of
17 neurologic, neurophysiological, and daily living
18 function. The trial was terminated early because
19 of a high rate of patient discontinuation due to
20 sensory and peripheral neuropathy.

21 Chu performed a dose escalation trial of
22 dichloroacetate in 24 patients with advanced solid

1 tumors. The starting dose was 6.25 milligrams BID,
2 and the highest dose administered was
3 12.5 milligrams BID. Toxicities included fatigue,
4 nausea, vomiting, diarrhea, and neuropathy. The
5 recommended phase 2 dose was 6.25 milligrams twice
6 daily.

7 Dunbar studied dichloroacetate in 15 adults
8 with recurrent high-grade glioma or brain
9 metastases from a primary cancer outside the
10 central nervous system.

11 Dosing was based on haplotype variation in
12 the GSTz1 MAAI alleles. Two patients experienced
13 paresthesias requiring dose modification.

14 In ongoing and published clinical trials of
15 dichloroacetate, no tumor responses have been
16 reported to date. FDA-approved products are
17 available for the treatment of many forms of
18 cancer.

19 Insufficient information is available to
20 determine how long dichloroacetate has been used in
21 compounding.

22 In summary, dichloroacetate is chemically an

1 easily characterized small molecule that is stable
2 in solid forms suitable for oral administration
3 only at lower temperatures and is unlikely to be
4 stable in an injectable form.

5 Safety concerns reported in clinical trials
6 of dichloroacetate include peripheral neuropathy
7 and gastrointestinal symptoms. Dichloroacetate
8 exhibits significant interindividual variation, and
9 absorption, and excretion, and accumulates over
10 time.

11 In published clinical trials of
12 dichloroacetate in patients with cancer, no
13 objective tumor responses were reported. We did
14 not find evidence of ongoing compounding of
15 dichloroacetate other than for investigational use.

16 Based on a balancing of the four criteria
17 articulated in the Federal Register, we find that
18 dichloroacetate is not a suitable substance for
19 compounding under Section 503A of the Food, Drug
20 and Cosmetic Act.

21 **Clarifying Questions from the Committee**

22 DR. VENITZ: Thank you.

1 Any questions? Dr. DiGiovanna?

2 DR. DiGIOVANNA: Yes. John DiGiovanna. You
3 showed an evaluation of safety from three clinical
4 trials. The efficacy of all of those trials is not
5 given. Were there no responders or how was that
6 assessed?

7 DR. BRAVE: That's correct. There were no
8 clinical responders, and the trials were
9 early-phase trials that were not designed to assess
10 efficacy. They were designed to find the dose and
11 establish and collect preliminary safety signals.

12 DR. VENITZ: Then can I follow up on the
13 dose? In those three studies that Dr. DiGiovanna
14 was referring to, you have doses ranging from 25
15 milligrams per kilogram to 6.25 milligrams. What
16 was the rationale? I mean those are huge
17 differences between doses. What was the rationale
18 as far as you can tell?

19 DR. BRAVE: I don't know. They were
20 typically in dose-finding studies. By nature of
21 the design of the study, the dose varies widely. I
22 mean, a wide range of doses is studied.

1 DR. VENITZ: But you also have a
2 pharmacokinetic study on one of your previous
3 slides where they gave 30 milligrams per kilogram
4 infusions. So is there any rationale, anything
5 that you could decipher from the literature how
6 those doses were selected?

7 DR. BRAVE: No.

8 DR. VENITZ: Okay. Thank you.

9 Dr. Vaida?

10 DR. VAIDA: You just asked my question.
11 Thank you.

12 DR. VENITZ: Dr. Carome?

13 DR. CAROME: I have the same question I
14 asked about the last drug. Does the safety data
15 that you reviewed raise significant safety risk
16 concerns?

17 DR. BRAVE: Yes, it does.

18 DR. VENITZ: Yes, Dr. Wall?

19 DR. WALL: You spoke that it's unlikely to
20 be stable as an injectable solution. What happens
21 when it becomes unstable?

22 DR. BRAVE: I'd have to defer to my

1 chemistry colleagues for that.

2 DR. VENITZ: Please introduce yourself for
3 the record.

4 DR. ZHANG: My name is Ben Zhang. In this
5 scenario, in aqueous solutions, it's likely to
6 hydrolyze and degradation to acetic acid and other
7 degradants.

8 DR. VENITZ: Thank you. Any other
9 clarifying questions for Dr. Brave?

10 (No response.)

11 DR. VENITZ: I see none. Thank you,
12 Dr. Brave.

13 Then let's proceed with the nominator's
14 presentation. We have one presentation on sodium
15 dichloroacetate and that is Dr. Anderson, please.

16 **Presentation - Paul Anderson**

17 DR. ANDERSON: Thank you again. Current
18 use, some of these were already mentioned.

19 I did want to bring up that, in addition to
20 the dose escalation and dosing studies mentioned,
21 between 2010 and 2016, there are human case reports
22 and trials that I will just show the citations for

1 and we can look at them briefly.

2 The newest is this one from Lemmo, et al.,
3 and it's a case study, prolonged survival. The
4 next is from Chu, a 2015 dose-escalation study,
5 then Dunbar. The next is Khan, and this is a
6 three-case series that showed stability of advanced
7 disease in advanced cancer. The next is Strum, and
8 this one, I believe, was mentioned earlier, but it
9 was talking about complete response with NHL.

10 Another one from similar authors was in a
11 different patient after progression with the
12 standard of care. The next is another one from
13 Khan, a colleague in Toronto using DCA for
14 remission in metastatic renal squamous cell.

15 Then going backwards in time, the first one
16 that Khan published was use of oral DCA in the
17 palliation of pain arising from differentiated
18 carcinoma. Then we have another NHL and then
19 thyroid carcinoma. So those are human case
20 reports. They're not large scale trials, but they
21 are published.

22 I have some other experience that I'll share

1 at the end. The other is papers that show recent
2 use for the scientific basis of DCA as having a
3 potential unique role in the therapy of advanced
4 cancer.

5 Also, as was mentioned earlier, it has been
6 studied some because of its mechanism of action in
7 metabolic illness as well. These are some current
8 research looking more into the basic science of the
9 drug.

10 With regard to safety -- this was very well
11 talked about already by Dr. Brave -- the biggest
12 concern really has been peripheral neuropathy and
13 that is believed to be related to the metabolism
14 through the GST-zeta pathway.

15 The potential for this was seen early. The
16 other paper that neither of us mentioned was a case
17 series from Michaelis which is where some of the
18 earlier ideas about dosing came from, and I
19 apologize for not putting that one in.

20 That was from, I believe, McGill, where they
21 looked at GBM patients with DCA. They did see in
22 that particular study the most common reason for

1 complaint was peripheral neuropathy.

2 That particular paper led our group to
3 develop protocols that would -- in the beginning,
4 they were theoretical as far as protecting the
5 peripheral nervous system during the treatment with
6 dichloroacetate.

7 What we found was that if we paired the
8 dichloroacetate therapy along with neuroprotective
9 nutrients that we did not experience -- patients
10 did not experience peripheral neuropathy.

11 At this point, my group has administered
12 over 10,000 doses of dichloroacetate. Those have
13 been both oral and intravenous, and I'll talk about
14 that coming up a little bit later.

15 Additionally, our Canadian research
16 colleagues have administered the same amount, and
17 we've had no high-grade adverse events. In our
18 particular clinical area in the U.S., we have not
19 had any peripheral neuropathy by using the
20 neuropathy abatement protocol. In Canada, we don't
21 have updated data, but they have very, very low
22 incidence at this point.

1 Alternatives, again, in this case, we're
2 looking at much like the cases that I showed the
3 citations for earlier. In this case, we're looking
4 at advanced cancers usually that have failed all
5 standard therapy.

6 There is, as yet part of our group, an
7 ongoing case series that is not published because
8 it is still ongoing. The criteria are that the
9 patient has to have failed all therapy, and they
10 have to be cleared by their oncologist as failed
11 therapy and no evidence of current standard of care
12 that would work.

13 In that particular case series, it is not
14 limited to one cancer type. It is limited to
15 complete failure of therapy, and so I'll talk about
16 those coming up.

17 The problem that we see is, with an
18 alternative to dichloroacetate, there really are
19 very few things that work like it does;
20 3 bromopyruvate and 2 deoxyglucose, two
21 experimental agents work similarly but not the
22 same. So as far as a mechanistic alternative, it

1 does not exist.

2 Although this was disagreed with earlier,
3 I'll make the point that I believe this should be
4 administered only by trained and qualified
5 practitioners because there are, like all drugs,
6 safety issues with it.

7 I believe that inclusion keeps it in that
8 ballpark, as opposed to people sourcing it from the
9 internet, et cetera.

10 In the cases that we have so far, in the
11 non-responder groups, what we look at then other
12 than survival, as I mentioned earlier in those
13 groups, are whether they get progression of disease
14 at the same rate or similar rate to when they fail
15 their standard therapy. So these are patients who
16 come and fail standard therapy.

17 There are too many for me to recount, and I
18 know I only had 10 minutes, so I didn't bring
19 summary slides on each patient. But essentially,
20 our metrics with those patients are whatever
21 objective data that they had that we were following
22 to follow their evidence of disease or progression.

1 And it was usually a combination of imaging,
2 sometimes laboratory markers such as peripheral
3 blast, and blast crises, and other things such as
4 protein spikes and multiple myeloma.

5 In a great deal of the cases, so far what
6 we are seeing is that we have had arrest of
7 progression or, in some cases, regression of
8 disease on imaging as we move forward. In the
9 first trial, this was developed as a salvage
10 therapy, so the patient had to, as I said, fail all
11 standard of care. Thank you.

12 **Clarifying Questions from the Committee**

13 DR. VENITZ: Thank you, Dr. Anderson.

14 Any questions? Dr. Wall?

15 DR. WALL: I have three questions. One, you
16 talked about appropriate dose. How do you
17 determine the appropriate dose? What is it that
18 you were looking at to get to an appropriate dose?

19 You said then you used over 10,000 doses.
20 How many doses to a therapy, for a person's
21 therapy? I mean, is it like for a month? Is it
22 forever and ever? What determines that therapy?

1 And then after those, I'll ask the last one.

2 DR. ANDERSON: Okay. Thank you. So to the
3 first question, early when we were determining
4 dose, we had just, at the time, the Michaelis
5 paper, which predates the papers that were
6 presented earlier.

7 Because it was done in a human cohort with
8 GBMs, we based our initial dosing upon that and
9 then in collaboration with our colleagues in
10 Canada, who are also using the dichloroacetate.

11 The dose ranges were slightly different from
12 the other papers that were shown earlier. The oral
13 dosing was between 15 and 25 milligrams per
14 kilogram BID on a rotating schedule. The rotating
15 schedule was for 14 days on and 7 days off to avoid
16 bioaccumulation.

17 In the intravenous form, actually, the
18 dosing was higher, but the frequency was lower. In
19 the intravenous form, the dosing was between 50 and
20 80 milligrams per kilogram, and that was done twice
21 a week for 2 weeks on and 4 weeks off, so the
22 dosing was quite different than the oral dosing.

1 As I said, the prophylactic measurements for
2 preventing the peripheral neuropathy, et cetera,
3 were postulated in the beginning, but we didn't do
4 any of this without doing that. We have not
5 experienced the peripheral neuropathy.

6 As far as duration of treatment, in the
7 group that is managed through our center -- and I
8 say that because the other centers have different
9 groups going on -- most of ours are with the
10 salvage therapy, so they failed all other types of
11 treatment. In most of the cases, it has been
12 ongoing dosing on those rotations over the course
13 of the remainder of the person's life.

14 The third?

15 DR. WALL: The third question is we've heard
16 that it is unstable. It breaks down to acetic
17 acid. How do you know that the IV product you are
18 giving them is not broken down?

19 DR. ANDERSON: Yes, that's an excellent
20 question. We have worked with three different
21 sterile compounding pharmacies that have done
22 assays.

1 As part of our protocol, we use the pharmacy
2 that is in closest proximity to us which is in the
3 same city for all of our product, and we have a
4 very short use date, which fits the stability that
5 was measured.

6 DR. VENITZ: Dr. Braunstein?

7 DR. BRAUNSTEIN: Yes. I just want to
8 preface that I'm speaking here as part of regulated
9 industry.

10 It sounds to me that what you're describing
11 here is an experimental compound. I'm very
12 comfortable with you conducting human experiments
13 with an experimental drug under an IND with proper
14 informed consent.

15 That's really the construct that we all live
16 in in regulated industry. I can't take a compound
17 and just do experimentation on people with a
18 compound that I might find on a shelf. I have to
19 get an IND. We have to identify the potential
20 risks. We have to inform patients of those
21 potential risks.

22 It's a regulated environment when we do

1 these experiments. We have to inform the FDA about
2 safety matters that come up. We have to first ask
3 the FDA's permission essentially under an IND to do
4 these studies. Of course, we have to -- all of
5 these studies are also under the auspices of IRBs.

6 So I have no problem with your doing that,
7 and I think that that's what you've described this
8 molecule is.

9 Certainly, the other problem I would just
10 point out is if we have molecules like this and we
11 put them on a list, that basically says that we
12 have two standards for molecules that can be used
13 in human experimentation.

14 Really, as an industry, I think that's not
15 the right way to go forward.

16 DR. VENITZ: Do you want to comment?

17 DR. ANDERSON: Just to the point, we did
18 have IRB approval and complete informed consent.

19 DR. VENITZ: Dr. Carome?

20 DR. CAROME: You had mentioned some degree
21 of NIH involvement or support for the two studies
22 you mentioned, CUSIOS, that's the ongoing one, I

1 guess. Is that true? Is that NIH funding?

2 DR. ANDERSON: The two are two different
3 funding streams. The NIH was involved in the first
4 one, and the CUSIOS is a Canadian-funded study, so
5 yes.

6 DR. VENITZ: Dr. Pham?

7 DR. PHAM: So I feel like this could be
8 similar to the quinacrine conversation we've had
9 previously. Are you familiar with the treatment
10 IND or intermediate-size population IND options?

11 DR. ANDERSON: I couldn't hear the first
12 half of what you said, sorry.

13 DR. PHAM: Sorry. I will speak into this.
14 I just think that in a former PCAC meeting that I'm
15 not sure you would have been aware of, there was a
16 similar conversation, I think, related to going
17 beyond expanded access or single-patient, the
18 intermediate-size, or the treatment IND option.

19 I wasn't sure if your group was familiar
20 with that or if there were other oncology groups
21 that could potentially go in together on something
22 like a treatment IND?

1 DR. ANDERSON: No, we were not aware of that
2 intermediate, yes. I would like to --

3 DR. VENITZ: Can I follow up on
4 Dr. Braunstein's question? In one of your earlier,
5 I think, first two or three slides, you reviewed
6 clinical studies. Right?

7 DR. ANDERSON: Yes.

8 DR. VENITZ: Can you go back to those
9 slides?

10 DR. ANDERSON: Sure.

11 DR. VENITZ: Because I was wondering, were
12 those phase 1 studies? Just looking at the title,
13 they appear to be. If so, were they done in the
14 United States or with or without FDA oversight
15 right here?

16 DR. ANDERSON: Yes. So the first one is
17 from Canada, and this is a case report. The second
18 one, I believe, is in the U.S. as an open-label
19 single-arm that I believe was done with FDA
20 oversight. The third one, I am unsure where that
21 originated.

22 DR. VENITZ: Okay. I think those were the

1 ones that I was -- yes.

2 DR. ANDERSON: Those were the ones that you
3 were -- yes.

4 DR. VENITZ: So two of those are labeled as
5 phase 1 studies. How can you do a phase 1 study
6 without an IND? I think that's what your comment
7 was, and I had the same question.

8 DR. ANDERSON: I believe that both of them
9 did. So I was not involved in neither one of
10 these, but --

11 DR. VENITZ: So this compound
12 has -- somebody has an IND on this compound --

13 DR. ANDERSON: I believe so.

14 DR. VENITZ: -- an investigational IND?

15 DR. ANDERSON: Right.

16 DR. VENITZ: So let me then turn around and
17 look at my FDA colleagues. How does that affect
18 then putting it or not putting it on the 503A list?
19 It's not an approved product, but it's a product
20 that is being studied under an IND.

21 DR. DiGIOVANNA: Yes. This is John
22 DiGiovanna. The Chu study apparently was done at

1 the University of Alberta, Department of Medical
2 Oncology. That's one of the studies that was
3 mentioned.

4 As the FDA presentation suggested, they did
5 not find any responses, but the end of their
6 abstract for their publication says, "Toxicities
7 will require careful monitoring in future trials."
8 So they did have, as the FDA presented, some
9 various toxicity issues.

10 So I think some of what's been presented
11 have been studies done in different places that
12 have been published. And those, I think are the
13 three that the FDA presented. Some of these others
14 may just be case reports.

15 DR. VENITZ: But what about the fact that
16 there are studies going on, phase 1 studies going
17 on with an IND on this product while we are
18 considering it as putting or not putting on the
19 503A list?

20 MS. BORMEL: That's an entirely separate
21 point. If something is nominated for the 503A
22 bulks list and the committee recommends and the FDA

1 ultimately puts it on the list, that could be used
2 irrespective of whether there's an IND. I mean,
3 anybody could -- any compounder could use it.

4 Under the IND, there are safeguards in
5 place. There's informed consent; there's the IRB;
6 there's different other standards that have to be
7 met in order for that product to be used.

8 I mean, they're very separate concepts.
9 There are no safeguards. They are not the same
10 safeguards that are present under an IND under a
11 drug that's put on a 503A bulk list.

12 DR. VENITZ: Thank you. I think we had
13 another question. Dr. Carome?

14 DR. CAROME: Mike Carome, again. In looking
15 at the description of the CUSIOS study on
16 ClinicalTrials.gov, it characterized it as a
17 prospective observational study.

18 The way that I read the description, it
19 sounds like the interventions that are given to the
20 patients who are in the study are sort of just
21 chosen by the practitioner. It doesn't appear to
22 me any standardization of the agent selected, the

1 dosing, the duration. Am I reading this
2 accurately?

3 DR. ANDERSON: Partially. The prospective
4 nature is supposed to allow each of the seven
5 centers to treat the patients as they come in, as
6 they normally would in an integrative oncology
7 setting. Under that banner then are whatever
8 therapies they would be using prior to that or know
9 of prior to that that they would have employed in a
10 non-study setting with their patients.

11 You would potentially have a patient with
12 the first type of cancer who would have a protocol
13 driven, so there would be dose duration. All of
14 that would be preset, but it would be chosen by the
15 clinician group at that particular site. Then they
16 would be followed.

17 Then the second patient, if the clinician
18 group decided that that particular therapy group
19 that the first patient got was not appropriate, the
20 second patient would get different therapy. It's
21 following them in survival over that time with
22 known therapies.

1 DR. VENITZ: Okay. Any other clarifying
2 questions for Dr. Anderson? Yes, Ms. Davidson?

3 MS. DAVIDSON: I believe Dr. Brave
4 characterized this as an EPA-established
5 carcinogen. In the 10,000 doses you've worked with
6 over the years, did you have a protocol for
7 handling for the preparers of the drug or do you
8 have any concerns about worker exposure to this
9 chemical?

10 DR. ANDERSON: Good question. As far as the
11 preparers and those compounding the intravenous
12 product which would be the ones that would be
13 exposed in our center -- those compounding the oral
14 product would be exposed at the pharmacy level --
15 we use the safety protocols for personnel that the
16 pharmacy developed and use the same ones in the
17 center for those who are handling it for IV use.

18 Was there a second question? Sorry.

19 MS. DAVIDSON: Just to clarify that your
20 workers knew that it was an established carcinogen
21 when they were handling it.

22 DR. ANDERSON: Right. Yes. Yes.

1 DR. VENITZ: Dr. Gulur?

2 DR. GULUR: You mentioned that you do have
3 an informed consent process. What do you
4 consent -- what do you make your patients aware of
5 with regard to this drug, and what alternative
6 strategies are offered to that patient?

7 DR. ANDERSON: In the case of our center
8 where the only group that were allowed to be
9 availed of the drug were non-responders, complete
10 nonresponders, the alternative was essentially
11 other palliative care, and they were consented.

12 They were consented. They were consented on
13 a number of levels, but they were consented
14 specifically for the dichloroacetate as to the
15 propensity for peripheral neuropathy, et cetera, so
16 the standard things that are in the data that was
17 shown earlier by my colleague. They were made
18 aware of all of that, and there were about four
19 layers of informed consent before they got to drug
20 consent.

21 **Committee Discussion and Vote**

22 DR. VENITZ: Thank you, Dr. Anderson.

1 Now, we have on our schedule another open
2 hearing, but we don't have any speakers, so we're
3 going to move right into our discussion. So I'm
4 opening the floor for any comments, discussions,
5 contribution. Dr. Braunstein?

6 DR. BRAUNSTEIN: I just want to point out to
7 the committee, I mean, I can speak from personal
8 history that in industry, we develop drugs.

9 Early in development, especially in drugs in
10 cancer patients for cancer, we do studies in
11 patients, I guess, similar to the kinds that we're
12 hearing here. These are patients who failed all
13 other treatments. Each one is a heartbreaking
14 case, of course, is a heartbreaking story. And we
15 do these initial studies under an IND with informed
16 consent, and under FDA oversight, and IRB
17 oversight.

18 Every now and then, you find a drug that
19 after studying the drug in maybe, I don't know, 25,
20 30 people, maybe a handful of them might respond.
21 Even before we do this, we have a lot of data in
22 animals that would support trying this new agent in

1 people.

2 If we get some data in a couple of patients,
3 maybe, maybe we'll go on to phase 2 and try and
4 demonstrate that, but we wouldn't come to FDA or to
5 a committee like this and ask for license to start
6 selling the drug to patients.

7 I mean it's not from -- and if we start
8 allowing that, then we really have a system that's
9 broken because it exposes patients to basically an
10 unregulated substance on the one hand.

11 The patients aren't necessarily
12 sophisticated enough to distinguish between what is
13 a regulated substance and this type of an
14 unregulated substance.

15 DR. VENITZ: Dr. DiGiovanna?

16 DR. DiGIOVANNA: John DiGiovanna. I think
17 you raise an important issue which -- I believe
18 over the prior meetings, the FDA has been
19 attempting to educate the committee and those of us
20 that by placing these various medications on the
21 list to be able to be compounded or not be able to
22 be compounded, what happens subsequently may be

1 beyond our expectation.

2 I think, as you are implying, it's a value
3 for us to consider; for example, populations who
4 may be wanting medications for untreatable
5 conditions or conditions with an unexpected soon
6 mortality, where if the medications are potentially
7 dangerous, it poses a risk.

8 I think in those situations, we need to be
9 cognizant that studying those medications under an
10 IND permits their efficacy to be identified and
11 their toxicities to be characterized. And I think
12 that's something we need to be cognizant about.

13 DR. VENITZ: Any other comments? Dr. Wall?

14 DR. WALL: What we keep running into is
15 that -- the origins of medicine was that it was all
16 compounded, it was all experimental, it was tried,
17 and see what's going to happen.

18 The question is, has science moved to the
19 point of where we -- and actually, safety moved to
20 the point where we need to totally stop that
21 practice or is there still a need for that practice
22 in certain circumstances? I think that's a

1 question I keep running up into.

2 When it comes to this product, we're dealing
3 with this really vulnerable population. I really
4 think it needs to be studied. These are generally,
5 at least in my mind, not emergencies. You watch
6 that they've been failing, and you plan, and you
7 work on what needs to happen.

8 You create those protocols, which are
9 prolific in the cancer communities, to deal with
10 it. But I really think with are running into this
11 conflict of cultures almost, in a way, of what we
12 have done which has not been bad, and it has
13 brought us to where we are to where we need to go.

14 DR. VENITZ: Dr. Pham?

15 DR. PHAM: I think that goes back to why I
16 previously asked the question about the treatment
17 IND or the intermediate size because, previously,
18 in discussions, we've also talked about the
19 challenges and resources needed for the single
20 patient or previously known as compassionate-use
21 IND or expanded access IND. We're going to hear
22 more about that.

1 I still think that there needs to be a lot
2 broader education about what this intermediate-size
3 one is, this treatment IND, because
4 quinacrine -- previously, we talked about there
5 being a group, more than just one specific
6 practitioner group, that had vested interest in
7 seeing that product still available.

8 Going back to some of these phase 1, phase 2
9 studies and dose-finding, if we can get those that
10 have vested interests to study it as one specific
11 dose and route of administration and have that
12 group be able to standardize in the treatment IND,
13 you will generate the standard protocol that then
14 increases the available information for that
15 specific dose, that specific frequency, that
16 specific route of administration, and all the
17 safety and efficacy that goes with that protocol.

18 I think it goes to the point you were
19 saying, that if we keep encouraging this access to
20 the treatment IND programs, hopefully, it will
21 generate the information that Dr. DiGiovanna says
22 is lacking for this vulnerable population.

1 But it creates a way to actually standardize
2 it and have like this community of collaboration
3 across the different groups. Like in this specific
4 case, it will obviously come from the oncology
5 practitioners. They all are going to be looking at
6 it for this patient population, but hopefully even
7 a specific indication.

8 DR. VENITZ: Dr. Braunstein?

9 DR. BRAUNSTEIN: I just want to state on the
10 record that this is very different than quinacrine.
11 Quinacrine is a substance that has been widely
12 used. It's considered a standard of care.

13 It's a substance whose safety is
14 well-characterized. Actually, it was an approved
15 drug for many years.

16 This is an experimental drug, essentially,
17 about which we know very little. So this would
18 not, in my mind -- I mean, we'll let the FDA talk
19 about it, but in my thinking about it, this is not
20 an expanded access type of drug.

21 An expanded access type of drug is for drugs
22 where there's reasonably good evidence for safety

1 and efficacy, perhaps the need to have some kind of
2 informed consent because there are some risks
3 that's not -- no drug is completely safe. I think
4 that was the FDA's position before and that makes
5 sense. But this is in my mind a very different
6 situation.

7 DR. VENITZ: Dr. Pham?

8 DR. PHAM: I think I appreciate that that
9 this obviously is of much more limited use and more
10 experimental. I feel like it's the compromise to
11 saying making it accessible in the 503A list is
12 obviously going to be a higher issue for access and
13 safety, whereas if there is a mechanism for those
14 that want to still be able to study it in a cohort,
15 at least it's available through a different
16 mechanism than placing it on the list.

17 I agree with you that I think it's not as
18 widely used and does not have the history
19 established data that quinacrine did, but in terms
20 of using it as the intermediate-size population,
21 you're allowing it to being used more than just the
22 single-patient emergent IND program.

1 DR. VENITZ: Dr. Carome?

2 DR. CAROME: Mike Carome. I think if you
3 were going to engage in studies under an IND for
4 this product, I think you'd want to do studies that
5 are more rigorous than the ones I've heard
6 described that are currently being conducted.

7 DR. VENITZ: Any further comments? So are
8 you ready to proceed? Dr. Jungman?

9 MS. JUNGMAN: I'm just going to jump in just
10 for a second. What I think is the theme of this
11 conversation is that we want to be careful that
12 we're not undermining the FDA approval process. We
13 are constantly bemoaning on this committee the lack
14 of data that we're having to work with.

15 I think this is a good example of a
16 substance where we really want to see not just the
17 patient protections, which are, of course,
18 important of the IND and the informed consent, but
19 also that ability to standardize protocols and to
20 gather good data.

21 DR. VENITZ: Anybody else?

22 (No response.)

1 DR. VENITZ: Okay. Then let's proceed with
2 the vote. If you vote no, you're recommending FDA
3 not place the bulk drug substance on the 503A bulks
4 list. If the substance is not on the list when the
5 final rule is promulgated, compounders may not use
6 the drug for compounding under Section 503A unless
7 it becomes the subject of an applicable USP or NF
8 monograph or a component of an FDA-approved drug.

9 What we are voting right now, as you can see
10 on the screen, whether dichloroacetate should be
11 placed on the list, yes or no?

12 Please press the button firmly on your
13 microphone that corresponds to your vote. You will
14 have approximately 15 seconds to vote. Go ahead
15 please.

16 (Vote taken.)

17 DR. HONG: Question 3, zero yes, 11 nos, and
18 zero abstain.

19 DR. VENITZ: Let's go around the table.
20 Let's start with Dr. Wall.

21 DR. WALL: Donna Wall. I voted no because I
22 think it really needs to be under a study. We are,

1 again, dealing with an extremely vulnerable
2 population. I believe there is time that it should
3 be studied and patients know that they are getting
4 good effective medicine.

5 DR. CAROME: Mike Carome. I voted no. I
6 think there are serious significant safety risks
7 with this drug. There's a complete lack of
8 evidence that it's effective.

9 Like the last one, I would urge the FDA to,
10 again, immediately place this drug on the
11 Category 2 list of drugs under the interim guidance
12 and not allow it to be compounded because it raises
13 significant safety risks.

14 DR. VAIDA: Allen Vaida. I voted no for the
15 same reasons. Basically, for the discussion that
16 we did have, this is a drug that needs
17 well-controlled trials.

18 DR. PHAM: Katherine Pham. I voted no. I
19 was concerned by the instability as an injectable
20 product and also the toxicities with the oral
21 product, particularly the peripheral neuropathy,
22 the fact that a safe and effective dose has not yet

1 been determined but potentially IND options could
2 help provide some more of that data.

3 MS. JUNGMAN: Elizabeth Jungman. I voted no
4 because of the significance of the safety concerns,
5 the lack of effectiveness data, and the
6 vulnerability of the population.

7 DR. HOAG: Steve Hoag. I voted no, and I
8 was worried about the formulations, the stability,
9 the safety. And I agree with many of the comments
10 said previously.

11 MR. HUMPHREY: William Humphrey. I voted
12 not for many of the same reasons. I'm also
13 concerned about the fact that it has to be
14 genetically dosed. And I'm not sure if we put it
15 on this list that everyone that would use it would
16 have that capacity.

17 MS. DAVIDSON: Gigi Davidson. I voted no
18 for many of the reasons stated and additionally
19 because of concerns about worker exposure to a
20 potential carcinogen.

21 DR. VENITZ: Jurgen Venitz. I voted no for
22 basically the same reasons that have already been

1 stated.

2 DR. GULUR: Padma Gulur. I voted no for the
3 same reasons, stability data, safety,
4 effectiveness, and would support the comment
5 earlier regarding the scientific rigor in any study
6 design, and the need for established protocols.

7 DR. DiGIOVANNA: I'm John DiGiovanna. I
8 voted no for all the reasons that have been
9 mentioned.

10 **Adjournment**

11 DR. VENITZ: Thank you. That concludes our
12 discussion of dichloroacetate. We are now going to
13 take an early break. No nap time because we won't
14 get together again until 1:00, so let me read you
15 the official language.

16 We will now break for lunch, and we will
17 reconvene again in this room at 1:00 p.m. Please
18 take any personal belongings you may want with you
19 at this time. The ballroom will be secured by FDA
20 staff during the lunch break.

21 Committee members, please remember that
22 there should be no discussion of the meeting during

1 lunch amongst yourselves, FDA, or with any member
2 of the audience. Thank you, and see you at 1:00.

3 (Whereupon, at 11:17 a.m., the morning
4 session was adjourned.)

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Thursday, June 23, 2016

1:00 p.m. to 5:08 p.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center
The Great Room (Rm. 1503)
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Cindy Hong, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Michael A. Carome, MD, FASHP**

11 *(Consumer Representative)*

12 Director of Health Research Group

13 Public Citizen

14 Washington, District of Columbia

15

16 **Gigi S. Davidson, BSPH, DICVP**

17 *(U.S. Pharmacopeial Convention Representative)*

18 Director of Clinical Pharmacy Services

19 North Carolina State University

20 College of Veterinary Medicine

21 Raleigh, North Carolina

22

1 **John J. DiGiovanna, MD**

2 Senior Research Physician

3 DNA Repair Section

4 Dermatology Branch

5 Center for Cancer Research

6 National Cancer Institute

7 Bethesda, Maryland

8

9 **Padma Gulur, MD**

10 Professor, Department of Anesthesiology and

11 Perioperative Care

12 University of California, Irvine

13 Orange, California

14

15 **Stephen W. Hoag, PhD**

16 Professor

17 Department of Pharmaceutical Science

18 University of Maryland, Baltimore

19 Baltimore, Maryland

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1 **William A. Humphrey, BSPHarm, MBA, MS**

2 Director of Pharmacy Operations

3 St. Jude's Children's Research Hospital

4 Memphis, Tennessee

5

6 **Elizabeth Jungman, JD**

7 Director, Public Health Programs

8 The Pew Charitable Trusts

9 Washington, District of Columbia

10

11 **Katherine Pham, PharmD**

12 Neonatal Intensive Care Unit Pharmacy Specialist

13 Children's National Medical Center

14 Washington, District of Columbia

15

16 **Allen J. Vaida, BSc, PharmD, FASHP**

17 Executive Vice President

18 Institute for Safe Medication Practices

19 Horsham, Pennsylvania

20

21

22

1 **Jurgen Venitz, MD, PhD**

2 *(Chairperson)*

3 Associate Professor, Virginia Commonwealth

4 University

5 School of Pharmacy, Department of Pharmaceutics

6 Richmond, Virginia

7

8 **PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Donna Wall, PharmD**

11 *(National Association of Boards of Pharmacy*

12 *Representative)*

13 Clinical Pharmacist

14 Indiana University Hospital

15 Indianapolis, Indiana

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1 **PHARMACY COMPOUNDING DRUGS ADVISORY COMMITTEE**

2 **INDUSTRY REPRESENTATIVE MEMBERS (Non-Voting)**

3 **Ned S. Braunstein, MD**

4 *(Industry Representative)*

5 Senior Vice President and Head of Regulatory

6 Affairs

7 Regeneron Pharmaceuticals, Inc.

8 Tarrytown, New York

9

10 **William Mixon, RPh, MS, FIACP**

11 *(Industry Representative)*

12 Former Owner

13 The Compounding Pharmacy

14 Hickory, North Carolina

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TEMPORARY MEMBERS (Voting)

Jeffrey Brent, MD, PhD

(Participation in DMPS discussion)

Distinguished Clinical Professor of Medicine
University of Colorado School of Medicine and
Colorado School of Public Health
Denver, Colorado

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P R O C E E D I N G S

(1:00 p.m.)

DR. VENITZ: Let's reconvene our meeting, please. Welcome to the afternoon session of the PCAC. We're now going to take a little detour, getting information on expanded access programs. We'll have Dr. Jarow present on expanded access to investigation of new drugs.

Dr. Jarow?

Presentation - Jonathan Jarow

DR. JAROW: Good afternoon, everyone. I'm back, for those of you who were at the last Compounding Advisory Committee meeting.

It was felt, after the last session and the questions that came up, that it'd be worthwhile to give an expanded-access IND-for-dummies talk to answer a lot of the outstanding questions that exist.

Although I wasn't here this morning, I was at another meeting, I understand that a lot of these issues came up again today.

So here's a summary of potential questions

1 that people might ask about this process, and I'll
2 give you the short answers here. And then
3 hopefully, you have a copy of my slides because, at
4 the end, there's two slides with resources that you
5 go to for much more in-depth information.

6 But question number 1, is there a model for
7 expanded access to an unapproved drug or a formerly
8 compounded drug? And the answer is yes.

9 The best, the only existent model for
10 something like that right now is domperidone, which
11 recent had the protocol and materials posted online
12 for people to access, but that's in single-patient
13 INDs.

14 I don't think that's necessarily the best
15 model for all situations. And the one that I'm
16 going to put forward today is something called an
17 intermediate-sized access IND. So yes, there is a
18 model.

19 Can the sponsor charge patients for the
20 costs incurred, as well as the drug? And the
21 answer is yes. Can administrative costs be passed
22 on? The answer to that is yes.

1 Who can serve as the sponsor of the IND? It
2 could be a manufacturer. It could be individual
3 physicians or other groups, and we'll get into some
4 details later on.

5 How is the drug dispensed? The sponsor
6 dispenses the drug directly or through an
7 investigator.

8 Are multiple courses of treatment possible?
9 The answer to this is also yes, provided applicable
10 requirements are met. This would be part of the
11 protocol.

12 I learned through practice talk internally
13 at FDA -- for those of you who have participated in
14 or run a multicenter clinical trial, this is simple
15 stuff, very routine and easy.

16 For those of you who never done this, it
17 probably seems very opaque and problematic. I'm
18 going to try and clarify this, but I'll also want
19 to say -- and it's going to come up again -- talk
20 to us. Talk to us. We are here to help.

21 So what are the eligibility criteria for an
22 expanded access protocol? One, the indication has

1 to be a serious or immediately life-threatening
2 condition. There has to be no comparable or
3 satisfactory alternative therapy.

4 The potential patient benefit justifies the
5 potential risk, and the risks are not unreasonable
6 in the context of the disease or condition to be
7 treated, and it's providing the drug will not
8 interfere with ongoing clinical investigations that
9 could support marketing approval of the expanded
10 access use of that drug.

11 There are multiple types of expanded access.
12 Expanded access is basically access to an
13 unapproved drug, which we're going to call an
14 investigational drug, outside of the clinical trial
15 setting.

16 This is not for research, although
17 frequently the information gathered from expanded
18 access protocols may be used as part of an
19 application. But in general, the intention is, in
20 expanded access, to treat patients.

21 It could be submitted as a freestanding IND
22 or a protocol under an existing IND. They come in

1 three flavors; single-patient, which would include
2 both emergency and non-emergency use, intermediate
3 size patient population, and a treatment protocol
4 or IND, which is for more widespread use.

5 For an intermediate-sized access IND, the
6 application must state whether the drug is being
7 developed for marketing.

8 The treatment protocols for INDs are
9 typically those drugs where there's an application
10 about to be submitted to the FDA. It's in the
11 final phase of development and it's usually used to
12 bridge the gap between completion of phase 3 trials
13 and marketing approval.

14 An advantage of the intermediate-sized
15 access IND is that many healthcare providers
16 treating patients with investigational drug under a
17 single IND sharing an IRB, a protocol, and a
18 consent form.

19 There would be a single sponsor of this IND,
20 and then there would be subinvestigators, which
21 would be the healthcare providers that had
22 individual or more than individual patients that

1 they were treating with the drug.

2 The key components to putting together an
3 IND application is identify a sponsor and principal
4 investigator, and they can be the same person;
5 write a protocol and informed consent; create an
6 investigator brochure, so you need labeling for the
7 drug product, and there's guidance on how to do
8 that on ICH E6; and identify a manufacturer.

9 One of the key components of this -- and
10 we're going to have a switch in terms for you here
11 at the compounding AC -- is that if it was a
12 formerly compounded drug and you're in an IND
13 setting, you are no longer compounding the drug.

14 The organization or manufacturer that's
15 making the drug is called a manufacturer now, not a
16 compounder, but it can be one and the same.

17 If you need help getting started with this
18 because this is all unfamiliar stuff, you need to
19 contact the review division in the Office of New
20 Drugs that will be receiving the application. The
21 division within the Office of New Drugs is
22 identified based on the indication.

1 For example, if it was an indication for
2 reproductive stuff, it would go to what's called
3 DBRUP, Bone, Reproductive, and Urologic Products.
4 If it was for lupus, or arthritis, or something
5 like that, it would go to DPARP, which is the
6 division that reviews rheumatology.

7 You may not know which division or the
8 telephone number of that division to contact if
9 you've never been through this process before, so
10 there are other avenues to gain access.

11 One is to contact the Division of Drug
12 Information in CDER, and I've provided their phone
13 numbers and email address. If you're a physician
14 in the office and you call, you're likely to get an
15 answering machine, and they actually -- I did an
16 experiment -- call back pretty promptly, but you'll
17 probably be on to your next patient and not be at
18 the phone, so it'd probably be wisest to email.

19 The other option is to call the Office of
20 Health and Constituent Affairs. We have a
21 representative here in the room from that office,
22 and they are extremely helpful.

1 We also recommend, in any of these
2 communications if possible, that you copy the CDER
3 compounding team who can also help facilitate your
4 navigation throughout the bureaucratic structure of
5 FDA.

6 One of the things you're going to want to
7 do, and you can do this more than once, is have
8 something called a pre-IND meeting with the people
9 in the review division.

10 This is not required, but it is extremely
11 helpful, particularly if you're never done this
12 before and so it's strongly recommended.

13 You will need to submit some stuff in
14 advance to the meeting. You would need background
15 information on what your plan is and then specific
16 questions, and these could be about the chemistry
17 and manufacturing controls, what kind of
18 documentation you need regarding the safety of that
19 drug, and whether your protocol looks good or has
20 any deficiencies in it.

21 This meeting can take place face-to-face, by
22 telephone or written responses only. I would

1 strongly suggest that you take one of the first two
2 options. Written responses only are great if you
3 know what you're doing, and you have a specific
4 question, and you'll understand the answer in FDA
5 jargon. However, if you need a lot of back and
6 forth, a face-to-face meeting or teleconference is
7 much better.

8 So what goes into an IND submission? You
9 need to have a qualified investigator, and that
10 includes the subinvestigators. That's done by
11 submitting their curriculum vitae or resume.

12 You need product information. If you're
13 having a single manufacturing site, it would just
14 be for that site. If you have multiple, it would
15 be for multiple sites.

16 It would require information regarding
17 purity, strength, quality, stability, and how
18 you're going to distribute the drug product.

19 You need information regarding safety. And
20 formerly, frequently for a new molecular entity,
21 that's all nonclinical research. Clinical
22 information trumps nonclinical and so for a

1 formerly compounded drug, you will have literature
2 that you could point to and provide a great deal of
3 safety information.

4 You also need some efficacy for the
5 rationale for the intended use of the drug and at
6 least preliminary clinical evidence of
7 effectiveness.

8 For instance, quinacrine, which was
9 discussed at the last advisory committee, you would
10 have the literature, again, to point to in terms of
11 efficacy and safety.

12 Then you need a protocol. Now, for a
13 regular IND, for non-expanded access, this is a
14 research protocol. We're going to take
15 300 patients. We're going to randomize them 1 to 1
16 to a drug and a placebo. We're going to have these
17 office visits to monitor them. We're going to give
18 them this dose. We have these monitoring plans in
19 place. We'll be checking their hemoglobin and
20 liver function tests every three months or
21 whatever, the whole plan.

22 You do the same thing for an

1 intermediate-sized treatment protocol, except there
2 wouldn't be the randomization, et cetera. You
3 would describe, in this protocol, how each of the
4 subinvestigators should manage their patients that
5 are on this drug. It would be basically a best
6 practice, a guideline basically, on how to manage
7 that disease with this drug.

8 It would have the proposed method of
9 administration of the drug, the dose, the duration,
10 eligibility criteria, clinical procedures, and
11 monitoring to evaluate effects and minimize risk.

12 Informed consent with IRB approval would be
13 required, a statement about product development, so
14 that's the one I referred to earlier. You could
15 essentially say it is not being developed. And
16 then the investigator brochure, which I referred to
17 earlier as well -- and you can get guidance on how
18 to prepare one of those from ICH E6.

19 With an IND comes some regulatory
20 responsibilities. Number one, you cannot begin
21 treatment of patients for 30 days unless you
22 receive notification from FDA sooner than that.

1 If you receive no notification that it's on
2 hold, you can proceed at 30 days even if you have
3 not heard back from FDA. You also need IRB
4 approval, of course.

5 During the course of the treatment of these
6 patients, IND safety reports should be submitted if
7 there are any serious unexpected, suspected adverse
8 reactions and annual reports as well.

9 You will have to notify FDA of any new
10 subinvestigators that are added on. So as a doctor
11 in another location learns about this
12 intermediate-sized protocol and contacts the
13 principal investigator and says, I have a patient
14 I'd like to treat, and they meet the criteria, they
15 can be added on as a subinvestigator. You would
16 then have to submit their CV to the FDA.

17 You also have to notify FDA of any product
18 manufacturing or changes in distribution. In
19 addition, if you're charging, there is an annual
20 renewal of charging authorization.

21 What are the rules on charging? They are
22 different for the different types of expanded

1 access INDs. There's a guidance that was recently
2 published on this, so you could refer to that.

3 Again, that's in the back of your slides.

4 You have to, one, provide reasonable
5 assurance to FDA that charging will not interfere
6 with drug development and so again, if you're
7 saying it's not being developed, that's an easy
8 thing to satisfy; provide documentation of the
9 calculated amount that you're charging the patient;
10 and provide a statement from an independent
11 certified public accountant that they've reviewed
12 this and approved the calculation.

13 You can recover direct drug costs and so
14 that has implication as to who the sponsor is. If
15 the sponsor is the manufacturer, you can recoup the
16 direct costs of making the drug. If someone else
17 is the sponsor, then they recoup the cost of
18 purchasing the drug.

19 You can recover costs of monitoring, IND
20 reporting requirements, and other administrative
21 costs directly associated with expanded access use.

22 You can also hire a third-party

1 administrator or CROs, as we affectionately call
2 them, to recover fees. They could hire them and
3 then recover the fees that were involved with that.

4 So these are the resources that I kept on
5 mentioning as to where you can find these forms and
6 these guidances. And thank you. I think we now
7 open it up for clarifying questions if I'm not
8 mistaken.

9 **Clarifying Questions from the Committee**

10 DR. VENITZ: Yes. Thank you, Dr. Jarow.

11 Any clarifying questions? Dr. Braunstein?

12 DR. BRAUNSTEIN: Hi. Ned Braunstein, I'm
13 the industry rep, and thanks for the talk. This is
14 stuff we do all the time in industry, but some
15 people around the table don't do all this. It's
16 good to have this.

17 I have one question though. For the
18 nonprofessionals who are going to be interacting,
19 will you accept paper INDs, or does everything have
20 to be electronic?

21 DR. JAROW: Emily, do you know when that
22 goes into effect that everything has to be

1 electronic? It currently isn't, I don't think.

2 MS. GEBBIA: Yes. I don't know off the top
3 of my head. I don't know, Rich, if you know when
4 the electronic requirements go into effect. We can
5 look into that, and it would be certainly something
6 that could be raised when you contact FDA for a
7 pre-IND meeting.

8 DR. JAROW: Pre-IND meeting, yes,
9 absolutely. Right now, I don't think it's a
10 requirement. It's much preferred by the review
11 division. So if you want a happy review division,
12 please send it electronically.

13 Any other questions? Yes?

14 DR. DiGIOVANNA: Yes, John DiGiovanna. It's
15 very helpful to see all of this. However, to an
16 individual investigator, it appears equivalent to
17 establishing a pharmaceutical company.

18 Going through my quick review of the -- I
19 guess what caught my eye first was the investigator
20 brochure which sounds like the IRS 1040 form, which
21 begins to get quite, quite large when one adds
22 additional things to it.

1 This ICH E6 is, again, 63 pages of, I guess,
2 rules about how to do this. So what goes into an
3 investigator brochure? I could envision a small
4 group coming together, and finding an IRB, and then
5 a public accountant, and various other specifics
6 that might need to be done.

7 But that seems to require a lot of
8 information about the compound and other things, so
9 how laborious is that?

10 DR. JAROW: Exactly. This is why I would
11 strongly urge where you anticipate it's going to be
12 more than a single patient or two or three patients
13 to go the intermediate-size expanded access
14 protocol or IND.

15 The reason is you only have to do it once.
16 Each physician in different parts of the country
17 wouldn't have to reinvent the wheel, if you will.
18 But it does require, as you point out, two areas of
19 expertise.

20 One is going to be the manufacturing side,
21 so a current compounder of the drug would likely
22 have all of that information. And then it's also

1 going to require someone with expertise in that
2 specific disease that's being treated, preferably
3 someone who has some background in clinical trial
4 design and research. Because, for someone with
5 that background, this stuff is not a huge hurdle.

6 For your average treating physician located
7 in the middle of Nebraska, let's say -- I don't
8 want to pick on Nebraska -- middle of Maryland,
9 this would be a huge hurdle, and they would look at
10 this and say, "I can't do this."

11 But for someone who's done it multiple times
12 already or been involved in it as a site
13 investigator, this is all pretty familiar stuff, as
14 the industry rep will share with you. But it is
15 intimidating at first.

16 The guidance that you referred to is
17 63 pages, but that's not on doing the investigative
18 brochure. That's good clinical practice, which has
19 a lot of stuff in there unrelated to this specific
20 issue.

21 Having said that, it's just like product
22 labeling. If you looked at -- a package insert, I

1 think, is the common term for this. It basically
2 contains those key components. What's the
3 indication? What's the safety profile? What's the
4 efficacy data?

5 It's going to be a lot of this stuff that
6 you're putting into the protocol itself to get the
7 IND opened up. It's not as bad as it sounds, but
8 again, I fully agree with you. For someone who's
9 never done this before, it would seem impossible.

10 That's why I would not encourage people to
11 do single-patient INDs for this unless they really
12 are just going to treat a single patient, but this
13 would be a mechanism to get it done.

14 Then once you let the community -- let's say
15 we're talking about quinacrine and lupus. You let
16 the community know that this is out there, and
17 there are ways that you can do that. Then you can
18 have them just join.

19 DR. DiGIOVANNA: So what you're suggesting
20 then, with respect to quinacrine, is that if there
21 was an organization who is interested in setting up
22 an infrastructure, that that organization could

1 either be an individual investigator, or perhaps a
2 patient advocacy group, or perhaps a manufacturer
3 of some sort, a compounding pharmacist who then
4 could bring together the expertise to develop the
5 protocol, the investigator brochure, the consent
6 form, the IRB, the other issues, the other
7 necessities that were involve.

8 If there were costs that were incurred for
9 that, they could be covered, and the medication
10 then could be available to physicians broadly
11 across the US who submit the proper documentation,
12 CV or whatever, to make them quote, unquote,
13 "investigators" in this enterprise.

14 Then they would not have to have their own
15 IRB; they would use their quote/unquote "central
16 IRB" and consent form, and the drug could then be
17 manufactured, made available if it was intended to
18 do so for only the costs that were necessarily
19 incurred in creating this whole enterprise, and
20 that this didn't have to be done multiple times.

21 It may have to require each investigator to
22 submit information about toxicities or adverse

1 events to the one investigator, but it in essence
2 could be done once by a small group and then made
3 available with controls of the toxicities and
4 adverse events submitted back to the FDA.

5 DR. JAROW: Right. And just to take it a
6 step further -- the industry rep will be familiar
7 with this -- there are large companies like
8 Pfizer -- I don't know your company -- that have
9 all the in-house resources.

10 Then there are small companies that actually
11 contract a CRO to do all the steps you're talking
12 about; write the investigator brochure, write the
13 protocol, write the informed consent. So they
14 can -- the sponsor can delegate these
15 responsibilities to a third party.

16 Emily, did you want to clarify anything?

17 MS. GEBBIA: I just wanted to make one quick
18 point about the individual-patient expanded access.
19 Dr. Jarow is right that it can be burdensome if,
20 each time, you're recreating the wheel.

21 We've been working really hard to be
22 responsive to people's request for information

1 about the use. And as he mentioned at the
2 beginning of his presentation, for example for
3 domperidone, there's a packet available online so
4 individual physicians who want to get access to
5 that information can do it and get the proper
6 paperwork.

7 Once there's an infrastructure in place and
8 under the right circumstances, it's not necessarily
9 having to recreate the wheel each time.

10 DR. VENITZ: Mr. Mixon?

11 MR. MIXON: I just wanted to clarify, did
12 you say that a compounder could be the
13 manufacturer?

14 DR. JAROW: So now, what we
15 would -- everything would be -- so now, a
16 healthcare provider is no longer called that.
17 They're called a subinvestigator. Potentially a
18 compounder is no longer called that. They're not
19 compounding under 503A if it's a drug that's not
20 compounded anymore. So now you're a manufacturer
21 and so that would be the situation.

22 MR. MIXON: Subject to CGMP?

1 DR. JAROW: Yes. So you would be subject to
2 CGMP.

3 DR. VENITZ: Dr. Braunstein?

4 DR. BRAUNSTEIN: Also, to help some of the
5 people, I thought I would like to clarify some
6 things to help with the discussion.

7 In theory -- and if you could help me on
8 this -- I think, like, a foundation could be the
9 sponsor. And they could designate a CRO to be
10 their agent. Right? And the CRO could then handle
11 all the safety reporting. Right? So that way, an
12 investigator in this case or one of the docs who
13 has a patient would send the information to the
14 CRO.

15 They'd make sure that it gets handled to FDA
16 on time so that -- like, the Lupus Foundation is
17 not worried about that, right, because that's not
18 their -- you can imagine how some of this stuff
19 could be daunting to a foundation. So a lot of
20 this stuff could be worked out.

21 Then it's my understanding the sponsor
22 could -- as part of the cost of the drug, these

1 administrative costs could be included, along with
2 the cost of procuring the drug could be included as
3 the cost to the patient. You'd have to figure
4 out -- you'd need an accountant obviously to figure
5 out how to do this right; would that be all
6 correct.

7 DR. JAROW: Yes. And I've noticed the
8 reaction in the audience, not by you, at the
9 mention of CGMP. So I also gave a resource, so
10 what would be required would be statutory CGMP, not
11 regulatory CGMP. And that may be a foreign
12 language to you, but the guidance for phase 1
13 research studies which is the statutory CGMP, will
14 be, is provided.

15 That's primarily risk-based and it depends
16 upon partly formulation, the vulnerable
17 populations, contaminants. A lot of the
18 requirements potentially could be handled with
19 literature. There's a significant amount of
20 flexibility there as well, but there would be CGMP
21 requirements for an investigational drug under an
22 IND.

1 DR. BRAUNSTEIN: Sorry. I was asked to
2 explain what is a CRO, a contract research
3 organization. There are lots of these companies
4 and they sell their services.

5 DR. JAROW: Yes. Right.

6 DR. BRAUNSTEIN: One other thing just to
7 clarify, you could have more than one manufacturer
8 in the IND, as long as they agreed to some common
9 standards; is that correct?

10 DR. JAROW: Yes, exactly. They would have
11 to meet the same CGMPs.

12 DR. VENITZ: Any other clarifying questions?
13 Dr. Hoag?

14 DR. HOAG: Could you repeat that again about
15 the regulatory and statutory CGMPs?

16 DR. JAROW: I'm not an expert on CGMPs, but
17 you can go to the guidance. The regulatory CGMPs
18 are quite extensive, and those are required as you
19 get to phase 3 in IND product development and, of
20 course, are required for marketed drugs.

21 The statutory CMGs [sic] are less stringent,
22 let's say, or they're different, and you

1 can -- someone wants to answer it?

2 Sarah, you want to help bail me out on this?

3 DR. ROTHMAN: Yes, sure. I'm Sarah Rothman.

4 I'm in CDER, Office of Compliance, in OUDLC.

5 Statutory requirements for GMPs are in Section
6 501A(2)(b) of the statute, and that's the statutory
7 authority for all of our CGMP regulations that
8 apply to conventional manufacturers, parts 210 and
9 211.

10 For anyone conducting a phase 1 study, we
11 understand that it might be smaller scale. You
12 might not have sophisticated manufacturing controls
13 at this point where you're making larger batches of
14 drugs.

15 We have a regulation. It's 210.2(c), 21 CFR
16 210.2(c) that says that statutory CGMP requirements
17 apply to phase 1 studies, so you have to comply
18 with CGMP requirements. But the CGMP regulations
19 and parts 210 and 211 do not apply with certain
20 exemptions.

21 We have a guidance that describes how you
22 can comply with statutory CGMP requirements, and

1 it's not what you would see in the regulations in
2 parts 210 and 211.

3 They're much more flexible. They take into
4 account that you might be doing smaller-scale
5 production at this point. And really, if you look
6 through the guidance, it's not what you would see
7 in the regulations.

8 DR. VENITZ: Thank you.

9 Dr. Wall? Last question.

10 DR. WALL: This is my real stupidity
11 showing, but what's the difference between expanded
12 access IND and a regular one?

13 DR. JAROW: A regular IND is meant for
14 research whereas expanded access is designed for
15 treatment. There are unique settings in which the
16 information needed to approve a drug comes out of
17 expanded access experience. But in general, it's
18 aimed at treating patients and hence the
19 requirements that I described which would not exist
20 for a regular IND.

21 It doesn't have to be a life-threatening or
22 a serious illness for a regular IND. It doesn't

1 have to be no-alternative therapies for a regular
2 IND. Those are the differences.

3 There will be restrictions. So if you have
4 a formerly compounded drug that's not treating a
5 serious or a life-threatening condition, this is
6 not an avenue for that. It would not be eligible.

7 DR. VENITZ: Okay. Thank you, Dr. Jarow.
8 We appreciate that, and I'm pretty sure we'll see
9 you again.

10 Now, let's move on to our next order of
11 business in continuing our review of bulk
12 substances, pyruvic acid. The FDA presentation
13 will be given by Dr. Carr. She's a medical officer
14 in the Division of Dermatology and Dental Products.

15 **Presentation - Brenda Carr**

16 DR. CARR: Good afternoon. As stated, I'm
17 Brenda Carr. For the next several minutes, we're
18 going to be discussing pyruvic acid.

19 I was the clinical reviewer for this
20 substance. Other members of the review team were
21 Ben Zhang, Carmen Booker, Doanh Tran.

22 Pyruvic acid, 40 to 50 percent, has been

1 nominated for inclusion on the list of bulk drug
2 substances that can be used in compounding under
3 Section 503A of the Federal Food, Drug, and
4 Cosmetic Act for the topical use and the treatment
5 of acne, melasma, and warts.

6 The next couple of slides will spend time on
7 the physical and chemical characterization of
8 pyruvic acid. Its chemical structure is depicted
9 on this slide.

10 The substance is soluble in water. It can
11 undergo decarboxylation reactions under both basic
12 and neutral conditions, and it's also sensitive to
13 sunlight. It's unlikely to be stable in ambient
14 environments, and structurally, it's
15 well-characterized.

16 This reaction presents a current synthetic
17 method. In regard to likely impurities, there
18 would be trace amounts of the starting materials
19 and byproducts, specifically acetic acid and lipoic
20 acid.

21 In conclusion, pyruvic acid is a
22 well-characterized small molecule. In the proposed

1 dosage form, it's unlikely to be stable without
2 proper storage, specifically careful sealing,
3 isolation from moisture, and being kept away from
4 light.

5 We'll move on to discuss the nonclinical
6 assessment of pyruvic acid. It's an intermediate
7 compound created in the metabolism of
8 carbohydrates, proteins, and fats. Its main
9 metabolite is pyruvate, which is a product of
10 glycolysis.

11 Very few repeat-dose studies have been
12 conducted with pyruvic acid. However, acute
13 studies show that it causes irritation to the skin
14 or corrosion and eye damage.

15 There's no nonclinical data to evaluate the
16 chronic dermal toxicity of pyruvic acid. There's
17 no information available pertaining to
18 mutagenicity.

19 Pertaining to developmental and reproductive
20 toxicity, one study found that pyruvate is
21 metabolized during organogenesis and that
22 interruption of this process could lead to neural

1 tube defects, as well as other developmental
2 toxicities. There is no nonclinical data to
3 evaluate the developmental and reproductive
4 toxicity of this substance.

5 There's no information available on
6 carcinogenicity. There's no nonclinical data to
7 evaluate the dermal carcinogenicity of pyruvic
8 acid.

9 Now, we'll move on to the clinical
10 assessment of pyruvic acid, and we'll begin this
11 section of the talk by presenting the safety
12 information.

13 We found reports of irritation, erythema,
14 stinging, burning, that erythema was reported to
15 persist anywhere from minutes to hours. Stinging
16 and burning were said to be readily relieved by
17 neutralization with sodium bicarbonate solution.

18 We also found reports of pain. And in the
19 setting of common warts, the discomfort is said to
20 be a possible indicator of the desired
21 destructive treatment effect. We also found
22 reports of scarring, pigmentation, and crust.

1 Pyruvic acid may emit pungent vapors that
2 are irritating to the upper respiratory mucosa. In
3 the absence of cautionary measures such as adequate
4 ventilation, these vapors could pose risks to
5 patients, providers, and assisting staff.

6 We found no pharmacokinetic information, and
7 we found no information on long-term outcomes.
8 However, as stated, scarring was reported as a
9 risk, and scars are permanent.

10 We'll transition now to discuss the efficacy
11 information that we found. Tossion and colleagues
12 evaluated pyruvic acid in all three nominated
13 conditions, especially acne, melasma, and common
14 warts.

15 Acne and melasma subjects were treated with
16 a 40 to 50 percent pyruvic acid pill every 2 weeks
17 for 1 to 3 months. Warts were treated with
18 70 percent pyruvic acid paint which was applied
19 twice daily for 2 to 3 weeks.

20 This group reported, for their acne
21 subjects, complete disappearance of lesions in
22 33 percent, disappearance of greater than

1 75 percent of lesions in 20 percent.

2 For melasma subjects, improvement of greater
3 than 50 percent was reported in 20 percent of
4 subjects and improvement of 25 to 50 percent in
5 33 percent.

6 A warts total clearing was reported for
7 80 percent of subjects and improvement which was
8 not otherwise defined was reported in 20 percent.

9 Cotellessa's group conducted an open-label
10 study of 50 subjects with papulopustular acne.
11 This group treated subjects with 40 to 50 percent
12 pyruvic acid every two weeks for 3 to 4 months.
13 They reported clinical disappearance of lesions in
14 40 percent, improvement of lesions without complete
15 disappearance in 50 percent, and no improvement in
16 10 percent of subjects.

17 Ardigo and colleagues conducted a pilot
18 study using reflectance confocal microscopy wherein
19 they evaluated pigment distribution in melasma
20 subjects.

21 In some of these subjects, 7 specifically,
22 they evaluated treatment response. Subjects were

1 treated with six cycles of a peeling with
2 50 percent pyruvic acid daily for 2 weeks, and this
3 was followed by a topical application of a
4 Kligman's formula containing 2 percent hydroquinone
5 which was applied daily for a total treatment
6 duration of 5 months.

7 Outcomes were largely reported in
8 histological terms and included a major reduction
9 in pigment at keratinocytes in the epidermis in two
10 subjects, and three subjects were found on
11 microscopy to have trace pigment.

12 Berardesca's group evaluated 50 percent
13 pyruvic acid formulation in subjects with photo
14 damage, superficial scarring, or melasma. These
15 authors did not specify how many subjects were
16 affected by each condition.

17 Subjects received four peeling sessions,
18 each of which was 2 to 5 minutes in duration, and
19 the peels were done once every 2 weeks. The peels
20 were neutralized with a 10-percent sodium-
21 bicarbonate-in-water solution.

22 They reported treatment outcomes which

1 included a significant reduction in the degree of
2 pigmentation in patients with melasma.

3 The last review charts 56 patients with
4 common warts treated with either a 70-percent
5 pyruvic acid or a combination of 70-percent pyruvic
6 acid with 8.5-percent 5 fluorouracil.

7 Seventy-five percent of the patients used
8 the prescribed product for 1 to 4 weeks, and the
9 remaining patients used the product for
10 1 to 2 months.

11 This is the table of results from the Halasz
12 publication, and we'll focus on the cleared column
13 where "cleared" was defined as all warts resolved.
14 Fifty-eight percent of subjects who received a
15 combination product cleared, and 78 percent of
16 subjects who received the pyruvic acid-only
17 formulation cleared.

18 Shahmoradi's group conducted a randomized
19 controlled trial in 60 subjects who had at least
20 two plantar warts. They treated subjects with the
21 70-percent pyruvic acid or a 16-percent salicylic
22 acid solution twice daily for 4 weeks.

1 They reported that the number and the size
2 of warts were decreased in both groups, but they
3 found no difference in efficacy between the
4 products.

5 We'll now just touch or present the approved
6 therapies for the nominated conditions. Approved
7 therapies for acne vulgaris fall into several
8 categories; antibiotics which are available for
9 topical and systemic administration,
10 bacteriostatics, topical retinoids, combination
11 products, hormonal products, and others such as
12 azelaic acid which is a dicarboxylic acid.

13 For melasma, a combination cream is
14 available. It includes the active ingredients of
15 fluocinolone acetonide, hydroquinone, and
16 tretinoin.

17 For warts, approved prescription therapies
18 are available only for genital warts. However,
19 over-the-counter therapies are available for
20 non-genital warts.

21 Pertaining to historical use, pyruvic acid
22 has been used in pharmacy compound for at least

1 three decades. Other dermatologic conditions for
2 which it's been used include seborrheic keratosis,
3 actinic keratosis, and photoaging. While the
4 precise extent of use could not be determined, it
5 appears to be worldwide.

6 In conclusion, pyruvic acid is
7 well-characterized both physically and chemically.
8 Reported adverse reactions generally appear to be
9 local, temporary in duration, non-serious in
10 nature, and readily manageable.

11 We found no information suggesting undue
12 concerns regarding respiratory exposure to vapors.
13 Although limited, available information did not
14 raise any major safety concerns associated with the
15 use of pyruvic acid.

16 The available information indicates that the
17 substance may have efficacy in the treatment of
18 acne, melasma, and warts, the nominated
19 indications.

20 Finally, pyruvic acid has been used in
21 pharmacy compounding for at least 30 years and its
22 use appears to be worldwide.

1 Based on our review, we recommend that
2 pyruvic acid for topical use be included on the
3 list of bulk drug substances that can be used in
4 compounding under Section 503A of the federal FD&C
5 Act. Thank you.

6 **Clarifying Questions from the Committee**

7 DR. VENITZ: Thank you, Dr. Carr.

8 Any clarifying questions?

9 (No response.)

10 DR. VENITZ: Let me ask you first, you
11 mentioned stability may be a problem, but in your
12 summary, that doesn't seem to be clinically
13 important.

14 DR. CARR: No. And I would defer
15 CMC questions to Dr. Zhang, who I see in the rear
16 there.

17 DR. VENITZ: Okay.

18 DR. ZHANG: My name is Ben Zhang from OPQ,
19 CDER. For this question, although in ambient
20 environments, this compound is not quite stable,
21 but as we have stated in the slides, when it's
22 carefully sealed and isolated from moisture,

1 oxygen, and sunlight, it is likely to be stable and
2 can be stored.

3 DR. VENITZ: Okay. Thank you. Second
4 question, what's the presumed mechanism of action?
5 What's it supposed to be doing relative to
6 salicylic acid, for example?

7 DR. CARR: Well, it thins the stratum
8 corneum, but the precise mechanism of action in
9 these indications is not understood.

10 DR. VENITZ: Thank you.

11 Any other questions? Dr. Carome?

12 DR. CAROME: Mike Carome. Given the
13 FDA-approved either prescription or
14 over-the-counter alternatives for each of the three
15 conditions and the nature of the conditions, what's
16 FDA's assessment of the clinical need for this type
17 of compounded product?

18 DR. CARR: Well, it just offers patients an
19 alternative therapy. In the case of acne, for
20 example, there may be patients who don't want to
21 take systemic medications or there may be some who
22 don't want to commit to long-term topical therapy

1 and who would prefer to have their acne treated
2 by entering into the physician's office once every
3 couple of weeks. It offers no advantage, just an
4 alternative.

5 DR. VENITZ: Mr. Mixon?

6 MR. MIXON: So is this product, if we were
7 to compound it, going to be dispensed to the
8 patient or given to the physician for office
9 administration?

10 DR. CARR: It would be for in-office use.

11 MR. MIXON: Thank you.

12 DR. CARR: You're welcome.

13 MS. BORMEL: Pursuant to a patient-specific
14 prescription.

15 DR. VENITZ: Dr. Vaida?

16 DR. VAIDA: Yes. I was going to ask that
17 same question. So you're saying it would be for
18 office use, but all those studies were saying it
19 was applied daily?

20 DR. CARR: No, not in all the studies.

21 DR. VAIDA: Well, it seemed like a few of
22 them that it was applied daily for a couple of

1 weeks. There was a couple that it was once every
2 two weeks, but it is always done at the office?

3 DR. CARR: Thank you for pointing that out.
4 You are correct. In some instances, it would be
5 perhaps allowed for home use.

6 DR. DOHM: Just to be clear, we won't be
7 able to limit where it's being used in terms of its
8 addition to the list or exclusion of the list. If
9 it's listed, it's just going to be a drug, but it
10 won't be limited in terms of whether or not
11 administering in a physician's office versus at
12 home.

13 MS. DAVIDSON: Gigi Davidson. I had a
14 question for Dr. Jarow that is somewhat related to
15 this that I didn't ask. I'll use this as an
16 example.

17 I think, by the four criteria here, this
18 would qualify for addition to the list, and that's
19 clearly FDA's recommendation. My question that I
20 had for you, Dr. Jarow, and I didn't ask, and I
21 should have -- the criteria for an IND are for a
22 serious or immediately life-threatening conditions.

1 This is for acne, melasma, and warts, so
2 this probably would not qualify for an IND if we
3 did not put it on the list. This is more for my
4 understanding of where that line is.

5 DR. JAROW: See, there are lawyers in the
6 room, so you've got to be careful how you say that.
7 It would qualify for an IND. It wouldn't qualify
8 for an expanded access IND. So just to be that,
9 but I'm not a dermatologist so if someone thought
10 that this was a serious illness and could support
11 that, then you potentially could with an unmet
12 need.

13 MS. DAVIDSON: You clarified that. Thank
14 you.

15 DR. VENITZ: Any other clarifying questions
16 for Dr. Carr?

17 (No response.)

18 **Open Public Hearing**

19 DR. VENITZ: Thank you, Dr. Carr, again for
20 your presentation.

21 We do not have a nominator, so no nominator
22 presentation. We're moving right into our

1 discussion.

2 Yes, I'm sorry. We have an open public
3 hearing. I apologize. Let me go through the
4 preliminaries.

5 We will now proceed to hear the open public
6 hearing speaker. I will read the following OPH
7 statement into the record.

8 Both the Food and Drug Administration and
9 the public believe in a transparent process for
10 information-gathering and decision-making. To
11 ensure such transparency at the open public hearing
12 session of the advisory committee meeting, FDA
13 believes that it is important to understand the
14 context of an individual's presentation.

15 For this reason, FDA encourages you, the
16 open public hearing speaker, at the beginning of
17 your written or oral statement to advise the
18 committee of any financial relationship that you
19 may have with the product and, if known, its direct
20 competitors.

21 For example, this financial information may
22 include the payment by a bulk drug supplier or

1 compounding pharmacy of your travel, lodging, or
2 other expenses in connection with your attendance
3 at the meeting.

4 Likewise, FDA encourages you, at the
5 beginning of your statement, to advise the
6 committee if you do not have any such financial
7 relationships.

8 If you choose not to address the issue of
9 financial relationships at the beginning of your
10 statement, it will not preclude you from speaking.

11 The FDA and this committee place great
12 importance in the open public hearing process. The
13 insights and comments provided can help the Agency
14 and this committee in their consideration of the
15 issues before them. With that said, in many
16 instances and for many topics, there will be a
17 variety of opinions.

18 One of our goals today is for this open
19 hearing to be conducted in a fair and open way
20 where every participant is listened to carefully
21 and treated with dignity, courtesy, and respect.
22 Therefore, please speak only when recognized by the

1 chair.

2 Thank you for your cooperation.

3 Our open public hearing speaker.

4 DR. DAY: Good afternoon. My name is
5 A.J. Day. I'm with Professional Compounding
6 Centers of America based out of Houston, Texas. We
7 do not have a financial conflict of interest.

8 PCCA has nominated a number of substances
9 for inclusion on the bulk substances list.
10 However, none of those are on the agenda today.

11 The topic that I'm here to discuss with the
12 committee is the IND process and the application
13 process. First, I must say that I'm deeply
14 appreciative of the opportunity to come here and
15 speak to this committee.

16 These public meetings are very beneficial
17 for all of us. I'm speaking for the compounding
18 community overall. We are very thankful to the FDA
19 for extending this opportunity.

20 We've heard a lot in all of the different
21 PCAC meetings since the first one last February
22 about the IND process. The first time that it came

1 up was in the first meeting, February of 2015, in
2 the context of adding medications to the withdrawn
3 or removed list.

4 If something was added to that list, how
5 might patients that were utilizing some of those
6 get access? That was the first time that that was
7 brought up in this PCAC process, and it continued
8 to be brought up in regards to some of the
9 substances that were being voted on for the bulk
10 substance list, the positive list, so to speak.

11 The FDA's recommendations on one of the
12 substances that we discussed at that time was
13 piracetam. Though their concerns were not about
14 safety or any kind of a safety signal, it was about
15 the lack of large scale clinical trials showing
16 efficacy on the scale that was expected.

17 When we talked about the IND process as an
18 alternative mechanism, we talked about the response
19 time for people getting the information back,
20 either a thumbs up or a thumbs down, from the FDA
21 with regard to the IND.

22 I've summarized some of the responses, and

1 I've put in quotes, and as I go through these
2 slides, there'll be a number of quotes. And my
3 purpose in doing that was not to disparage anybody
4 who made these statements or to make them appear in
5 a negative light, but really to show the context in
6 which the discussions occurred and to be as
7 transparent and factual about where these
8 statements came from as possible.

9 In that voting session for piracetam, some
10 of the comments regarding why the committee members
11 cast their votes the way they did talked about the
12 IND process explicitly, if there's an alternative,
13 so they won't be denied medication or the drug.

14 There's an alternative to putting it on the
15 list; they can still go through an IND process. It
16 also sounds like they may -- like it may be made
17 available for the specific cases through the
18 expanded-use IND, and that was in the context of
19 some of the patient cases that I had presented for
20 that meeting.

21 The individual cases of the
22 patients -- there was another avenue which we heard

1 yesterday and that's because it was a two-day
2 meeting; the IND process was initially discussed
3 the day before -- is the rather rapid response.

4 The FDA had presented that the response time
5 was typically less than 24 hours, so I do not see
6 that the patient access should be denied because of
7 that.

8 Fast forward to the October meeting of last
9 year when we discussed the domperidone. A
10 physician testified as to the difficulty accessing
11 an institutional review board when trying to submit
12 the IND for domperidone.

13 In that meeting, there were two different
14 experts from the FDA. One of them said that our
15 form says that, if IRB review cannot be
16 accomplished, it directs them to contact the FDA
17 Human Subject Protection Branch. Dr. Korvick added
18 on, so again, we try to help facilitate that issue
19 if they're working with us.

20 We also have individual patient INDs under
21 this program or there are physicians who apply to
22 enroll multiple patients if they have a clinic that

1 has more than one patient.

2 This IRB content in the IND process comes up
3 in every single meeting, and we spend a lot of time
4 discussing what is involved, what are the
5 limitations, how do we actually navigate the
6 process.

7 Continuing in that October meeting,
8 Dr. DiGiovanna talked about -- and he made a
9 statement, "To use in the equation that the
10 expanded IND is an acceptable alternative really
11 suggests to me that that's coming from someone who
12 hasn't tried to get an expanded IND."

13 Dr. Davidson added on, "Would this drug,"
14 referring to domperidone, "be eligible for an
15 emergency IND?"

16 The FDA's Dr. Griebel said, "An emergency
17 IND is just another expanded access version. A
18 single-patient IND in which a patient is in an
19 emergent situation, you still have to have a form
20 1572. The only difference is that you can submit
21 to the IRB after the fact of submitting the IND
22 application. And the division has to scrutinize

1 the situation to see if this is truly an emergency
2 situation for the patient."

3 Again, that same conversation amongst the
4 committee, Mr. Humphrey, "I do recognize that there
5 is a clinical need for this drug, but you can get
6 it through the IND process. I may be somewhat a
7 little biased because of where I work, but we deal
8 with expanded access drugs nearly every week. And
9 while the process is cumbersome and onerous when
10 you first do it, after a few times, it gets a lot
11 easier."

12 Dr. Pham added on, "I feel like I'm getting
13 confused by our own advisory committee because I
14 swear, in previous meetings, we've had votes where
15 we voted no based on the fact that there was an IND
16 process. I remember that being people's
17 justification. The conversation in the past has
18 always been, if there's a way to get it through an
19 IND, go that route and hope for the FDA approve the
20 process to -- especially if there's such a
21 compelling need that they are going to be providers
22 that will be looking to create a product that's

1 going for FDA approval."

2 So what are the criteria that the committee
3 had agreed to that the FDA had put forth for
4 consideration in this committee? There are four
5 criteria: physical and chemical characterization
6 of the substance, any safety issues raised by the
7 use of the substance, historical use of the
8 substance in compounding, and efficacy, any data of
9 effective use of lack of effectiveness.

10 No single one of those criteria is
11 dispositive. Those are the sole four criteria.
12 Topics which end up taking a lot of committee
13 discussion time and a lot of resources from both
14 the committee and FDA but are absent from the
15 evaluation criteria is the investigational new drug
16 options, including expanded access. That is not
17 one of the criteria to be evaluated. The vote
18 should not be based on that.

19 FDA-approved medications for similar
20 conditions as a nominated substance, we just heard
21 about some of those in the case of pyruvic acid.
22 What are other medications that are available?

1 That is not one of the criteria for any of
2 the FDA processes here with the PCAC. Going back
3 to the first meeting in February when that item was
4 brought up, Dr. Venitz asked, "How important is the
5 availability of alternative therapies to your
6 ultimate decision?"

7 The FDA's Dr. Kashoki responded, "It is an
8 important consideration, particularly when you
9 think of the nature of the condition being
10 treated."

11 We're adding in criteria to what is going
12 in, but it's informal. It's off the record. The
13 last thing that I see a lot of the conversations
14 taking up time in the discussion on what should be
15 evaluated is how a substance may be marketed.

16 There are rules over what can and cannot be
17 said about compounded medications. If there are
18 concerns about how something may be marketed once
19 it's on the list, there are regulatory policies in
20 place and appropriate action should be taken to
21 carry out the existing regulations.

22 Let's discuss some of this IND process. The

1 FDA's presentations for the IND process in the
2 past -- and I'm grateful to Dr. Jarow today for
3 expanding on a lot of this and making it much more
4 clear.

5 Every time I hear him talk, I swear it seems
6 just so absolutely simple and I feel like I can
7 take it on all by myself, which is not entirely
8 true, so we'll talk about that a little bit.

9 Domperidone is the only medication for which
10 we have an expanded-use packet available, a full
11 protocol that's available. However, for the other
12 discussions that we've had, there's a lot of
13 unknowns.

14 What are the inclusion criteria for the
15 patients that might be allowed to get into that
16 protocol? Will the medication be compounded or is
17 it going to be like in domperidone where it has to
18 be a finished manufactured dosage form which is
19 imported? And then, how does it get to the patient
20 because, for domperidone, it goes through a single
21 pharmacy. And nobody else is allowed to
22 participate, regardless of their location in the

1 country.

2 If it's being compounded, what is the
3 requirement for the letter of authorization that is
4 a requirement in the IND process? And the biggest
5 issue that we're finding in the community setting
6 is access to the institutional review boards.

7 Something else that was presented today was
8 also in the documents that were released by the FDA
9 two weeks ago. It's that the FDA has 30 days to
10 review the IND submissions.

11 In previous meetings, there have been
12 discussions that the response time is typically
13 24 hours or about one business day. And there is
14 no requirement for that kind of a timeframe to
15 happen, so the discussion about patient access will
16 become very relevant.

17 If we look at domperidone, and we took a
18 step back, and I said, if the rules have been set
19 that we need to go through an IND process, if we
20 play exactly by the playbook that's been given to
21 us by FDA, can we navigate it? Can we set up a
22 system such that patients and physicians can easily

1 sign on to this and access the medications?

2 Now, one thing to note is that the
3 expanded-access form for single-patient use is Form
4 3926, and the domperidone IND packet specifically
5 says that it requires Form 1571 and 1572 which, as
6 the FDA said, are not really tailored for
7 single-patient use or for compounded medications.

8 So 3926 is valid only for individual patient
9 INDs, and as we heard repeated many times in the
10 presentation just a few minutes ago, for
11 intermediate-sized and treatment INDs, you must use
12 Form 1571. That is what we're really looking at
13 for the patients affected by the decisions you're
14 talking about.

15 The entire expanded access Form 3926 that's
16 expedited and should take less than 45 minutes to
17 fill out is not applicable to this patient
18 population or to any of the substances that we're
19 describing for the conditions we're discussing.

20 The form 3926 versus 1571 -- in the March
21 meeting of this year, when we talked about
22 quinacrine, Dr. Jarow talked about the

1 simplest, "If I was on the other side, if I was a
2 rheumatologist who wanted the easiest, least
3 burdensome approach, it would be if someone opened
4 a treatment expanded-access IND that would be the
5 least burdensome."

6 That is consistent with what we heard today.
7 Adding on to that discussion, Dr. Jenkins from the
8 Office of New Drugs added that, "There seems to be
9 an assumption that no one is going to develop this
10 drug," referring to quinacrine, "for a commercial
11 use. And I don't think we should assume that to be
12 the case. If it's not on the list, that may prove
13 to be the incentive that someone needs to bring an
14 application to bear."

15 Again, this is another criteria or another
16 consideration that is not part of the criteria for
17 evaluating should this substance be available for
18 use in compounding.

19 Going back to IRB access, can we navigate
20 this process? How feasible is it in a community
21 setting? We contacted over 32 institutional review
22 boards at hospitals and research institutions

1 around the country, including the institutions for
2 every single voting member on this committee.

3 Before doing that, we even contacted and did
4 a lot of research online. Indiana University's IRB
5 does provide some details directly on their website
6 that say before submitting the application to the
7 IRB, you have to complete a 16-module training
8 course per person.

9 Each investigator that signs on has to do
10 this, and it takes a minimum of four hours to
11 complete. There's paperwork submission that's over
12 25 completed pages, and if any single page is
13 missing, it will not be reviewed. Approval is
14 granted for one year and must be renewed annually.

15 We also contacted commercial IRBs, as well
16 as physician groups, and patient groups for
17 assistance with accessing IRBs and navigating the
18 IND process, including the American
19 Gastroenterologists Association and American
20 College of Gastroenterology, along with a few other
21 patient groups.

22 When all of those fail to give us anything

1 helpful with actually working with an IRB, we
2 contacted individual physicians who we knew had
3 previously prescribed domperidone to find out if
4 they'd attempted to, had success with, or had
5 roadblocks accessing and navigating the IND process
6 for domperidone.

7 So the big question, can a physician, a
8 community physician contract with your IRB at your
9 institution or your research facility without being
10 employed by or otherwise directly affiliated within
11 a financial sense your institution?

12 The universal answer was no. We're located
13 in Houston, Texas, where we have the Texas Medical
14 Center. It's the largest medical center in the
15 country. Contacted every single one of those
16 hospitals and they all told us the same, no.

17 Can a physician contract with your IRB
18 without being employed by or affiliated with your
19 institution? Again, the institutions that you are
20 all affiliated with universally said no or they
21 refuse to call us back or respond to our emails,
22 and we tried multiple times.

1 Now, if we look back at the guidance
2 documents that FDA released two weeks ago regarding
3 IND treatment uses, they talk about the requirement
4 for a full IRB review. Partial review is not
5 allowed.

6 They also talk about some of the
7 complications, and they recognize that that
8 proposes an additional barrier. However, the ends
9 justify the means. There's a reasonable need for
10 that full IRB review.

11 That's another requirement that we've got to
12 pose to the IRBs when we're asking, can they be the
13 IRB of record for domperidone. And the request was
14 very simple. We've got an FDA-approved published
15 packet. We simply needed somebody to be the IRB of
16 record. The protocol is already approved.

17 When we contacted the commercial IRBs, only
18 two of them responded to our outreach. The other
19 two were completely unresponsive both via phone and
20 email.

21 None of the IRBs had any experience with
22 compounding medications. All of the INDs that

1 they've ever dealt with are through drug
2 manufacturers, pharmaceutical companies.

3 There was one IRB that, after several days
4 of back and forth where they're telling us, no, we
5 will not do it and we're finding information on
6 their website that indicates they might, they
7 finally said, okay, we could be the IRB of record,
8 but we'd never done this before. And here's our
9 fee structure again. It's designed to work with
10 the industry.

11 For a single-patient review IRB, the fee
12 structure exceeded, well exceeded \$3,000. And they
13 asked me not to reveal the specifics because they
14 consider that to be proprietary information.

15 That was an estimated fee because, again,
16 they've never dealt with a compounded medication
17 and a protocol that was already approved, so they
18 don't know if that structure is going to get more
19 expensive or not.

20 As far as timelines for the IRB, they said,
21 depending on the workload for their full IRB, the
22 turnaround for the full review could be as short as

1 10 to 12 business days, in addition to a couple of
2 days to verify that the submission is complete. So
3 you're looking at about three weeks calendar time
4 in a best-case scenario.

5 Now, if we go back to the FDA guidance
6 documents that were published, they actually talk
7 about two different levels of individual patient
8 expanded access. One is the IND. One is the
9 protocol.

10 Now, based off of the conversations we have
11 had in the PCAC meetings prior, we understood that
12 the response could be very rapid, and you could
13 initiate therapy for your patients immediately.

14 Well, the expanded access IND has a 30-day
15 waiting period, but the protocol doesn't. So
16 there's a little bit of confusion on our end about
17 which one would be the best to approach and how do
18 we have that discussion with the IRB.

19 We're having difficulty understanding the
20 process, as well as a lot of difficulties securing
21 IRB review. What do we do then?

22 The FDA instructs you, contact us, we're

1 here to help you. Now, in the domperidone packet,
2 there is instruction specifically on contacting the
3 Human Subject Protection Branch, along with a name
4 and phone number.

5 We did call them. And just to note, they
6 couldn't even respond to our request for help in
7 less than 24 hours. When we did speak with
8 somebody, we were told that we cannot make any
9 specific recommendations of an IRB to use.
10 However, there's an independent, for-profit IRB
11 that kind of, as a business model -- and one of
12 them would be the best to use -- those would be the
13 ones that we contacted and we got a fee structure
14 for.

15 They also referred us to an IRB database
16 online where we could search by state. However,
17 that was not very useful because a lot of those are
18 for military sites, for private institutions that
19 we don't have access to.

20 In addition to that, there's another packet,
21 these documents that the FDA has released two weeks
22 ago. The expanded-access physician fact sheet says

1 that, "If you need assistance with this, contact us
2 here," and it's the Division of Drug Information.

3 So we did that and we contacted with a very
4 nice, very professional pharmacist who was trying
5 to help us, but didn't have a lot of knowledge
6 about this process herself.

7 We asked, is that letter of authorization
8 needed for domperidone? And we were told the
9 packet does not say anything about it. That's why
10 we asked. But moving beyond that, what type of IND
11 do we need to file? There's the expanded access
12 IND or expanded-access protocol.

13 The response was, I don't know what expanded
14 access protocol is. I'm here to refer you to the
15 FDA's website. You should carefully review the
16 domperidone packet on the website.

17 When we directed her to the page that
18 discussed the expanded-access IND versus the
19 expanded-access protocol -- you saw the screenshots
20 earlier -- her response was, we cannot interpret
21 for you. We can only give you publicly available
22 information. We can direct you to areas of our

1 website, but we cannot interpret anything for you.

2 So we asked, who would be able to help us
3 determine what we need to apply for, interpret some
4 of these things, so we're actually getting the
5 right things done? And the response was, you need
6 to hire a consultant.

7 If we go back to the FDA's guidance
8 documents -- and we heard about, can you charge
9 patients for some of these things -- it
10 specifically says that you can charge for direct
11 costs only, but you cannot charge or get reimbursed
12 for administrative costs.

13 I'd like to some clarification on that at
14 some point because it's directly contradictory to
15 what Dr. Jarow just presented, along with the other
16 requirements of what is required to apply and ask
17 permission to recoup some of your direct costs.

18 What can you recover? You cannot recover
19 your indirect costs and that includes the IRB fees
20 and expenses, so you're looking at a minimum of
21 \$3,000 for the single-patient IRB review.

22 From our experience, that's going to be just

1 one piece of it, then if you're having to hire a
2 consultant to navigate the IND process with the
3 FDA, another fee to hire a certified public
4 accountant. All of these fees add up.

5 Going back to the quinacrine discussion,
6 Dr. Jarow said that if he or she, referring to the
7 healthcare provider or the physician in a small
8 community, does not have a local IRB, they can use
9 a central IRB. And many of those provide their
10 service for free for expanded access or
11 compassionate use.

12 We've searched high and low for that unicorn
13 and have been unable to find them, so we'd greatly
14 appreciate some assistance, but when we asked for
15 that assistance, we're told, "We cannot tell you
16 any. We can't recommend an IRB to utilize."

17 One of the other criteria of expanded access
18 is that the patient -- they are not a good
19 candidate for an ongoing clinical trial. So in the
20 case of quinacrine, if something is being studied
21 for lupus, but this patient has been on quinacrine
22 for lupus, yet they meet the inclusion criteria for

1 a clinical trial, they would have to go to that
2 clinical trial before they could get lupus through
3 an expanded-access IND. That is a requirement for
4 expanded access.

5 The other point that he made was that
6 there's no question if one was to take a
7 single-patient approach in this. It would be more
8 burdensome. The burden in patient access issues
9 here are really the crux of our concerns on this
10 entire discussion about INDs as it relates to
11 compounding.

12 So there's a lot of confusion about -- to
13 begin with, which form do we use? Do we use this
14 expedited form, 3926, or are we required to go to
15 the more convoluted less clear forms, 1571 and
16 1572? Confusion about expanded-access IND versus
17 the expanded-access protocol and patient waiting
18 periods -- when can we start treating our patient?

19 Extreme difficulty finding an IRB to work
20 with, as well as the insurmountable fees for the
21 IRB which would be typically shouldered by the
22 physicians or, as presented today, whoever the

1 sponsor is -- however, even in that case, you have
2 a number of fees for hiring a consultant to
3 navigate the IND and the certified public
4 accountant. And when you have all of these
5 indirect fees -- and you're not allowed to make a
6 profit on any of this.

7 You may be able to recover some of your
8 direct cost with accessing the specific drug, but
9 there's no profitability allowed through this
10 entire process.

11 So who's going to be able to sustain this in
12 the long run? Several hours of paperwork
13 requirements for both the IRB, as well as then the
14 FDA -- and through all of that, you still don't
15 have specific information on how the patient will
16 ultimately get the medication, assuming that the
17 IND is submitted and approved.

18 Will it be compounded? Will it be an
19 imported manufactured product? What sites will be
20 allowed to participate in this process? And this
21 notion of being under GMP -- the entire premise of
22 503A and community compounding pharmacy is, it's

1 exempt from GMP. So to note that as an added
2 regulation and the regulatory status of the
3 pharmacies is a tremendous burden as well.

4 Going back to that quote from
5 Dr. DiGiovanna, "To use in the equation that the
6 expanded-access IND is an acceptable alternative
7 really suggests to me that it's coming from someone
8 who hasn't tried to get an expanded IND."

9 In the case of quinacrine, it really seems
10 like we're looking for ways where we have all of
11 the evidence, but still have it go through an IND
12 and have an IRB look at it rather than allowing it
13 for use in compounding.

14 So my ask to the committee is that the IND
15 process specifically should have no bearing on the
16 PCAC evaluation process. It is not one of the
17 criteria in evaluating substances for inclusion on
18 the 503A bulk substance list. Thank you very much.

19 DR. VENITZ: Thank you, Dr. Day, for this
20 very detailed presentation.

21 I'll allow one or two comments or questions
22 by the committee. If there aren't any, if the FDA

1 desires in wanting to give a response given the
2 fact that several potential shortcomings of the
3 current process were detailed?

4 DR. JAROW: This is Jonathan Jarow again.
5 I'm from the Office for the Center Director. I
6 apologize that there is significant confusion, and
7 part of that is FDA jargon.

8 One, as I mentioned in my talk, there are
9 things called protocols and INDs. So when you open
10 an IND, you have to submit a protocol. Let's just
11 talk research INDs, get away from expanded access.

12 You open up an IND for a specific drug
13 that's under investigation, and you submit a
14 protocol. The FDA has 30 days to review that, and
15 if you do not hear back from us, you can start that
16 protocol. The protocol is the clinical trial,
17 let's say.

18 If you hear back from us saying you can
19 proceed, you could proceed earlier than 30 days.
20 If there are, as a response from the FDA, that
21 there are hold issues, clinical hold issues that
22 you can't proceed, then you have to address those

1 before you can proceed. So none of this would be
2 for an emergency situation. That's number one.

3 Number two, once you have an open IND that's
4 proceeding and you're doing your protocol -- our
5 industry person knows all about these things -- you
6 can then add another protocol to that IND.

7 There is not a 30-day safety review period
8 for an additional protocol submitted under an
9 existing IND. And I did mention that in my talk,
10 and it'll be in the transcript, I suppose.

11 If you're submitting a protocol to an
12 existing IND, you don't have an existing IND for
13 any of this, so you can't do this, but if you
14 already have an existing IND and you submit a
15 protocol, you don't have to wait the 30 days. That
16 could be an expanded-access protocol or it could be
17 a research protocol. It could be either one to an
18 IND.

19 Let's talk about single-patient versus
20 intermediate-size IND. Single-patient INDs have
21 different regulations than an intermediate-sized
22 IND.

1 All the things you just heard from him about
2 charging under a single-patient IND are correct.
3 You cannot charge administrative costs. However,
4 under an intermediate-sized IND -- so if you go to
5 the guidance that I put in the resources for you
6 and look at that, there's a different section on
7 intermediate-sized INDs. And you can charge in
8 that situation.

9 So again, if you're doing a single-patient
10 IND for domperidone, you cannot charge
11 administrative costs. Okay? And I guess I'm not
12 allowed to mention specific IRBs, but there is an
13 IRB that opened a foundation, basically a
14 charitable foundation for doing free IRB, or not
15 free, but it's paid for by the foundation, for
16 single-patient INDs. That wouldn't count for an
17 intermediate-sized IND, but you have access to
18 that.

19 In terms of timing and review, I would not
20 recommend the intermediate-size IND, expanded-
21 access IND for anything that you wanted as an
22 emergency. This is not intended for emergency

1 treatment.

2 This would be something that you would set
3 up, and then you can then use it and expand it to
4 different healthcare providers.

5 An emergency IND is a single-patient IND.
6 It's a completely separate situation. You'd need
7 to submit it as that. There are different rules
8 required for it. You don't have to have the IRB
9 approval at the time of submission, although you're
10 expected to get it, I think, within 12 days.

11 Rich? Richard left. But anyway, that's
12 typically emailed, faxed, or telephone called-in to
13 FDA. You speak to the review division, and you
14 typically get a response within hours.

15 Regular expanded-access INDs, you do not get
16 a response within one day. They typically take
17 longer. The Office of Oncology recently looked at
18 their data, and I think it was -- for a
19 non-emergency, the average was, like, about two or
20 three days.

21 For an intermediate-sized treatment -- I
22 shouldn't use the word "treatment" --

1 intermediate-sized population expanded-access IND,
2 it's going to take a lot longer and there's
3 probably going to be back and forth during those 30
4 days, unless you got everything perfect in your
5 protocol, et cetera. So there'll be a back-and-
6 forth to get typically, I would anticipate,
7 particularly if you are not experienced with doing
8 this.

9 What else did I want to address? I think
10 the general principle is that -- and I'm not the
11 compounding committee here. The principle is that
12 if you have a drug that you don't think that there
13 could be safe use for all the potential indications
14 that would be in a compounding environment that
15 would normally be addressed by product
16 labeling -- let's say if it was an approved drug,
17 and you're concerned because, as was mentioned
18 before, if you put it on the compounding list, you
19 can't limit it to a specific indication -- correct
20 me if I'm wrong -- unless you could sometimes by
21 formulation, if it's IV or something like that, and
22 you're only compounding the pill.

1 But if you're concerned about alternative
2 uses -- and since you don't have product labeling
3 to instruct healthcare providers and patient
4 labeling to instruct patients for safe use of that
5 product with contraindications for other things,
6 but there is a specific indication that is for a
7 serious or life-threatening disease where you have
8 no alternatives, patients have exhausted all their
9 alternatives.

10 You want it to be available to them in that
11 setting, and it's not an emergency situation, the
12 intermediate-sized expanded access IND is -- as I
13 kept on saying, for someone who has never done it
14 before, it's not easy, but it's doable. You could
15 set it up once and then it's ongoing at that point.

16 It is for a specific indication, so to enter
17 that intermediate-sized IND, you would have entry
18 criteria that describe the exact situation where
19 you think the benefits outweigh the risks for that
20 specific drug and it's worthwhile for patients to
21 have access to that in that setting.

22 They would meet those eligibility criteria,

1 they would be entered into that, and they could be
2 treated chronically with that drug or for just a
3 course of treatment, depending upon what the drug
4 and the indication were.

5 I'd be happy to answer any clarifying
6 questions.

7 DR. VENITZ: Okay.

8 DR. DOHM: If I may respond to two other
9 points that were made by Mr. Day --

10 DR. VENITZ: Go ahead.

11 DR. DOHM: -- if you don't mind, there was a
12 point at which there was a suggestion that the
13 committee, at various times, has considered or
14 taken in consideration factors that aren't explicit
15 in the four-factor analysis that we use for
16 evaluating whether or not to include a bulk drug
17 substance on the list and I just want to make two
18 points of clarification.

19 One is that the availability of therapeutic
20 alternatives, including the availability of
21 FDA-approved drugs, is a consideration that was
22 brought to the committee as part of the safety and

1 effectiveness analysis that are factors in deciding
2 whether or not to include a bulk in the list.

3 The second thing I wanted to mention is that
4 Mr. Day is correct that the IND program is not one
5 of the factors that we consider when we're
6 determining whether it's on the list, but it
7 certainly is a potential avenue to access a drug
8 that is not placed on the list.

9 It, of course, provides safeguards for use
10 of the product that aren't attached to a drug
11 that's compounded outside of the IND process.

12 Thank you.

13 **Committee Discussion and Vote**

14 DR. VENITZ: Thank you. I'm pretty sure
15 this topic will be continued in the future. Let's
16 go on. Thank you, Dr. Jarow, and I'm pretty sure
17 we'll see you again.

18 That takes us out of our open public hearing
19 session, and we're moving back into our review
20 discussion and vote as our next agenda item. We're
21 back to the pyruvic acid. Any comments for
22 discussion? Yes, Dr. Vaida?

1 DR. VAIDA: Just a quick one on this
2 administering it. I know that FDA doesn't have any
3 control on how it would be administered, but I
4 guess just from the committee members,
5 Dr. DiGiovanna, have you ever prescribed this
6 pyruvic acid and did you administer?

7 DR. DiGIOVANNA: I haven't used it. It's my
8 understanding it's used as a peeling agent. So my
9 understanding of it is a physician would order it
10 and would apply it in the office.

11 I could imagine how under some
12 circumstances -- although I personally am not
13 certain -- it could be taught to the patient how to
14 do it, for example, on a specific lesion like a
15 wart, and it might happen that way. But my
16 understanding is it's generally used a peeling
17 agent for large areas, pigmentation, acne, and that
18 sort of thing, usually applied in the office.

19 DR. VENITZ: Dr. Jungman?

20 MS. JUNGMAN: Just again clarifying, so you
21 talk about you order it. So you would diagnose the
22 patient, you figure out what they need, and then

1 sort of send them away to get the product, and have
2 them come back? Or how does that work, given that
3 it would be available for office use?

4 DR. DiGIOVANNA: Again, I believe what would
5 happen would be that a physician who tends to do
6 this on a regular basis would have it in the office
7 for the patients that have that, and then it would
8 be applied at a certain time.

9 I don't know logistically how it would
10 happen going forward. My understanding would be
11 that, in the past, I believe they would have
12 ordered an amount of it for them to be used for
13 that week, or two weeks, or month, or however long
14 it's useful for and apply it in the office.

15 MS. JUNGMAN: You'd typically be ordering it
16 from a pharmacy as opposed to compounding it in the
17 office. Correct?

18 DR. DiGIOVANNA: I would expect that, yes.

19 MS. JUNGMAN: Okay.

20 DR. VENITZ: Any other discussion items?

21 (No response.)

22 DR. VENITZ: Then let's proceed with the

1 vote. The question is posted on the screen. If
2 you vote no, you are recommending that pyruvic acid
3 not be placed. If you vote yes, you're obviously
4 on favor of it being placed on the list.

5 If the substance is not on the list when the
6 final rule is promulgated, compounders may not use
7 the drug for compounding under Section 503A unless
8 it becomes the subject of an applicable USP or NF
9 monograph or component of an FDA-approved drug.

10 You know the voting process. Please press
11 the button firmly on your microphone that
12 corresponds to your vote.

13 (Vote taken.)

14 DR. HONG: For pyruvic acid, we have
15 9 yeses, 2 nos, and zero abstain.

16 DR. VENITZ: Let's go around the table,
17 starting with Dr. DiGiovanna.

18 DR. DiGIOVANNA: So I voted yes. While I
19 haven't used this specific product, I've used other
20 similar to it, my understanding is they're applied
21 in the office, and I think the FDA has done a good
22 job of reviewing the materials on it. And I agree

1 with them that it should be available.

2 DR. GULUR: Padma Gulur. The safety data
3 presented does not appear to pose any significant
4 risks to the patients, and there's reports of
5 efficacy. Based on that, I believe that it should
6 be placed on the list.

7 DR. VENITZ: Jurgen Venitz. I voted yes. I
8 would add to my predecessors that there is plenty
9 of information of clinical efficacy, probably more
10 than I've seen in any previous meetings.

11 MS. DAVIDSON: Gigi Davidson. I voted yes
12 for the reasons stated. There's plenty of evidence
13 to support efficacy and no concerns about safety.

14 MR. HUMPHREY: William Humphrey. I voted
15 yes. I agree with the FDA's assessment.

16 DR. HOAG: Steve Hoag. I voted yes. The
17 risk to benefit ratio seem favorable.

18 MS. JUNGMAN: Elizabeth Jungman. I also
19 voted yes primarily because that kind of risk
20 benefit calculation seemed to be favorable, given
21 the evidence of effectiveness in human trials.

22 I did think that this one was harder because

1 of the -- the clinical need was not clear given the
2 FDA-approved alternatives. But given the lack of
3 concern about long-term safety effects -- and I
4 also find it comforting given that, under 503A, you
5 would not be able to use this product for -- you
6 wouldn't be able to stock it for office use. That
7 would likely create a preference for the FDA-
8 approved product.

9 So you'd be using this really in situations
10 where the clinician determined that there was a
11 real need.

12 DR. PHAM: Katherine Pham. I voted yes for
13 previous reasons stated and that I agree with the
14 FDA assessment.

15 DR. VAIDA: Allen Vaida. I voted no. I
16 really didn't think that was really that much of a
17 hindrance for the other products that were
18 available that the FDA said.

19 I still have concerns about if this was put
20 in the hands of the patient to use because of the
21 vapors and that.

22 DR. CAROME: Mike Carome. I voted no for

1 many of the same reasons Allen mentioned. I don't
2 see a compelling clinical need for this product
3 given the nature of the conditions and given the
4 availability of FDA-approved alternatives. And
5 there are very limited data on the efficacy of the
6 product.

7 DR. WALL: Donna Wall. I voted yes for many
8 of the reasons stated, but one last thing is that
9 this product really needs to be prescription only.
10 I would hate for someone else to be using it
11 because of the risks associated with scarring and
12 other things. It needs to be absolutely
13 prescription only.

14 DR. VENITZ: Thank you. That concludes our
15 vote, and we are moving to our next bulk substance
16 to review, tea tree oil. We have Dr. Ko giving the
17 FDA presentation. He is a medical officer in the
18 Division of Dermatology and Dental Products.

19 Dr. Ko?

20 **Presentation - Hon-Sum Ko**

21 DR. KO: I'm Hon-Sum Ko, the medical officer
22 in the Division of Dermatology and Dental Products,

1 and the topic now is on tea tree oil.

2 Tea tree oil has been nominated for
3 inclusion on the list of bulk drug substances to be
4 used in compounding under Section 503A of the
5 Federal Food, Drug, and Cosmetic Act for topical
6 use in the treatment of nail fungus. The
7 nomination has proposed use of tea tree oil at
8 strengths of between 5 to 10 percent.

9 This slide just briefly goes over the
10 condition that we are talking about, nail fungus
11 infection. And I'll use the term onychomycosis
12 synonymously with nail fungus infection.

13 This condition is most commonly caused by
14 dermatophytes, and it can also be caused by other
15 fungi like candida species and other yeasts. Tea
16 tree oil has been reported to be used for this
17 condition as applied to the nails undiluted, or
18 with neat tea tree oil, or in combination with
19 another antifungal in diluted formulation.

20 Now, I'm going to discuss the physical
21 chemical characterization of tea tree oil. And for
22 the purpose of this discussion, we are talking

1 about tea tree oil derived from the native
2 Australian tree, *Melaleuca alternifolia*, just to
3 make the terminology straight because there have
4 been usage of the term "tea tree oil" to include
5 oil derived from other plants.

6 For tea tree oil from *Melaleuca*
7 *alternifolia*, there are two very similar standards
8 to assure the quality of the oil. One is
9 international and the other is from Australia, but
10 they're very similar.

11 Tea tree oil is a mixture of organic
12 compounds with over 90 percent of the contents
13 fully characterized as monoterpenes,
14 sesquiterpenes, and their associated oxygenated
15 analogues. This slide shows some of the examples
16 with strengths as recommended in those standards.

17 Impurities in tea tree oil, the likely ones
18 are the one from the usual botanical sources, like
19 heavy metal impurities from the source material for
20 extraction, or the bioburden, like microbial
21 content.

22 Now, with tea tree oil, the impurities are

1 expected to be low because the steam distillation
2 process would not concentrate the heavy metals.

3 Also, tea tree oil has antimicrobial properties.

4 In conclusion, for physical and chemical
5 characterization, tea tree oil, when we're talking
6 about that which meets the international or
7 Australian standards, is a well-characterized
8 natural product from a native Australian tree,
9 *Melaleuca alternifolia*, produced by a relatively
10 simple extraction process which is steam
11 distillation.

12 Its major components have been fully
13 characterized and quantified to account for over
14 90 percent in a typical sample, again, standards
15 available to assure the quality control and natural
16 variations.

17 As to the minor components accounting for
18 the less than 10 percent of tea tree oil content,
19 they are basically of the same type of terpenoids
20 with similar physical chemical properties as those
21 major components. And complete characterization or
22 quantitative analysis of all the components is not

1 feasible.

2 Now, I'm going to go over the nonclinical
3 assessment for tea tree oil. Pharmacology -- as we
4 discussed earlier, tea tree oil has antimicrobial
5 properties. In this nomination for nail fungus, we
6 actually focus on the antifungal properties of tea
7 tree oil. These have been documented in a number
8 of in vitro and in vivo nonclinical studies.

9 As to acute toxicity, when administered
10 orally, the LD50 for tea tree oil in rats is
11 between 1.7 to 2.3 grams per kilo while rats dosed
12 with a lower dose, such as 1.5 grams per kilo,
13 would appear lethargic and ataxic. And it showed
14 depressed activity levels.

15 For dermal application, with 5 grams per
16 kilo of tea tree oil, experiments have shown in
17 rabbits 2 deaths out of 10 treated animals. And
18 with a lower dose, 2 grams per kilo, it caused
19 slight diarrhea in the rabbits. We have not found
20 repeat-dose toxicity data for tea tree oil.

21 For mutagenicity, tea tree oil and many of
22 the components were negative in the Ames test. One

1 of the compounds, terpineol, exhibited mutagenicity
2 in the Ames test.

3 Other in vitro systems such as the human
4 lymphocyte micronucleus and chromosome aberration
5 tests showed that tea tree oil was not genotoxic.

6 Again, in vitro studies of some of the
7 components including cineole, d-limonene, linalool,
8 phellandrene, beta-pinene, beta-myrcene, these were
9 not genotoxic in in vitro tests with mammalian
10 cells.

11 One of the components, beta-myrcene, was
12 also studied with oral administration in rats. And
13 it was shown that it was not genotoxic in bone
14 marrow cells. So overall, available data on the
15 mutagenicity of tea tree oil and individual
16 components indicates low mutagenic potential.

17 Regarding developmental and reproductive
18 toxicity, there are no published studies conducted
19 with tea tree oil available.

20 Two of the components, alpha-terpinene
21 induced delayed ossification and skeletal
22 malformation in an oral embryofetal and

1 developmental study in rats while another,
2 beta-myrcene, caused a higher resorption rate and
3 higher incidence of retardation and fetal skeleton
4 anomalies in the oral embryofetal and developmental
5 studies in rats.

6 The limited data from the oral rat
7 embryofetal developmental studies conducted with
8 those two components just mentioned suggest that
9 tea tree oil may pose embryofetal toxicity when
10 ingested orally at relatively high doses. However,
11 the limited data are not adequate to make a final
12 determination.

13 For carcinogenicity, also, there are no
14 published studies conducted with tea tree oil
15 available.

16 One of the components, alpha-terpinene, was
17 not carcinogenic when given intraperitoneally in a
18 mouse study. But this is not a standard
19 carcinogenicity study design.

20 Another component, beta-myrcene, was studied
21 in mice and rats in a two-year oral carcinogenicity
22 study and showed that carcinogen activity was

1 demonstrated in kidneys of rats and in mouse liver.

2 In conclusion for the nonclinical
3 assessment, for acute toxicity, tea tree oil can be
4 toxic when ingested or topically administered at
5 high dose.

6 There's low mutagenic potential for
7 carcinogenicity, developmental and reproductive
8 toxicity. There are no data per se for tea tree
9 oil, but the limited data available for some of the
10 components suggest risks for embryofetal toxicity
11 or carcinogenicity if given orally at relatively
12 high doses.

13 Overall, the limited nonclinical safety data
14 available are not adequate to determine whether
15 neat tea tree oil is safe to use as a bulk drug
16 substance in compounding.

17 This slide deals with human
18 pharmacokinetics. There are no in vivo study
19 reports for human pharmacokinetics to document
20 systemic exposure after application of the
21 components in tea tree oil.

22 There have been in vitro data. Overall,

1 this data from in vitro skin penetration studies
2 suggest that components of tea tree oil can be
3 absorbed after topical application.

4 Under dosing a condition of 10 grams per
5 square centimeter, up to 8 percent of the applied
6 dose could penetrate through the epidermis in
7 vitro.

8 Now, I'm going to turn to human safety data.
9 Adverse reactions from tea tree oil when applied
10 dermally primarily would cause irritant and
11 allergic contact dermatitis reactions.

12 For oral injections, there can be
13 significant toxicity, including central nervous
14 system depression, unsteady gait, abdominal pain,
15 diarrhea, and generalized erythema.

16 There have been reports of some reactions of
17 special concern, including prepubertal
18 gynecomastia, linear IgA disease, as well as
19 stomatitis and colitis.

20 Now, clinical trial data regarding human
21 safety -- there have been dedicated human dermal
22 safety studies on tea tree oil. Both pure and

1 diluted tea tree oil can cause skin irritation.

2 A study with 150 subjects for contact
3 sensitization potential showed about 2 percent
4 sensitization. For phototoxicity and
5 photoallergenicity with tea tree oil, we don't have
6 information.

7 Again, regarding clinical trials, we have
8 not found safety data from clinical trials using
9 tea tree oil in compounded products. Adverse
10 reactions from clinical trials with tea tree oil
11 are based on the use of neat tea tree oil or
12 diluted formulations.

13 Again, these include the reactions described
14 earlier such as irritation, erythema, edema,
15 dryness, itching, and scaling, but systemic
16 hypersensitivity has also been reported.

17 So in conclusion, for human safety, the
18 safety data from use of tea tree oil suggests that
19 systemic administration such as oral ingestion may
20 be associated with significant toxicities.

21 Adverse effects from topical administration
22 are primarily related to irritant and allergic

1 contact dermatitis reactions. Although systemic
2 sensitivity has also been reported.

3 Next, I'm going to turn to a discussion
4 about efficacy in the treatment of onychomycosis
5 with tea tree oil.

6 We have found two randomized, double-blind,
7 controlled clinical trials involving the use of tea
8 tree oil for onychomycosis. One is with a
9 comparison of two topical preparations for the
10 treatment of onychomycosis with the tea tree oil
11 and also with clotrimazole.

12 Another one was on the treatment of toe nail
13 onychomycosis with a combination product having
14 2 percent butenafine and 5 percent tea tree oil in
15 a cream formulation.

16 I apologize in this slide and the next
17 because the order has been reversed. This is the
18 study by Syed, et al. in 1999. It compared
19 2 percent butenafine hydrochloride plus 5 percent
20 tea tree oil in a cream base with placebo cream.
21 And this is for toe nail fungus due to
22 dermatophytes.

1 The treatment was under occlusion 3 times a
2 day for 8 weeks. And at the end of 36 weeks,
3 80 percent of subjects who used the combination
4 cream but none of those that used the placebo cream
5 had overall cure.

6 You may note that, in fact, the placebo
7 cream was a matching cream also containing tea tree
8 oil. This study actually demonstrates
9 effectiveness of the combination product, but does
10 not demonstrate contribution of the 5 percent tea
11 tree oil because, first of all, the placebo was not
12 giving -- patients who use the placebo did not show
13 any overall cure.

14 Also, there's no treatment arm with
15 butenafine hydrochloride alone. Without that, we
16 don't really know whether the 5 percent tea tree
17 oil has contributed to the effectiveness of this
18 combination product or not.

19 This next slide is actually on the study by
20 Buck in 1994. He compared 1 percent clotrimazole
21 solution against neat tea tree oil. The products
22 were administered topically 2 times a day for

1 6 months in patients having toe nail onychomycosis
2 with dermatophytes.

3 At the end of 6 months of therapy, partial
4 or full clinical resolution was reported in
5 61 percent of the subjects treated with
6 clotrimazole and a comparable percent in those with
7 tea tree oil.

8 However, this study did not have a placebo
9 arm, and the clotrimazole solution is not an
10 approved product, so we are comparing it with
11 something that we do not know definitely about
12 efficacy.

13 So unless the tea tree oil is shown to be
14 superior to a product not approved, we really
15 cannot say that it is showing efficacy in
16 onychomycosis.

17 In conclusion, about the efficacy studies,
18 we do have two randomized, double-blind, controlled
19 trials to look at the treatment effect either with
20 neat tea tree oil or in combination with an
21 antifungal for onychomycosis.

22 Unfortunately, these have design problems,

1 and we cannot conclude that tea tree oil is
2 effective either as a neat tea tree oil or has
3 combination to efficacy in combination with another
4 antifungal.

5 There are approved therapies for toe nail
6 fungus, including oral, as well as topical drug
7 products. Among the oral products are
8 griseofulvin, itraconazole, and terbinafine. The
9 topical products include ciclopirox, tavaborole,
10 efinaconazole.

11 This slide is about historical use in
12 compounding. Although tea tree oil-containing
13 products have been available commercially for over
14 three decades, they are available as topical
15 formulations for a wide variety of skin, ocular,
16 oral, vaginal conditions.

17 We couldn't find much in a way of
18 information on pharmacy compounding with tea tree
19 oil.

20 In conclusion regarding the four criteria we
21 use for assessment, tea tree oil meeting the
22 international or Australian standards is considered

1 well-characterized in physical and chemical
2 properties.

3 For topical use, tea tree oil may cause
4 local reaction such as irritation, erythema, edema,
5 dryness, itching, and scaling while systemic
6 hypersensitivity has also been reported.

7 There's a lack of evidence of efficacy in
8 the treatment of onychomycosis with tea tree oil.
9 There's also lack of information on past use of tea
10 tree oil in pharmacy compounding.

11 For these reasons, we do not recommend tea
12 tree oil be included on the list of bulk drug
13 substances to be used in compounding under
14 Section 503A of the Federal Food, Drug, and
15 Cosmetic Act.

16 **Clarifying Questions from the Committee**

17 DR. VENITZ: Thank you, Dr. Ko.

18 Any clarifying questions for Dr. Ko?

19 Dr. DiGiovanna?

20 DR. DiGIOVANNA: Yes, John DiGiovanna. I
21 guess it's my understanding that because this was
22 nominated for onychomycosis, that its topical use

1 for other conditions such as acne where there have
2 been studies published is not something that's
3 considered?

4 DR. KO: Well, we focused on nail fungus
5 because the nomination provided one reference to
6 support its use and the reference is about
7 antifungal properties.

8 In fact, the nomination has not stated
9 explicitly what exactly the proposed uses it has.
10 It states that it has past use including nail
11 fungus, something like that.

12 So back to your question about acne and
13 these other things, we actually did look at them.
14 It's just not in the presentation or in the
15 document that you have.

16 According to a review by Natural Medicines
17 assessed last year, most of the uses that people
18 advocate for tea tree oil lack very good evidence.
19 The three that the review stated that are possibly
20 effective -- and these include the onychomycosis,
21 tinea pedis, and acne.

22 We did review acne and also tinea pedis.

1 Again, those studies have all have design issues,
2 so they actually would still not be able to support
3 efficacy.

4 Now, I can't go through all of them at this
5 point, but if you are interested, we can go offline
6 on that.

7 DR. DiGIOVANNA: I guess what I'm trying to
8 understand is that if we decide that this is not
9 available for compounding, that we decide that on
10 the basis of the information that we have.

11 If we only have the information where it's
12 been evaluated for onychomycosis, we aren't even
13 evaluating where it has been -- the studies that
14 have been done for other indications and then it's
15 not available for any indication topically.

16 Does that mean that, subsequently, if
17 another nominator wanted to come back to the FDA
18 and nominate it, for example for use in acne, that
19 that would be acceptable to do that?

20 DR. KO: Well, that would be again reviewed.
21 As I said, we did review those. It's just not in
22 the document.

1 DR. DOHM: The answer is yes, that if it
2 was -- you could renominate the same substance but
3 for a different use, and then we would consider
4 that nomination.

5 DR. DiGIOVANNA: Then is it clear somewhere
6 that this has been nominated only for that
7 indication and that someone on the outside would
8 know that they could come back for and have, for
9 example, the studies done on acne?

10 DR. KO: I think the nomination documents
11 are in the package, so people can see what has been
12 nominated for the compound at this point.

13 MR. FLAHIVE: This is Jim Flahive. The
14 reviews state at the beginning what each bulk was
15 reviewed for. If you look at the nominations, we
16 try to review what was both nominated as a use and
17 supported.

18 I highly recommend that people look at the
19 nominations because it's not always cut-and-dried
20 to tell what use is someone is trying to nominate.
21 We do our best effort to do that.

22 DR. DiGIOVANNA: So that's kind of why I'm

1 asking this because it includes a mouthwash, and
2 gels, and creams, and a whole variety of things.
3 It does say nail fungus treatment in there, but it
4 also says about use in surgery, and burn care, and
5 dental care.

6 I find it difficult to extract from this
7 exactly what the nomination is. And I guess my gut
8 is assumption is what the FDA is presenting to us
9 is a global presentation.

10 If that's not correct, then I need to
11 understand the information that I'm getting. Do
12 you understand what I mean? And if we decide that
13 this is not going to be available for compounding
14 based upon the onychomycosis failure of efficacy,
15 then somehow it should be clear that the other
16 potential indications weren't assessed.

17 DR. VENITZ: Mr. Mixon?

18 DR. DOHM: I would just mention that the
19 review is clear as to the use it was evaluated for
20 and what was presented with adequate support.
21 That's the source that people could go to, to find
22 out what, in fact, it was evaluated for and then

1 could, of course, renominate the same substance for
2 a different use that it wasn't evaluated for. And
3 we would consider that.

4 MR. MIXON: Yes, and it would be years
5 before it came back up.

6 I just want to remind the voting members of
7 this committee that pyruvic acid was nominated and
8 FDA recommended approval of it.

9 In 16 years, I've never been asked to
10 compound pyruvic acid whereas frequently, we're
11 asked to put tea tree oil in a nail fungus
12 preparation. And here, we are going to lose that
13 for reasons that are totally unclear to me. I know
14 there's no studies, but you know how expensive
15 studies are.

16 Most studies are done by manufacturers who
17 want to bring a \$300-a-month prescription to the
18 market. And the alternatives for nail fungus that
19 are FDA-approved are very expensive, and they
20 are -- for the oral ones, there's a lot of
21 toxicity.

22 You can go on Amazon and buy pure tea tree

1 oil. Here's one right here that says, "Best for
2 skin tag removal, nail fungus treatment,
3 aromatherapy." To me, that's a medical claim.

4 Why tie the hands of the compounder who are
5 just trying to help patients with their nail fungus
6 and let stuff like that go?

7 DR. VENITZ: Dr. Braunstein?

8 DR. BRAUNSTEIN: Yes. I just did a little
9 Google search and tea tree oil is recommended as a
10 topical treatment by Dr. Weil and is listed also in
11 WebMD. That's just two sources, and there's a lot
12 of sources on the web for this. And as we pointed
13 out, as Bill Mixon pointed out, it's available from
14 Amazon for this use.

15 DR. KO: Right. We agree with you that
16 there are many products on the market with tea tree
17 oil, both 100 percent as well as those in other
18 formulations.

19 DR. VENITZ: Dr. Davidson?

20 MS. DAVIDSON: I asked Dr. Axelrad this
21 question before. I'll ask it again. In the case
22 of dietary supplements, there would be nothing to

1 prohibit a pharmacist from going and purchasing a
2 dietary supplement off the shelf, and using that to
3 prepare a therapy for a patient and prescribed --
4 pardon me; that's my background -- by a physician.

5 I'm a little confused about why this is even
6 on the list because if I were going to buy tea tree
7 oil, I would probably get it from all the sources
8 that have previously been mentioned.

9 Is this truly a bulk? And not placing this
10 on the list, does that prevent us from buying pure
11 tea tree oil from CVS, or Amazon, or some place
12 that supplies it as a labeled product to make a
13 preparation?

14 MR. FLAHIVE: This is Jim Flahive. I think
15 that's a great observation, and a key difference is
16 you can buy tea tree oil that's a cosmetic, but
17 we're looking at tea tree oil as a drug.

18 Our review division evaluated tea tree oil
19 and the data for it for its use as a drug and
20 people simply want to make drug claims with tea
21 tree oil that they use as a drug.

22 MS. DAVIDSON: But just to clarify, I still

1 could go buy pure tea tree oil as a cosmetic
2 because it's not a bulk drug substance and use it
3 to prepare a toe nail remedy if directed by a
4 physician.

5 MS. BORMEL: Well, you're talking about
6 buying tea tree oil as a cosmetic and making a
7 compounded drug out of it. What we're assessing
8 here is whether you can use the bulk ingredient for
9 use under 503A.

10 I mean, if this does not go on the list
11 until the time and then it becomes final in a rule,
12 then that particular bulk could not be used in
13 compounding a drug substance. The bulk could not
14 be used to compound a drug under 503A.

15 Right now, you're saying that -- nothing
16 would happen until the rule is final in terms, but
17 yes, eventually, if it's something that is not on
18 the final rule of bulk substances that can be used,
19 you wouldn't be able to use it in compounding a
20 drug product under Section 503A. I mean,
21 availability as a cosmetic, availability as a
22 dietary supplement, they're regulated in different

1 manners.

2 MS. DAVIDSON: I just wanted to confirm
3 because that conflicts a little bit with what we
4 had heard in a previous meeting about going and
5 purchasing dietary supplements, and reformulating
6 them.

7 DR. DOHM: One thing I'd like to add to that
8 is there is a provision of the statute that allows
9 for compounding from ingredients other than bulk
10 drug substances. That's not at issue today and not
11 being addressed today. But there is another
12 provision with respect to that.

13 MS. DAVIDSON: Okay. I'm purely asking the
14 question based on access. If someone wanted to go
15 buy pure tea tree oil and paint their toe nails
16 with it, there's nothing in our decision today that
17 would prevent them from doing that.

18 DR. DOHM: Right.

19 MS. DAVIDSON: Okay.

20 DR. DOHM: We're only talking about
21 compounding. I think the discussion that we were
22 talking about in previous sessions -- maybe I'm

1 mistaking what you were thinking about.

2 We did discuss about compounding. If
3 somebody were to buy a dietary or to get dietary
4 supplement ingredients and compound another dietary
5 supplement within the purview of CFSAN regulations,
6 we're not addressing that at all.

7 We're only addressing it in the context of
8 using a bulk ingredient for the drug, compounding a
9 drug under 503A. So remember, dietary supplements
10 have to be for oral ingestion. Cosmetics can
11 affect the structure, the appearance of the skin or
12 something like that.

13 DR. VENITZ: Two more questions. Mr. Mixon?

14 MS. DAVIDSON: Gigi, I think it's my
15 understanding that even if we bought 100 percent
16 pure tea tree oil from Amazon, or a mutual drug, or
17 anybody else, we still couldn't incorporate that
18 into a compound regardless of where it came from.

19 MS. DAVIDSON: I'm just trying to understand
20 where the line is for when something is a bulk drug
21 substance and when it's not. And I think they
22 clarified for me that it's when it's used as a drug

1 regardless of its source. Am I correct?

2 DR. VENITZ: Dr. Pham?

3 DR. PHAM: I was just looking for more
4 clarify on the statement about there being systemic
5 hypersensitivity reported because, right now, I'm
6 kind of leaning towards feeling like the topical
7 may have a place, and there's local irritation side
8 effects. I don't know that those were significant.

9 I'm more concerned about just that one-line
10 bullet point about there being systemic
11 hypersensitivity. What were those types of
12 reactions? Were they respiratory stress, hives?
13 And how often did that occur?

14 DR. KO: I found from, actually, the
15 database from FAERS, the FDA reporting database,
16 information about systemic hypersensitivity in
17 case, which could have been confounded too. That's
18 why we didn't have a lot of further discussion and
19 just mentioned it since it also occurred.

20 DR. VENITZ: Last question, Dr. Jungman?

21 MS. JUNGMAN: So related clarifying
22 questions here, so given that most of the most

1 serious AEs with the substance are related to the
2 oral formulation and that this committee has, in
3 the past, made recommendations that are specific to
4 a particular formulation, I'm wondering would this
5 substance -- and you might be the right person to
6 direct this to.

7 Is there enough of a distinction between
8 the oral and topical formulation that you could
9 make a recommendation like this or is it just
10 you're using the oil either way? And if so, if we
11 were to consider just the topical formulation,
12 would that alter FDA's recommendation in any way?

13 DR. KO: So let me clarify this. So-called
14 oral formulation are basically oral rinses.
15 They're not really for ingestion.

16 DR. VENITZ: Okay. Thank you, Dr. Ko.
17 Let's then proceed with the nominator. We have
18 Dr. Pytlarz from NCPA is going to be giving the
19 nominating presentation.

20 **Presentation - Alexander Pytlarz**

21 DR. PYTLARZ: Good afternoon. Thank you for
22 your time today. The first couple of slides are

1 the origin, and the previous presenter did a well
2 job, so I'm going to kind of skip right through
3 those and get to the heart of the presentation.

4 He mentioned the physical characteristics as
5 well as the distillation process and the chemical
6 component, so I won't focus on that too much.

7 This was an in vitro study that we found
8 that talked about tea tree oil and the use of
9 exposure to a couple of the fungi, and bacteria,
10 and whatnot. And in this study, they looked at the
11 minimum inhibitory concentrations and the minimum
12 bacterial fungicidal concentrations of tea tree oil
13 exposed to those.

14 In this study, they reviewed a few modes of
15 measurement to determine the effectiveness of this
16 tea tree oil. So again, I won't harp on the slides
17 on these but just focusing on seeing that even
18 small amounts of the tea tree oil, when done in
19 vitro, had significant benefits over placebo . You
20 can see the slides that go into the details of each
21 of those.

22 As I mentioned, it talked about the

1 effectiveness on microbe respiration and again, the
2 benefits of the tea tree oil, even at those small
3 concentrations, had positive aspects and impact on
4 that, as well as cell wall integrity.

5 I want to get more into the discussion of
6 human use which is important for our discussion
7 today. As the previous reviewer said, there's
8 information out there that does show effectiveness
9 and possible effectiveness not only in the fungal
10 nail infection but in use in acne and in use in
11 athlete's foot. And the rest of the presentation
12 is here to focus on all aspects of that.

13 I did speak to the presenter of this, NCPA,
14 and it was the intention of tea tree oil to be
15 available to compounders in all aspects and not
16 just for use in fungal nail infection. So to the
17 question about that, at least that was the
18 intention for NCPA for the submission of this bulk
19 product.

20 As was mentioned in the previous presenter
21 about the Buck study that was done in 1994. And it
22 was concluded that because clotrimazole 1 percent

1 solution is not an approved treatment, it kind of
2 makes the study a little flawed. But please note
3 that back in 1994, there actually were no topical
4 approved treatments of nail fungus for medication
5 use out there.

6 So the effectiveness can be hopefully
7 concluded from that, that the approved treatments
8 of topical fungal nail fungus was in 1994, 2014,
9 and again 2014 respectively, so kind of something
10 to keep in mind that even that study was done,
11 there was no approved topical treatment.

12 There was a little bit of concern with that
13 in that study that the numbers were a little bit
14 flawed, but the authors of that study did come out
15 and say that there was a 35-percent loss within
16 that study due to culture follow-up.

17 We kind of reviewed that study on our own
18 and looked at it from a standpoint of how many were
19 actually enrolled, how many were lost, how many
20 patients were then left over, and comparing that
21 clotrimazole 1 percent to the tea tree oil at
22 100 percent.

1 You can see that the effectiveness now at
2 the bottom was pretty comparable at 11 percent for
3 clotrimazole 1 percent, and tea tree oil at 7, as
4 well as for culture negativity. And then full or
5 partial resolution was about 61 or 60 percent
6 respectively. The study did provide some useful
7 information.

8 Again, the study did not compare anything
9 with what was approved, but of course, at the time,
10 there was no FDA-approved information on that. The
11 study does provide information that tea tree oil
12 may be helpful in relieving symptoms, improving
13 nail appearance, and possibly assisting with
14 mycological cure.

15 Of course, as was approved in 1999 and
16 further, there are nail lacquers that represent an
17 option for physicians to administer topical
18 formulations that allow the vehicle to evaporate
19 and form an occlusive layer that allows for direct
20 administration of tea tree oil and other components
21 directly to the area to help with that.

22 Compounding pharmacies really give

1 prescribers the option to include tea tree oil in
2 preparations in combination therapies.

3 At the time of our submission of slides, we
4 didn't have the opportunity to this, but on the
5 21st, NCPA received a written letter from a local
6 physician, and I've got copies available for anyone
7 that's interested, who wrote, "As a practicing
8 physician since 1995, I've had the opportunity to
9 treat fungal infections with a vast array of oral
10 and topical agents.

11 "The use of tea tree oil has become an
12 integral part of topical therapy in my practice due
13 to its safe and effective nature and to remove it
14 from the list of available compounds would be a
15 detriment to my patients." Signed, Dr. William
16 Knudson, dated June 21st of this year, a physician
17 testimonial that I have regarding the use of tea
18 tree oil.

19 Again, the second study that was presented
20 looked at the double-blind, placebo-controlled
21 comparing placebo with the combination tea tree
22 oil.

1 I found it interesting that the previous
2 presenter said that there was no studies out there
3 that compared the safety of compounded
4 preparations, but this really is a compounded
5 preparation when you're combining two or more
6 products together in any lab. That's basically the
7 definition of compounding.

8 We do have some information about the safety
9 of it out there. And we agree that there
10 was -- it's hard to conclude because there was no
11 comparison information, but we want to use this
12 information, too. And this is just an outlay of
13 the way the study was laid out in the treatment
14 program.

15 But I want to really focus on the area that
16 there was about an 80-percent cure rate with this
17 with minimal side effects. And when you take this
18 information and you -- especially in our world of
19 compounding where there aren't a lot of -- we
20 recognize that there aren't a lot drug-drug trials
21 out there that have the information. You've got to
22 take pieces of information and utilize it in

1 different areas.

2 When you'd look at that cure rate, and you
3 compare it to FDA-approved products that is down in
4 the bottom graph, and you show mycological cures of
5 55, and 60, and 32 percent or overall cure rates of
6 anywhere from 1 to 52 percent, and you compare that
7 against a combination therapy that does have tea
8 tree oil that rates around 80 percent, you feel
9 that there is some effectiveness that can be
10 concluded from the use of that.

11 Again, we wanted to touch on a couple other
12 areas because, again, this wasn't just completely
13 focused on nail fungus. We did find a couple of
14 study on the effectiveness with athlete's foot, and
15 this was again a randomized placebo-controlled
16 study that used tea tree oil at 25 and 50 percent
17 with a third arm of being placebo.

18 It was a 4-week trial that looked at the
19 clinical response of that, and again, just a layout
20 of the way the patients were enrolled and the
21 different outcomes that were related to this.

22 Again, this information was provided to you

1 ahead of time, so I'm sure you've had the
2 opportunity to look at that.

3 Again, looking at the tables, you can see on
4 table 2, over to the very right, again, the
5 mycological cure rates for placebo versus 25,
6 versus 50 percent.

7 The authors were able to conclude that the
8 tea tree oil did have a higher rate of cure when
9 compared to placebo, and that was considered
10 statistically significant.

11 The clinical response at the end of 4-week
12 treatment with four patients was significantly
13 higher, and they felt that the effective cure rate
14 was appropriate with tea tree oil.

15 Again, the last part with the efficacy in
16 acne, this was a review study that was looked at on
17 the efficacy, tolerability, and potential modes of
18 action.

19 The authors looked at seven studies for the
20 use of tea tree oil in acne. Five of those seven
21 studies were looking at tea tree oil at greater
22 than 5 percent versus -- the previous presenter

1 talked about large, large amounts of tea tree oil
2 which, at least, in compounding is not really
3 utilized.

4 We're talking about, again, that 5 percent
5 range where they looked at that over a 4- to 8-week
6 treatment area. And the summary slide, again, will
7 provide some information, but the author suggested
8 that tea tree oil applied twice daily for multiple
9 weeks is likely to reduce the number of lesions
10 seen in acne.

11 I want to focus on really just the first
12 slide or the first line items that talk about
13 comparing tea tree oil 5 percent with benzoyl
14 peroxide and the efficacy, 45 versus 29 percent,
15 but the big thing that jumps out to me is the
16 tolerability and the frequency of adverse effects
17 where benzoyl peroxide is around 79 percent versus
18 tea tree oil at 44 percent.

19 Here, to present some information about the
20 safety of that product even at a 5 percent range,
21 of course, the outcomes of this both show that
22 treatments were significantly reduced and

1 comparable.

2 The study concluded that -- they looked at
3 five of the seven studies, and they reported
4 adverse effects. One of the seven studies reported
5 no serious adverse effects, but the rates of
6 adverse reactions were actually higher and really
7 the mainstay product for acne, which is benzoyl
8 peroxide, compared to tea tree oil and that
9 concluded tea tree oil was similar tolerability
10 with other facial acne medications.

11 One final point about safety, a second
12 review that was done -- and this is a quote from
13 the study -- that looked at the rationale for
14 continued use of oil rests largely on the apparent
15 use for oil over almost 80 years.

16 The authors examined oral toxicity, included
17 that incidence of oral poisoning in children and
18 adults resulted in no deaths and everybody
19 responded and recovered, as well as dermal
20 toxicities really rarely ever happened.

21 I think for compounders, we are looking for
22 the use of this in topical applications, not oral

1 for sure.

2 So just some final words, of course, they
3 were already expressed again, but just to reiterate
4 the importance that tea tree oil is readily
5 available without a prescription as was mentioned.

6 Tea tree oil really provides physicians and
7 allows patients access to alternative methods that
8 will help improve medical conditions, allow
9 physicians to provides patients with options when
10 they failed standard treatments, and again as was
11 mentioned, to allow options where it's not systemic
12 medications that have the potential for other
13 adverse effects that wouldn't be seen in tea tree
14 oil, and lastly, because of what pharmacists can do
15 to work with our patients to help them prevent any
16 kind of adverse effects that may be seen with
17 inappropriate use or storage and help prevent any
18 incidental side effects.

19 I thank you for your time, and I'm happy to
20 try to answer any questions you may have.

21 DR. VENITZ: Thank you, Dr. Pytlarz.

22 Any questions? Any clarifying questions by

1 the committee?

2 (No response.)

3 DR. VENITZ: I see none. Thank you, again.

4 DR. PYTLARZ: Thank you.

5 DR. VENITZ: We appreciate it.

6 **Committee Discussion and Vote**

7 DR. VENITZ: Now, we are supposed to have an
8 open public hearing, but we have no open public
9 hearing speaker, so we're going to move right into
10 our discussion and vote.

11 I'm looking for any discussion items.

12 Dr. DiGiovanna?

13 DR. DiGIOVANNA: Yes, John DiGiovanna. I
14 appreciated the last presenter showing some of the
15 data in a little bit more detail. It reminded
16 me -- and I'm not certain that I'm exactly accurate
17 about this, but it did remind me that it was 1999
18 that Penlac was approved. It reminded me that I
19 was on the advisory committee at the time.

20 There was a discussion, my recollection,
21 that it shouldn't be approved because its efficacy
22 was so poor. However, my recollection is that I

1 argued at the time that there were no alternatives
2 and that for a large percentage of the population,
3 more so as the population aged, that has poor
4 circulation in lower extremities from diabetes and
5 congestive heart failure, that chronic dermatophyte
6 infections in part that spurred and difficult to
7 treat because of involvement of the nails,
8 onychomycosis, leads to a scenario where frequent
9 breaks in the skin lead to recurrent cellulitis,
10 and lymphangitis, and progressive difficulty, and
11 sometimes is really tremendously debilitating and
12 leads to mortality and loss of limbs.

13 This is a chronic problem and having a
14 topical therapy for individuals that couldn't
15 tolerate systemic therapy because of other
16 medications was a real need.

17 We didn't need to demonstrate so much that
18 it was going to cure everyone or cure most of the
19 individuals, but managing the disease was a
20 distinct advantage.

21 I'm sure it wasn't because of my comments,
22 but many people recognized that there was an

1 advantage for having a topical preparation for
2 this. And there are others now. However, there
3 are many patients who do not respond to those and
4 having an additional therapy would be often a
5 reasonable thing to have.

6 For tea tree oil, I understand, from the
7 FDA's presentation, the toxicity is minimal. It's
8 with the systemic utilization of the preparation,
9 which probably is not related to this indication.
10 It would seem to me that, if we could recommend
11 that this be available, limited as a topical,
12 considering it is so widely used in so many
13 cosmetics and would have a real indication here for
14 a population that could have some use for it over a
15 long period of time, I think it would be a benefit.

16 Another reason why it's useful to have an
17 additional treatment for a chronic infectious
18 disease is because the organisms get resistant to
19 the things that we use.

20 When someone has a condition like this for
21 many decades, they've used most of the things that
22 are available. I'm sure that most of you don't go

1 through the dermatologic literature as a regular
2 basis, but some of the things that people have
3 brought up and studied are, for example, treatments
4 like Vaseline for treatment of the nails and a
5 variety of topical agents that you wouldn't
6 necessarily think would be of benefit and may not
7 be of benefit.

8 There's a great need for people to try to
9 manage these chronic infections. And my
10 perspective seems to be that the toxicity of this
11 seems to be limited. The safety seems to be good,
12 and I think there may be a role for it.

13 DR. VENITZ: Thank you. Any other comments?

14 (No response.)

15 DR. VENITZ: So is everybody ready for the
16 vote? You've got the go-ahead.

17 DR. KO: I would like to address some of the
18 issues brought up by the nominator. This is in
19 regard to the other indications that were brought
20 up, and also, Dr. DiGiovanna asked about them.

21 Regarding tinea pedis, the discussion was
22 brought out on the Satchell study. Now, the

1 nomination for tea tree oil that we have is for a
2 strength of 5 to 10 percent whereas where the
3 Satchell study used tea tree oil with 25 percent
4 and 50 percent, so we're not exactly dealing with
5 what is being nominated.

6 The other indication that was discussed was
7 on acne. Studies regarding tea tree oil in
8 comparison with benzoyl peroxide was brought up.
9 And yes, there was a study showing that it was
10 having percentage reduction in total lesions.

11 On the other hand, there was also another
12 study comparing 5 percent tea tree oil to benzoyl
13 peroxide that showed that it was inferior. In
14 addition, there was another study that showed tea
15 tree oil being inferior to an unapproved product as
16 well.

17 I think we haven't fully known the efficacy
18 of tea tree oil in these other indications, and so
19 that's why we haven't actually put those into the
20 review package.

21 DR. VENITZ: Okay. Thank you, Dr. Ko.

22 Any final comments? Yes, Dr. Pham?

1 DR. PHAM: I appreciate all the context. I
2 do think, though, that when we were talking about
3 the tea tree oil against the clotrimazole -- and
4 the historical context definitely helps -- it's not
5 like clotrimazole is placebo here.

6 It is also an active antifungal agent.
7 Obviously, its absorption into that site is
8 probably questionable, but the fact that it was not
9 inferior to me still feels like a comparable
10 conclusion.

11 I'm just curious, and I don't know if this
12 information is available, whether there's actually
13 that much of a fluctuation in strength that's being
14 compounded. Can it can go from 5 to 25 percent?
15 I'm not sure who would be best be able to speak to
16 that.

17 DR. VENITZ: I'm calling back our nominator.

18 DR. PYTLARZ: Thank you. You're asking the
19 question that if it's available from 5 to
20 25 percent?

21 DR. VENITZ: Introduce yourself again,
22 please.

1 DR. PYTLARZ: Thank you. Alexander Pytlarz
2 from the National Community of Pharmacists
3 Association.

4 Just to understand the question, were you
5 asking if it's available in strengths of 5 to
6 25 percent?

7 DR. PHAM: Yes, I was just wondering if
8 there was kind of like an industry standard that
9 limited the frequency. Like, in the frequency that
10 you see, is it pretty much a tighter control than
11 that or can it have that variable of a strength?

12 DR. PYTLARZ: In my experience from the
13 physicians that we've worked with, it ranges
14 anywhere from about 5 to 30 percent, 5 to
15 25 percent, yes.

16 I guess it's the experience of the physician
17 when they've seen it used, in addition, when it's
18 combined with other products like clotrimazole or
19 terbinafine and stuff, they might reduce it.

20 DR. VENITZ: Thank you.

21 Are we ready for the vote then? This time
22 my preliminaries are much shorter than usual. I

1 don't know why. If there's no further discussion,
2 we will now begin the voting process. Please press
3 the button firmly on your microphone that
4 corresponds to your vote.

5 (Vote taken.)

6 DR. HONG: Tea tree oil, we have 8 yeses,
7 2 nos, and 1 abstain.

8 DR. VENITZ: Let's go around the table. I
9 think we're going to start with Dr. DiGiovanna at
10 this time.

11 DR. DiGIOVANNA: I voted yes. I think that
12 with the large percentage of the population that
13 battles dermatophytes in this area that have
14 frequent resistance to the available therapies and
15 the limited number of available therapies, I think
16 there's a potential utility for this.

17 I think that the FDA showed quite well that,
18 topically, there's very little adverse events that
19 have been observed, and it's widely available. And
20 I think, as a topical agent, there's a role for it
21 so I voted yes.

22 DR. GULUR: Padma Gulur. I voted yes as

1 well, for it's a well-characterized substance, and
2 it is widely available. The toxicity data
3 presented was minimal.

4 While there may be some questions with
5 regards to the efficacy, there is still data
6 available that it is showing some efficacy in that
7 area. And I feel like, given all of these
8 considerations, it should be added to the list.

9 DR. VENITZ: This is Jurgen Venitz. I voted
10 yes. I would add to my two previous speakers the
11 longstanding use that has been around since '82,
12 maybe even longer than that.

13 MS. DAVIDSON: Gigi Davidson. I voted yes
14 for the reasons previously stated. I also think
15 there's a pretty good body of evidence to support
16 other multiple indications that weren't mentioned
17 here like anal fissures and seborrheic dermatitis.

18 I also wanted to recognize what the
19 presenter brought out at the conclusion of his
20 presentation that the triad, the
21 prescriber/pharmacist/patient relationship, could
22 be a better arena to prevent misuse of OTC

1 products, that this would be a very carefully
2 controlled environment to prevent misuse.

3 I would qualify all these statements by
4 suggesting that if it is added to the list, it be
5 limited strictly to topical use.

6 MR. HUMPHREY: William Humphrey. I voted
7 yes for many of the same reasons already stated.

8 DR. HOAG: Steve Hoag. I voted abstain
9 because I support its use topically, but in other
10 routes, I'm not so sure. It may not be
11 appropriate, but for topical use, I would support
12 its use, so I kind of split the difference.

13 MS. JUNGMAN: Elizabeth Jungman. I voted no
14 because I didn't find the evidence of effectiveness
15 compelling in light of other alternatives. I will
16 qualify that, though, by saying that I considered
17 only the nomination that was included in the
18 briefing documents.

19 If there are other indications for which
20 there is more compelling evidence of effectiveness,
21 that wasn't part of my vote.

22 DR. PHAM: Katherine Pham. I voted yes. I

1 found that the comparison to other active
2 antifungal agents was enough for an indication that
3 is difficult to treatment to begin with and that
4 even the FDA-approved therapies can sometimes fail,
5 that this could be another alternative.

6 I would hope that it was being used for
7 refractory use, but I know that we can't control
8 for that here. I was a little concerned still by
9 the multiplier of strength that can be prescribed.

10 I don't know that the evidence presented is
11 compelling enough to say that it should not just be
12 limited topical but also to its strengths, probably
13 like 10 percent or less, and I'm not in any place
14 to say that. But if it did get brought back for a
15 topical use for other indications, it would also be
16 helpful to see potentially some recommendations
17 steering towards optimal concentration.

18 DR. VAIDA: Allen Vaida. I voted yes,
19 although with other drugs on the market, I usually
20 don't vote yes for things like this, but I really
21 didn't think there was a strong case against
22 safety, that this was an unsafe product. And I

1 know this is oftentimes a tough condition to treat.

2 DR. CAROME: Mike Carome. I voted no
3 primarily because I think there's insufficient
4 evidence that it's effective for the proposed use
5 that we were asked to consider.

6 DR. WALL: Donna Wall. I voted yes for the
7 reasons previously stated. Again, this is yes for
8 topical use only.

9 DR. VENITZ: Thank you. We are almost done,
10 but before we can really wrap it up, we're going to
11 take a break. So I want to remind everybody on the
12 committee not to talk about any of the topics that
13 have been discussed as a committee. And let's all
14 reconvene at 3:45 p.m. for our last session.

15 (Whereupon, at 3:35 p.m., a recess was
16 taken.)

17 DR. VENITZ: Let's reconvene the meeting,
18 please.

19 Before we begin the last session, I want to
20 introduce our newest addition, a special government
21 employee who will be part of our discussion. He is
22 Dr. Jeffrey Brent, distinguished clinical professor

1 of medicine at the University of Colorado, and he
2 will help us on the DMPS topic. Thank you.

3 We will now continue with the FDA
4 presentation first. And I'm asking Dr. Suh, who is
5 a clinical team leader in the Division of
6 Hematology Products, to give us the lead.

7 **Presentation - Kathy Robie Suh**

8 DR. SUH: Good afternoon. My name is Kathy
9 Robie Suh. I'm a clinical team leader in the
10 Division of Hematology Products in the Office of
11 Hematology and Oncology Products in CDER.

12 Today, I will present the assessment for
13 dimercapto-1-propanesulfonic acid, which I will
14 refer to as DMPS in this presentation. This slide
15 shows the review team for this nomination. The
16 DMPS nomination is for the use, treatment of heavy
17 metal poisoning. The applicable routes of
18 administration for the nomination are oral, and IV,
19 and intramuscular injection.

20 The materials received for this nomination
21 consisted of literature publications which were
22 mostly anecdotal case reports and uncontrolled

1 series of cases of exposures to various heavy
2 metals in patients who were treated with DMPS. The
3 available information for the assessment was
4 limited, but what was available was reviewed.

5 No product containing DMPS is marketed in
6 the US. The available chemistry information for
7 DMPS was obtained from the Heyl Scientific Product
8 Monograph, which is a document that has information
9 regarding a DMPS product that is marketed in
10 Germany.

11 FDA does not have access to the information
12 used to support the market approval of the European
13 DMPS product.

14 DMPS is a chemically-synthesized small
15 molecule. It is usually supplied as its sodium
16 salt. It is non-hygroscopic and exists as the
17 monohydrate.

18 DMPS sodium salt monohydrate has a molecular
19 weight of 228.3 Daltons. The monohydrate is stable
20 in the crystalline form. It's relatively stable in
21 aqueous solution, but it's labile to oxidation.

22 The Heyl Monograph states DMPS is purified

1 by release from the lead salt. There are potential
2 in-process impurities including lead, allyl
3 bromide, allyl sulfonic acid, and
4 2,3-dibromopropane-1-sulfonic acid.

5 Potential heavy metal contamination can be
6 monitored using USP compendial methods. However,
7 as you know, in the U.S., compounding regulations
8 do not require evidence of adherence to good
9 manufacturing process requirements, so there's no
10 assurance that the in-process levels of impurities
11 do not exceed safe levels.

12 These next two slides summarize available
13 animal and nonclinical information for DMPS, again,
14 based on the German product monograph and also a
15 2009 World Health Organization document.

16 DMPS chelates heavy metals, but the
17 mechanism of action is not fully characterized. It
18 increases urinary elimination of arsenic and
19 interferes with arsenic methylation.

20 For mercury, it promotes excretion and
21 protects against mercury-induced renal damage by
22 inhibiting mercury accumulation in renal proximal

1 and distal tubular cells.

2 Administered intravenously, it mainly
3 distributes in plasma and kidneys and has an
4 elimination half-life of about 20 to 60 minutes.

5 In nonclinical studies, DMPS has relatively
6 low acute toxicity and relatively low chronic
7 toxicity in dogs and rats. There's no evidence of
8 adverse effects on cardiovascular,
9 gastrointestinal, or renal systems. There are no
10 data available on central nervous system or
11 respiratory system effects.

12 DMPS is not mutagenic in the Ames test and
13 it shows no reproductive toxicity or
14 teratogenicity. These toxicity assessments do not
15 address the potential toxicities of any potential
16 impurities such as, for example, lead or allyl
17 bromide, which is a known mutagen. There is no
18 information available on carcinogenicity of DMPS.

19 This slide summarizes the safety information
20 that we know. Exposure to DMPS is not without
21 risk. There have been cases of serious skin
22 reactions, including the case of Stevens-Johnson

1 syndrome in an 11-year-old boy and one death due to
2 severe diffuse desquamation in a patient who
3 received DMPS.

4 The most common reported adverse reactions
5 are dermatologic reactions, nausea and vomiting,
6 hypotension, increases in serum transaminases,
7 transient bronchospasm, fever, and leukopenia.
8 Most reported reactions have been typically mild or
9 moderate in severity.

10 This slide summarizes the clinical
11 evaluation of effectiveness. There are a number of
12 publications of clinical experience with DMPS in
13 the literature for various uses, including the uses
14 listed here.

15 Most of the reports are uncontrolled
16 investigations or anecdotal cases and are cases of
17 treatment of various heavy metal exposures.

18 The literature reports do not include
19 sufficient information to reliably evaluate the
20 effectiveness of DMPS for treating heavy metal
21 poisoning, though as mentioned earlier, the
22 nonclinical studies clearly establish that DMPS can

1 chelate heavy metals. The reports of use in humans
2 do not allow a conclusion of a clinical benefit of
3 administration of DMPS to people.

4 Most of the studies described a single or
5 group of persons with exposure to heavy metals who
6 are given DMPS and show an increase in excretion
7 with those metals.

8 Though symptoms are sometimes described, the
9 symptoms are non-specific such as fatigue, memory
10 loss, headache, and change in those symptoms, if
11 it's documented, is not shown to correlate with
12 degree of metal excretion.

13 Most series lack controls, and where
14 controls are used, the studies do not adequately
15 establish baseline characteristics, do not control
16 for factors such as effects of supportive care such
17 as the hydration, removal from the source of
18 exposure to heavy metals, for instance. Most of
19 these studies do not include a clearly stated
20 measure of treatment success.

21 There are no adequate scientific studies
22 that demonstrate the effectiveness of DMPS as used

1 in drug products for the treatment of heavy metal
2 poisoning or other uses.

3 There are FDA-approved drug products for
4 treatment of heavy metal poisoning as listed in
5 this slide. These drug products were approved on
6 the basis of safety and efficacy data submitted to
7 the Agency to support adequate labeling for the use
8 of these agents for the treatment of toxicity due
9 to the various heavy metals as indicated.

10 The drug products include calcium disodium
11 versenate for lead, Chemet or succimer for lead,
12 BAL for arsenic, gold, and mercury poisoning,
13 Cuprimine, a penicillamine for Wilson's disease.
14 It's also approved for cystinuria and active
15 rheumatoid arthritis and trientine approved, a
16 second line in Wilson's disease.

17 This slides summarizes the historical use of
18 DMPS in compounding. At the 1998 meeting of the
19 Pharmacy Compounding Advisory Committee, it was
20 stated that compound dates to the mid-1980s.

21 In the literature, we find clinical use of
22 DMPS mentioned as early as 1958. Just internet

1 searches, just looking at intended uses implied or
2 asserted on those sites, seems to focus on two
3 things: this very large representation of
4 treatment of persons with presumed mercury toxicity
5 due to mercury amalgam dental fillings. And also,
6 there are some mention of treatment of persons with
7 autistic disorders.

8 In conclusion, our review has found that
9 DMPS is well-defined and can be identified
10 consistently, but manufacture may leave residual
11 impurities including lead, and we do not know the
12 levels of these in compounded products.

13 Clinical investigation of use of DMPS has
14 not been adequate to establish safety, and there's
15 no clear evidence for clinical benefit of DMPS as
16 currently used.

17 There are FDA-approved medications available
18 for treating heavy metal poisonings. Historical
19 use dates to the 1950s.

20 In conclusion, based on the information that
21 we have, we recommend that DMPS not be included on
22 the list of bulk drug substances that can be used

1 in compounding under Section 503A of the Federal
2 Food, Drug, and Cosmetic Act. Thank you.

3 **Clarifying Questions from the Committee**

4 DR. VENITZ: Thank you, Dr. Suh.

5 Let me ask the first questions. The
6 uncontrolled and anecdotal reports that you
7 reviewed -- what was the preferred route of DMPS
8 administration?

9 DR. SUH: In most of the administrations,
10 the route was oral. We see a lot of oral
11 administration in the mercury amalgam studies, but
12 there also were parenteral administrations.

13 DR. VENITZ: Were they single-doses or were
14 they repeat doses?

15 DR. SUH: Some were single-dose, and some
16 were multiple dose. Many of the studies looked at
17 administration of a dose and then urinary excretion
18 of the heavy metal.

19 Maybe one thing to note is that even in
20 cases where the agent was being given, the DMPS was
21 being given to treat, let's say, mercury poisoning
22 due to dental amalgams, even in studies where some

1 patients did not even have such amalgams, an
2 increase in excretion was seen. So the efficacy of
3 the treatment really has not been established in
4 any of those controlled studies.

5 DR. VENITZ: Thank you. Then my second
6 question; in the approved agents right now for
7 lead, arsenic, and mercury poisoning, how were they
8 approved? What clinical evidence did support their
9 role?

10 DR. SUH: Well, the approvals date, I
11 think -- our earliest approval is BAL, I think,
12 which was approved back in 1945. And then there, I
13 think, in 1953, we had versenate, calcium disodium.

14 DR. VENITZ: What they did actually look at
15 clinically?

16 DR. SUH: There are studies that provide
17 sufficient data to support the labeling of the
18 product. And this both has to do with a
19 demonstration of efficacy, as well as a
20 demonstration of safety for the product as
21 marketed.

22 DR. VENITZ: Was efficacy defined as

1 increased excretion of the heavy metals or did they
2 look at clinical symptomatic?

3 DR. SUH: Excretion; excretion is measured.

4 DR. VENITZ: Okay. Thank you.

5 Any other questions? Dr. DiGiovanna, did
6 you want to --

7 DR. DiGIOVANNA: Yes, John DiGiovanna. I'm
8 not familiar with the management of this group of
9 diseases, but are the approved medications useful
10 for all of the heavy metals or is there an unmet
11 need? Are there some toxicities that are not
12 managed by the approved drugs?

13 DR. SUH: If you look at the literature,
14 you'll certainly find -- now, I'm thinking about
15 U.S. use and U.S. labeling. You find that some
16 products are used for agents for treatment of
17 toxicity of agents that they're not really approved
18 for, if you will.

19 For instance, BAL is really the only product
20 that is labeled, if you will, for arsenic
21 poisoning. However, penicillamine, if you look at
22 textbooks and reviews, recommendations and things

1 that are also used, we do find that
2 penicillamine and succimer, for instance, are used
3 for arsenic poisoning, though neither one of those
4 had sufficient data to support labeling for those
5 uses. However, those approved products have some
6 quality assurance in the manufacture.

7 DR. VENITZ: Dr. Gulur?

8 DR. GULUR: Of the approved products that
9 are FDA-approved, how many of them can be given
10 intravenously?

11 DR. SUH: Intravenously, as labeled, if you
12 want to speak to what we have labeled, the BAL is
13 administered. It's an oil-based product, and it's
14 administered by deep intramuscular administration.
15 The others are oral products as labeled.

16 DR. GULUR: Do you see an indication,
17 especially with, say, arsenic and mercury in a
18 large dose toxicology or poisoning, where
19 intravenous might offer an additional benefit to
20 intramuscular?

21 DR. SUH: The intravenous
22 administration -- well, let me just say, for BAL,

1 there is known -- it's an uncomfortable one,
2 uncomfortable treatment that has to be given on a
3 repeated base, so we certainly would welcome
4 alternatives. And of course, alternatives would
5 have their own set of adverse reactions or
6 problems. But would an alternative be welcome?
7 Certainly.

8 DR. VENITZ: Dr. Brent?

9 DR. BRENT: I wonder if I could speak to
10 several of these points, and thank you for that
11 nice overview.

12 You had mentioned that you didn't feel that
13 there was sufficient efficacy data for DMPS and
14 that we had other agents for which efficacy has
15 been demonstrated.

16 The answer, the truth is that none of the
17 agents, whether you're talking about the approved
18 ones or DMPS, have ever shown efficacy in terms of
19 outcome for metal poisoning.

20 What they have shown is efficacy in terms of
21 enhancing metal excretion, and DMPS has shown that
22 just as well as the other agents that are currently

1 approved.

2 To get to the question that was raised about
3 intravenous, it's true we do not have now a water
4 soluble intravenous chelator available for serious
5 heavy metal poisoning.

6 This is a really serious deficit. Now, most
7 of the times for metal poisoning, we can get by
8 with oral chelators. We can sometimes give BAL,
9 but BAL, as you mentioned, is very difficult drug
10 to give. It has a high side effect profile.

11 It cannot be given intravenously. It's a
12 deep, painful injection. It's in peanut oil.
13 People can be allergic to it. And it's a very
14 inadequate agent. We also have very little
15 experience with it. It's been used, but there's
16 very little experience with it.

17 DMPS is a good intravenous chelator in terms
18 of enhancing metal excretion. So in that sense, it
19 does fulfill a niche that is currently not filled.

20 Patients who have serious arsenic or mercury
21 poisoning in the acute phase, which is a time when
22 you want to treat them, can have significant amount

1 of gastroenteritis, and it can be very hard to
2 actually get them to take an oral medication.

3 There is this niche in terms of an
4 intravenous chelator that DMPS will definitely
5 fill. All that being said, I'm very sympathetic to
6 your observation that so much of the use of DMPS in
7 this country today, as compounded, is for things
8 like treating people with dental amalgams and
9 treating autism, for which there's no evidence of
10 any efficacy. But in terms of serious heavy metal
11 poisoning, it does potentially, as an intravenous
12 preparation, fulfill a very important niche.

13 DR. SUH: I should say that this nomination
14 came in for all routes of administration and was
15 evaluated as such. And the other point I would
16 make is that in saying that DMPS has not been shown
17 safe and effective, I am not saying that it is not
18 safe and effective.

19 We do though, I guess, also have to be
20 cognizant that, at least, as in the German
21 monograph cited that being as it's purified from a
22 lead-containing source itself. In the compounding

1 arena, we have no knowledge of what the levels of
2 those residual impurities from manufacture might
3 be.

4 DR. VENITZ: Dr. Davidson?

5 MS. DAVIDSON: In veterinary medicine, they
6 use an injectable arsenical to treat heartworm
7 disease in dogs. And we are frequently presented
8 with unintentional self-administration by a student
9 or a veterinarian, and they have become intoxicated
10 with arsenic.

11 In years past, we have researched heavy
12 metal chelators for treatment of those incidents,
13 and we commonly came across a German product, which
14 was available from a company in Houston, Heyltex.
15 And that was listed as the internationally
16 recommended drug of choice for arsenical and
17 mercury poisoning.

18 Is that product still available? Does that
19 represent an alternative to patients in acute need
20 of heavy metal chelation for mercury or arsenic?
21 And what would be the options there?

22 DR. VENITZ: Do you want to answer?

1 DR. SUH: Others may know, but to my
2 knowledge, that European product is still
3 available. And I think when we look at global,
4 worldwide, what might be the preferred drug being
5 marketed in Europe, that very well could be. But I
6 know that if you look in some others, you, again,
7 get -- well, from the U.S. perspective, you get a
8 different first-line, if you will, recommendation.

9 In terms of availability, we've talked some
10 about getting things under IND, so I don't
11 particularly want to rehash those routes. Being
12 able to obtain that product under an appropriate
13 IND setting for emergent use is possible.

14 DR. VENITZ: Dr. Brent?

15 DR. BRENT: Yes, you do bring up a good
16 point, and the product is the European by Heyl as a
17 manufacturer.

18 With regard to this issue about potential
19 lead contamination, Heyl actually has a certificate
20 of analysis that they provide. And there's not
21 much lead in it. It's about 4 micrograms
22 associated with a 2-gram dose.

1 So lead poisoning would not really be a
2 significant issue, particularly since you really
3 only need to use this drug for a very short period
4 of time where you'll get people over the acute
5 phase, and then they can be transitioned to an oral
6 agent. So I don't think the lead contamination
7 issue is a significant issue.

8 DR. VENITZ: Thank you. Any final question
9 for Dr. Suh?

10 (No response.)

11 DR. VENITZ: Thank you, Dr. Suh.

12 Then we have our nominator. Third time is a
13 charm. Dr. Anderson is going to nominate.

14 **Presentation - Paul Anderson**

15 DR. ANDERSON: Thank you. So many, many of
16 the points I'm going to make have been discussed,
17 so I'll go through this reasonably quickly.

18 Under efficacy, I did want to bring up a
19 severe case of mass acute poisoning where DMPS was
20 used and was life-saving. That was in 2003 in
21 Maine, and it was a felonious poisoning of some
22 people at a church. Sixteen people were poisoned

1 and transported to ER.

2 Cary Medical Center was the first place that
3 they went where they were exhibiting all of the
4 signs of acute arsenic poisoning. We were able to
5 contact, first, Dr. Karen Simone, who was involved
6 in the triaging and assessment of the drugs to be
7 used. She's currently the president of the
8 American Academy of Clinical Toxicology.

9 They took the sickest people over to Eastern
10 Maine Medical Center, and they were put on the
11 standard BAL therapy because as was mentioned
12 earlier, BAL is the only one with the on-label
13 arsenic indication.

14 Knowing, as was mentioned, the painfulness
15 of that approach -- the treatment protocol is Q4
16 hours for two days, and then you decrease after
17 that in the acute phase.

18 The worst patients got the BAL right away,
19 and the BAL was failing according to the
20 toxicologist. So the medical resident got a hold
21 of Dr. Simone. She called a group of
22 toxicologists, including Dr. Michael Kosnett, and

1 they recommended to start DMPS.

2 Dr. Kosnett also sent us a note -- neither
3 of these doctors could be here to bring this, but
4 they sent notes for me to present, so this is his.

5 "Thank you for bringing this to my
6 attention." He read the FDA review brief and
7 believes it's incorrect in several instances. And
8 he believes that, in toxicology, there is a clear
9 need for DMPS and would like it to be available.

10 At the time, in 2003, Dr. Kosnett was aware
11 of a compounding pharmacy in California which was
12 actively producing injectable parenteral DMPS and
13 so they were called after hours and were able to
14 get the product because it was already in
15 production.

16 It should be of note, when considering
17 emergency use in an acute arsenic poisoning, for
18 instance, that if a compounding pharmacy had to
19 make product from base raw material, it takes a
20 minimum of 16 days to get the material produced
21 into a parenteral form. So that would be outside
22 the window of use for an acute poisoning.

1 Fifteen out of the 16 were treated with IV
2 DMPS. For reasons that I could not unearth in the
3 investigation, the one patient who was not was the
4 only patient who died out of the acute group.

5 There were no adverse events reported and
6 the Attorney General is on record as confirming it
7 was arsenic poisoning that was done. Essentially,
8 the person laced the coffee with a large, large
9 amount of arsenic.

10 We also sought counsel from UCSF and the
11 Vancouver Poison Control Centers, and obviously the
12 caveat that every poisoning is unique in
13 individual. They also recommend the intravenous
14 route over the BAL, Q4 hours, and then decreasing
15 the dose for a couple of reasons.

16 One is their feeling is that the IV use of
17 DMPS would be a faster and more efficacious way of
18 getting the arsenic out of the body and also, it's
19 also much more tolerated by the patient, pain-wise,
20 et cetera.

21 As was mentioned earlier, there is a large
22 amount of peanut oil in the injection, and not

1 everybody can handle that.

2 The other thing that the poison control were
3 clear on is that the side effect profile are lower
4 with DMPS than BAL.

5 The other thing, as was mentioned just a few
6 minutes ago, is in many cases, especially in
7 arsenic poisoning where there's a great deal of
8 nausea and vomiting going on, the oral products
9 that are available may not be appropriate for use
10 in the acute stage.

11 With regard to safety, as was mentioned in
12 the first setting, a lot of the data -- and in
13 fact, all of the data that we could unearth really
14 comes from European sources because that's where
15 the drug began, as the Heyl monograph was mentioned
16 but others as well.

17 Looking at human safety using the FAERS data
18 system we looked at, there were two cases that came
19 up. Of interest, the first case was a moderate
20 adverse event of a hypotensive crisis when the
21 physician gave the DMPS intravenously too rapidly
22 which later I'll bring up.

1 This is a drug that I've used in clinical
2 practice a fair amount; that is, one of the
3 administration cautions is there's a definite
4 administration rate that is supposed to be used.
5 The patient recovered.

6 In the second case, the association of DMPS
7 administration and the patient's death in my, and
8 my most people who have read the case, opinion are
9 not correlative because the patient injected
10 themselves with elemental mercury.

11 Complicating that as a method of suicide, he
12 received the inappropriate treatment of
13 diphenhydramine and was sent home, which is an
14 unusual treatment for elemental mercury injection.

15 Then 10 days later, he went to the ED after
16 he had had a DMPS treatment, and he died of mercury
17 deposition throughout the body which would've come
18 from the mercury injection most likely.

19 These are the citations. Again, all are
20 European, but they look at human use of unithiol
21 and its use as an antidote in a number of instances
22 of poisoning.

1 This is an American pharmacy that is
2 ISO 9001 compliant, and so their adverse event
3 reporting system is ISO 9001 compliant and follows
4 GMP.

5 Since 1999, there's been 10,000 plus orders.
6 Patients receiving it are estimated because of the
7 dose size versus the dose administration so quite a
8 large number of DMPS at just this one pharmacy and
9 there are a number of compounding pharmacies that
10 do produce DMPS.

11 They're approximating doses at around
12 67,000. The complaints received through their
13 ISO 9001 compliance system to-date have been zero
14 and that was the one pharmacy I could get clear
15 data from.

16 Now, alternatives were brought up, and the
17 discussion I'm about to give has already been
18 really given so I'll just give it very briefly, but
19 I'd want to put a point on it.

20 Versenate, the only metal that is not a
21 label indication as far as poisoning with versenate
22 is really arsenic and then mercury. Chemet is an

1 oral, as you know, substance, and it does not have
2 a label indication for arsenic either. It is also
3 going to be oral and probably not appropriate in
4 acute toxicity.

5 We talked a lot about BAL. And the major
6 issue with BAL is the volume of inert oil that's
7 being given; that's peanut oil. The pain, the
8 frequency, and in the case, at least in 2003, where
9 they started with that, is both the product they
10 could get and the standard of care, they had to
11 abandon it for non-efficacious use.

12 Penicillamine and syprine don't have an
13 arsenic indication either. With mercury, there's
14 maybe possibly a little bit of crossover, but
15 arsenic and mercury are really excluded from most
16 of these.

17 As was brought up, there were the U.S. label
18 indications. But if the experience, at least in
19 that one very bad acute poisoning, was of note, it
20 probably is true that DMPS is preferable in acute
21 arsenic poisoning.

22 I've done many thousands of parenteral

1 administrations with DMPS over the last 20 years.
2 We have not had any serious life-threatening or
3 high-grade adverse events during that time.

4 I discontinued the use of BAL and
5 penicillamine mostly due to oral intolerance with
6 penicillamine and pain, and patient compliance with
7 BAL. Also, occasionally, there's difficulties in
8 sourcing drug.

9 So again, it's extremely safe when ordered,
10 monitored, and managed by a qualified physician.
11 And as was brought up a little bit earlier, another
12 one of the substances, having it available through
13 503A would assure that it was only filled through
14 qualified physicians.

15 The other thing that I think becomes of note
16 is if it is going to be used in an emergency, and
17 the product has to be synthesized from base
18 product, it would not be able to be synthesized in
19 enough time to deal with the emergency. Thank you.

20 **Clarifying Questions from the Committee**

21 DR. VENITZ: Thank you, Dr. Anderson.

22 Any comments or questions? Mr. Nixon?

1 MR. MIXON: Thank you. First of all, I'd
2 like to just say how fortunate we are to have
3 Dr. Brent here. I just finished looking through
4 your 50-page CV. I'm very impressed; clinical
5 emeritus professor of toxicology.

6 My question is for Dr. Anderson. I'd like
7 to get a little more clarification on why you think
8 it would take 16 days for a compounding pharmacist
9 to produce this preparation. That's just not true.
10 We can have it done in a matter of hours if we had
11 the pure active ingredient.

12 DR. ANDERSON: I will defer the answer to
13 that to the pharmacist who will be commenting in
14 the public session.

15 MR. MIXON: Okay. I just didn't want
16 the --

17 DR. ANDERSON: Yes.

18 MR. MIXON: -- the committee to have the
19 wrong impression about that.

20 DR. ANDERSON: Thank you.

21 DR. VENITZ: Dr. Carome?

22 DR. CAROME: In the numbers you gave on your

1 personal use, Dr. Anderson, you said 5,000 doses or
2 5,000 patients you used --

3 DR. ANDERSON: Doses.

4 DR. CAROME: Doses.

5 DR. ANDERSON: Doses, yes.

6 DR. CAROME: What number of patients would
7 that translate into approximately?

8 DR. ANDERSON: At this point in the day, I
9 don't have the reverse math written down. It is
10 over a 20-year period, though. So it's a series as
11 was mentioned earlier, and so there's some division
12 involved there.

13 DR. CAROME: With those, are the majority of
14 those -- was that for acute arsenic or mercury
15 poisoning or did you also use it for some of the
16 other indications that we see being used like
17 autism and concerns about amalgam-related mercury?

18 DR. ANDERSON: I see. Yes. So that's a
19 very excellent question which I should've prefaced
20 with. I've never used DMPS or any other chelator
21 for things like any of those instances.

22 In the beginning, I was in practice in an

1 area where there were still arsenical pesticides
2 available and being used, and we had a lot of
3 exposures to deal with. So really, it was that
4 exposure, yes.

5 DR. CAROME: If you could go to your slide
6 13, if someone could put it up? So these are
7 numbers from one pharmacy alone?

8 DR. ANDERSON: Correct.

9 DR. CAROME: I guess you probably don't know
10 this. Do you think this will be an extraordinary
11 high incidence of arsenic and mercury poisoning to
12 be making this much?

13 What is the incidence? Do we know the
14 incidence roughly in the U.S. of arsenic and
15 mercury poisoning?

16 DR. ANDERSON: Yes. Because I'm not
17 connected to and don't have the background data
18 from this pharmacy, I really can't speak to that at
19 the moment. I can only speak to what my practice
20 has been. Yes, sorry.

21 MS. DAVIDSON: I did research that before
22 this meeting, and the most recent data I could find

1 was 2010. There were 927 arsenic exposures in the
2 U.S., no statistics on mortality.

3 DR. VENITZ: Dr. Brent?

4 DR. BRENT: You were referring to poison
5 center data. Poison center data generally reflects
6 far more exposures, or even possible exposures, or
7 non-exposures than really serious exposures.

8 I had an opportunity to mine a database that
9 we use, which is called the Toxicology
10 Investigators Consortium -- it's a big consortium
11 with almost all practicing toxicologists across the
12 country -- to see their use of DMPS

13 The consortium started in 2010. Since 2010,
14 not a single medical toxicologist has found a
15 reason to use DMPS in this country, the reason
16 being that we would reserve it for really high
17 quality acute arsenic or mercury poisoning, which
18 is rare, which is very rare.

19 As we can see here, there's probably a lot
20 of illegitimate use of it, and I recognize that as
21 a concern. And that is a big concern. I was
22 listening a little while ago when you were

1 talking in the presentation that was given, I
2 believe, by Dr. Jarow.

3 I gleaned from that, that while we can
4 advise for routes of administration, we cannot
5 advise approval for indications. But I think even
6 the routes of administration issue is a big one
7 because a lot of it is being given orally and
8 there's no real legitimate oral need for it.

9 I think one suggestion to get around this
10 problem would be to only allow intravenous use of
11 the medication and probably would be even better,
12 if possible -- and I notice this was the American
13 College of Medical Toxicology's recommendation as
14 well -- to allow it to be used for intravenous in-
15 hospital use. And I think that would cut down a
16 huge amount of the illegitimate use that we see.

17 DR. VENITZ: Thank you, Dr. Brent.

18 Any other? Dr. Davidson?

19 MS. DAVIDSON: I just had one comment on the
20 availability of the alternatives. Being, again, in
21 a veterinary institution, I'm constantly looking
22 for chelators because our patients ingest all kinds

1 of heavy metals all the time.

2 Calcium versenate is gone. It is not
3 available. It can be compounded, I believe,
4 because it does have a monograph. BAL is currently
5 available but is frequently on the short supply
6 list. And penicillamine right now is available for
7 \$25,000 for a bottle of a hundred tablets.

8 So it does leave many practitioners with no
9 alternative, except some sort of compounded
10 preparation. In this case, it would be calcium
11 versenate or maybe the DMPS.

12 DR. VENITZ: Dr. Dohm?

13 DR. DOHM: I just want to comment that the
14 committee can certainly recommend limitations
15 outside of route of administrations such as
16 hospitalization use. But it's unclear that we
17 would be ever be able to enforce such a limitation
18 or put that limitation on the substance because
19 it's so downstream from the compounder.

20 So the compounder doesn't need to know
21 necessarily whether or not the drug will be used in
22 a hospital setting or otherwise for purposes of

1 compounding the drug.

2 Although that can be a recommendation as to
3 the limitation, it's clear that we would be able to
4 do much about it, just so you know.

5 Then the other point I'd like to make is
6 that with respect to intravenous formulation alone,
7 it's my understanding -- and please correct me if
8 I'm wrong -- some of these other uses such as for
9 autism is also IV.

10 DR. VENITZ: Dr. Gulur?

11 DR. GULUR: This is just a clarification on
12 what you had asked. So if we were to say in-
13 hospital use, that cannot be enforced, but
14 intravenous can be enforced?

15 DR. DOHM: We can limit the route of
16 administration so we can limit the compounder to
17 IV. But as I said, I believe that the autism
18 use -- and I'm not sure about the dental
19 amalgam -- is also IV.

20 DR. VENITZ: Any final comments to
21 Dr. Anderson's presentation?

22 DR. DiGIOVANNA: I have one.

1 DR. VENITZ: I'm sorry. Go ahead.

2 DR. DiGIOVANNA: It's my understanding that
3 the discussion we had earlier about different types
4 of INDs is that the single-patient emergency IND
5 that is one that could be enacted within a short
6 period of time, 24 or 48 hours, would be one that
7 would be applicable for a rare event that would
8 occur a few times a year in the U.S. and might be
9 managed in a tertiary care center would be an
10 appropriate way of fulfilling the need for that
11 rare situation.

12 DR. VENITZ: Mr. Mixon?

13 MR. MIXON: If we'd limit the drug to that
14 extent, it just simply won't be available, period.
15 I mean IND or not, compassionate use or not, it
16 won't be available. I just want to echo what Gigi
17 said. Remember, we have drug shortages all the
18 time. And when this drug is going to be needed,
19 it's going to be needed now, not three weeks from
20 now, and that's where the compounder can really
21 come to the table and help the patient, if it's
22 available.

1 DR. VENITZ: Last comment. Dr. Jungman?

2 MS. JUNGMAN: I actually just want to
3 understand Mr. Nixon's comment. So what would it
4 be that would make it unavailable? In my
5 understanding, you said that, if it's not available
6 sort of for the broad spectrum of uses, then there
7 wouldn't be a case for continuing to keep it
8 available for this kind of acute toxicity use. Or
9 what would be the reason that it would become
10 unavailable if we had to kind of go through that
11 emergency IND step?

12 MR. MIXON: If the committee votes to add it
13 to the do not compound list, then that's the end of
14 it. If the committee votes for it to be available,
15 whether it's only intravenous or intravenous for
16 use in hospitals, then presumably, our chemical
17 manufacturers will continue to produce it, and
18 stock it, and make it available. So the
19 availability would be there.

20 Does that answer your, Elizabeth? I'm not
21 sure.

22 MS. JUNGMAN: I guess. Thank you.

1 other expenses in conjunction with your attendance
2 at the meeting.

3 Likewise, FDA encourages you, at the
4 beginning of your statement, to advise the
5 committee if you do not have any such financial
6 relationships.

7 If you choose not to address this issue of
8 financial relationships at the beginning of your
9 statement, that will not preclude you from
10 speaking.

11 The FDA and this committee place great
12 importance in the open public hearing process. The
13 insights and comments provided can help the Agency
14 and this committee in their consideration of the
15 issues before them. With that said, in many
16 instances and for many topics, there will be a
17 variety of opinions.

18 One of our goals today is for this open
19 public hearing to be conducted in a fair and open
20 way where every participant is listened to
21 carefully and treated with dignity, courtesy, and
22 respect. Therefore, please speak only when

1 recognized by the chair. Thank you for your
2 cooperation.

3 So I'm now asking our last open public
4 hearing speaker to come to the podium or the
5 microphone and present.

6 MR. MCGUFF: All right. Thank you very
7 much. My name is Ronald M. McGuff; call me Ron. I
8 am the owner of McGuff Compounding Pharmacy
9 Services, Incorporated in Santa Ana, California.
10 We've been in business for 17 years. We compound
11 with bulk drug substances. We create sterile and
12 non-sterile drug products.

13 I have some background information based on
14 some of the questions that have been asked. The
15 Heyl product is available in the United States. It
16 just returned. It is being compounded now by
17 compounders.

18 I need to go back to the first part, which
19 says I do have a financial relationship with this
20 product, and I paid for my own way to get here.

21 The FDA has indicated in its brief to you
22 and at this meeting, the FDA has indicated a vote

1 by this committee against inclusion to the approved
2 bulk drug substance list will not restrict access
3 to DMPS.

4 FDA indicates a physician or a hospital that
5 needs DMPS will be able to obtain this drug through
6 the expanded-access or intermediate-sized access
7 IND process.

8 This may not be true. Let me explain. One
9 of the most difficult activities of a compounding
10 pharmacy performs is to locate raw material
11 manufacturers that are willing to sell very small
12 quantities of active pharmaceutical ingredients and
13 comply with the regulatory overhead that is part of
14 compounding pharmacy today.

15 The economic reward for these manufacturers
16 is very small, and there is the added potential for
17 regulatory review and product liability lawsuits.
18 Please understand, there will be no access to any
19 drug if a raw material or API is not available.

20 Simply put, if the API is not available to
21 the manufacturer, no drug will be available to use
22 in an IND.

1 The 15 persons in the Maine poisoning, who
2 were just talked about here, were poisoned and
3 survived. They were very fortunate because we had
4 the DMPS on hand and available when this emergency
5 occurred.

6 The current system requires the physician to
7 write a prescription for an identified patient to
8 obtain the drug. This works. This system works
9 very well.

10 Today, under the current system, DMPS API is
11 available. If the FDA does not include DMPS on the
12 approved list, the API is deemed not to be safe and
13 not to be effective for compounding. This
14 obviously is not good news to the DMPS
15 manufacturer. This alone may cause the
16 manufacturer to leave the U.S. market.

17 A bit about Heyl. Heyl is the only company
18 that we have been able to locate that manufactures
19 DMPS that meets all the requirements for the FDA.
20 We've looked high and low at alternative sources,
21 and we cannot find one, so we are dependent upon
22 one manufacturer for DMPS.

1 But the FDA tells us to replace the current
2 prescription system with the expanded access or the
3 intermediate-sized IND process. I believe the
4 additional bureaucratic overhead will keep many
5 physicians away, as they are already overloaded
6 with work. This will lead to an even smaller
7 market for DMPS.

8 The DMPS API manufacturer has to balance the
9 FDA statement of not safe and not effective,
10 smaller purchases in an IND market, higher cost,
11 and greater liability to the economic particulars
12 of staying in the market.

13 I believe based, on my experience with Heyl
14 and 17 years of working with suppliers, that the
15 sole API manufacturer will want to reduce their
16 liability and simply exit the market.

17 The reward is not equal to the risk. Again,
18 there will be no access to any drug if the raw
19 material or the API is not available. It makes
20 sense to keep the status quo. It works.

21 Additionally, there's no guarantee that a
22 manufacturer, physician group, or physician will

1 apply for an IND of any type, no guarantees to
2 that. If there is no active IND, DMPS will not be
3 available. There will not be a market to sell to,
4 simple as that, so the DMPS in the United States
5 will not be available.

6 So how long will it take to get DMPS to a
7 physician to treat a patient if another arsenic
8 poisoning exists? Unfortunately, I disagree with
9 Bill here. When you compound a sterile drug, just
10 the act of proving that it's sterile takes 14 days.
11 By the time you understand there's a need for
12 production, and if you can get it in production on
13 day 1, you bring it out, you put in quarantine, you
14 wait for 14 days until you get the sterility test
15 back.

16 Then on the 16th day, you go ahead and
17 deliver. This does not take into effect or account
18 the time of getting an emergency IND together, the
19 time of getting DMPS from Europe through customs,
20 which is an interesting thing all by itself, to us
21 to compound. This is merely the time it takes to
22 compound a sterile drug, 16 days.

1 For acute poisoning, 16 days may be too
2 late. Patients will probably die and for no good
3 reason. FDA has not reported a single death
4 directly attributable to DMPS in 47 years of record
5 keeping. The system, as it stands now, works. The
6 status quo works. No harm will be done if you vote
7 to include DMPS to the approved list.

8 (Pause.)

9 MR. MCGUFF: A vote against inclusion is a
10 vote to potentially remove DMPS API from U.S. soil,
11 significantly increase the time to obtain sterile
12 DMPS in case of another poisoning, take away a
13 readily available tool for physicians to improve
14 patient healthcare, and it adds bureaucratic burden
15 to physicians when none is needed.

16 In addition, just one other quick comment,
17 the CDC recognizes that arsenic poisoning could be
18 used as a terrorist agent. We've kind of shown
19 that in Maine, that 16 people ingested arsenic
20 poisoning. I believe that would relate today to a
21 terrorist attack.

22 So thank you for your time.

1 DR. VENITZ: Thank you. Are there any
2 questions or comments by the committee? Mr. Mixon?

3 MR. MIXON: I just want to clarify. Thanks,
4 Ron, for letting us know about the sources of this.
5 I just assumed that PCCA and others had it. My
6 comment about we could have it available in hours
7 of course assumes we have the active ingredient on
8 hand, so Ron just added valuable information about
9 that.

10 DR. VENITZ: Dr. Carome?

11 DR. CAROME: Mike Carome. I'm just a little
12 confused what the status quo is. When you get
13 someone acutely intoxicated with arsenic or
14 mercury, are you making IV preparations of DMPS and
15 waiting 14 days for sterility test? Or are you
16 making it and then using it? Are you not using
17 sterile -- so I'm completely confused by the status
18 quo.

19 MR. MCGUFF: No problem. No problem. I
20 understand the question is about is it available
21 currently and how is it available, if it is
22 currently available.

1 We get enough prescriptions, and this is how
2 it works. We receive a prescription from a
3 physician, and we compound for that prescription.
4 Under 503A, they allow us to anticipate those
5 prescriptions.

6 It's anticipatory compounding. We do keep a
7 supply of DMPS on hand all the time in anticipation
8 of those prescriptions that we're going to receive.
9 It is on hand, and it is from the Heyl raw
10 material.

11 DR. CAROME: Just to follow up, how many
12 prescriptions are you filling a week, say, or a
13 month?

14 MR. McGUFF: The information that you saw
15 was from my pharmacy.

16 DR. CAROME: So you have an epidemic of
17 arsenic poisoning, or you're using it for other
18 things?

19 MR. McGUFF: We respond to prescriptions
20 from the physicians.

21 DR. DiGIOVANNA: That was sort of my
22 question, but can you give me a little bit more

1 about the demographics? I believe was that 5,000
2 prescriptions or what geographic area?

3 MR. MCGUFF: The McGuff Compounding
4 Pharmacy -- I'm sorry. The geographic area we ship
5 to -- we have licensing in every state that
6 requires licensing; 49 out of 50 states require
7 licensing. The territories and protectorates, we
8 also are allowed to ship to.

9 Basically, we're allowed under California
10 law, which is where we're located. We can ship to
11 any US licensed physician within the United States.

12 Yes. Sorry.

13 DR. GULUR: He's my boss. So what age group
14 are you dispensing the majority of your
15 prescriptions to?

16 MR. MCGUFF: I beg your pardon?

17 DR. GULUR: How old are the patients?

18 MR. MCGUFF: I don't recall. Excuse me. I
19 am not involved in the prescription receipt
20 process. We have pharmacists that when we receive
21 prescriptions, if we don't have enough information
22 relating to other drugs that the patient is taking,

1 allergies and things of that nature, we will call
2 the physician back and ask about that.

3 Typically, physicians don't indicate what
4 the treatment is actually for. It's just they're
5 looking for this particular drug.

6 DR. GULUR: Is the age group difficult to
7 determine from the prescription, the age of the
8 patient, perhaps by dose, the dose that you are
9 dispensing?

10 MR. MCGUFF: As a gut feeling, I would say
11 we don't -- we do get birth dates so we have the
12 data. Have we extrapolated that from the data? We
13 have not, but we can certainly do so if you'd like
14 to, if you'd like us to do that.

15 DR. GULUR: Thank you.

16 DR. VENITZ: Last question. Dr. Davidson?

17 MS. DAVIDSON: I'd like to follow up on that
18 just a little bit. The medical toxicologist
19 recommended -- they recognize an appropriate use of
20 DMPS, and they recommended in their letter
21 monitoring of physicians by appropriate state
22 regulatory agencies.

1 I would like the committee to consider that
2 if we try to change prescribing practices by
3 limiting supply, have we really changed prescribing
4 practices? I would suggest that, not with just
5 this drug but if we're really concerned about
6 inappropriate prescribing, I would mention pain
7 gels as another possible example of that, that we
8 focus on getting the appropriate regulatory
9 agencies to consider appropriate actions for those
10 prescribers and not cut off supplies of drugs to
11 needy patients.

12 I realize that is entirely out of the
13 purview of this committee and the FDA, but I would
14 suggest that as a place to start instead of cutting
15 off supply for people that really need it.

16 MR. MCGUFF: Thank you.

17 **Committee Discussion and Vote**

18 DR. VENITZ: Thank you for your
19 presentation.

20 That concludes the open public hearing
21 portion of this meeting, and we won't take any
22 further comments from the audience.

1 Now, we're moving on the committee's
2 discussion and vote. We already had a lively
3 discussion, but I'm opening the floor for any
4 comments, discussion items. Dr. Pham?

5 DR. PHAM: I just wanted to give a little
6 context also in use in pediatrics and actually ask
7 this of Dr. Brent because I believe BAL does not
8 have any pediatric indication, or information, or
9 sort of dosing data. So I think that only oral
10 options are available.

11 However, there is oral. There's data on
12 oral dosing of DMPS in children. It's not IV, but
13 with a lot of things with pediatrics, we have to
14 extrapolate. So just any sense of place in therapy
15 for pediatric poisoning?

16 DR. VENITZ: Dr. Brent?

17 DR. BRENT: Certainly, we see significant
18 heavy metal poisoning in pediatrics in lead
19 encephalopathy, for example, which is an absolute
20 medical emergency that mandates IV therapy where we
21 don't have IV agents really available. So there is
22 a very important role there, yes, totally agree.

1 DR. VENITZ: Dr. Carome?

2 DR. CAROME: Mike Carome, again. As you
3 know, I don't get to vote on this one because 1999
4 Public Citizen opposed including this product on
5 the bulk drug list with concerns that it was
6 being -- the compounding of it was being abused.

7 I am pretty much convinced that there is a
8 narrow need for this drug for patients with acute
9 severe arsenic or mercury poisoning and that the
10 drug is -- there's data to support its use in that
11 narrow thing.

12 I remain concerned that there's a tremendous
13 amount of abuse and misuse of this drug when it's
14 compounded. But I think there is a narrow
15 appropriate use, and doctors should have access to
16 it in that case.

17 DR. VENITZ: Dr. Jungman?

18 MS. JUNGMAN: Yes. I think, basically, I
19 was going to say something very similar here that
20 we have to acknowledge that the majority of the use
21 here is not in these acute toxicity situations.

22 So I'm just kind of thinking through this

1 supply problem because what I hear us struggling
2 with is, should we encourage a use for which there
3 is very little evidence of effectiveness in order
4 to maintain a level of supply for the very limited
5 use that we -- and I think that's -- I don't really
6 actually know how to resolve that.

7 How do you convince a manufacturer to
8 continue to maintain supply without allowing kind
9 of broad uses that are not supportable? But I
10 think that is -- certainly, I wanted to kind of at
11 least make it explicit what I think we're kind of
12 talking about.

13 DR. VENITZ: Dr. Brent?

14 DR. BRENT: Your point is exactly right.
15 And that's I think what we're all struggling with
16 here.

17 To me, the best way of dealing with
18 this -- and I realize we can't police this
19 necessarily -- but at least to express the spirit
20 of the way it should be done would be to have it
21 available for in-hospital intravenous use.

22 Nobody is going to be admitting people to

1 hospitals to treat their autism with chelating
2 agents or to treat their dental amalgams with
3 chelating agents.

4 Will people expand outside of that? Well,
5 yes, I suppose they do to some degree at their own
6 risk. But I think that's the best we can do here
7 to try to encourage legitimate use and discourage
8 illegitimate use.

9 DR. VENITZ: Mr. Mixon?

10 MR. MIXON: Dr. Brent, when your patient
11 population needs this drug, where is it obtained
12 from, do you know? Is your hospital able to
13 compound it?

14 DR. BRENT: Medical toxicologists are all
15 aware that when we need it, if we need it, that we
16 go to McGuff because they're the ones that have the
17 pharmaceutical-grade preparation available. They
18 can get it very quickly from them.

19 DR. VENITZ: Last question. Dr. Jungman?

20 MS. JUNGMAN: I think I hear your point. I
21 think realistically, if we put this on the 503A
22 bulks list, there's a big market here, and it will

1 continue.

2 I think that the idea that we sort of count
3 on folks to say, "Well, this committee thought
4 that, really, it should only be used in hospital
5 use so we're not going to compound it outside of
6 that setting," I think is unrealistic. If it's on
7 the list, it's on the list. It's legal for people
8 to do it.

9 DR. VENITZ: Very last --

10 DR. DiGIOVANNA: Sorry. If we were to be
11 able to put it on for only in-hospital use, would
12 that include infusion centers, which are pretty
13 widely available?

14 DR. VENITZ: Very, very last --

15 MR. MIXON: I'll make it brief. If we say
16 it's available only for in-hospital use, I will
17 submit that Mr. McGuff will not be able to provide
18 it on a timely basis because he won't have the
19 demand for it to keep it available ahead of time.

20 I'm not speaking for him. I'm just
21 speculating, but I bet you that'll be the outcome.

22 DR. VENITZ: Let me proceed with the vote

1 because we're already behind schedule.

2 DR. BRENT: I'm sorry. Can we make this
3 vote contingent upon the requirement for
4 in-hospital intravenous use?

5 DR. VENITZ: I was going to read -- this is
6 your first vote, so the vote is yes, no, or
7 abstain, but then I'm going to go around the table,
8 and you can add any comments like any additional
9 restrictions that you'd like on the record. But
10 the vote is you have three buttons to push
11 basically.

12 Let me just read the whole preliminaries
13 again since we do have Dr. Brent joining us.

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

21 In order to perform the voting process,
22 please press the button, yes, no, or, abstain,

1 three times on your microphone. You will have
2 approximately 15 seconds to vote.

3 After you've made your selection, the light
4 will continue to flash. Let me know if there's any
5 problems. So go ahead and vote.

6 (Vote taken.)

7 DR. HONG: For DMPS, we have 7 yeses, 4 nos,
8 and zero abstain.

9 DR. VENITZ: Now, let's go around the table.
10 And Dr. Brent, let's go ahead and start with you.

11 DR. BRENT: I believe I've already expressed
12 my beliefs here of what would be the appropriate
13 way of using this drug. There's a lot of
14 illegitimate use in this country. We want to
15 discourage that.

16 We do want this to be available where it is
17 necessary, and sometimes it is necessary. To me,
18 the best way to attain that would be to have it
19 available as an intravenous preparation for
20 in-hospital use. I realize that could still be
21 misused, but I think that's the best we can do.

22 DR. VENITZ: So no, you voted to not put it

1 on the list?

2 DR. BRENT: I voted not to support the --

3 DR. VENITZ: So we have the correct the
4 official records. You meant to vote in favor of
5 putting it on the list, which is not what it
6 currently rates. That's all right.

7 The actual vote is going to be --

8 DR. BRENT: My actual vote was to be yes.

9 DR. VENITZ: Right. So it would be 8, 3.
10 It would be 8 yes, 3 no.

11 Dr. DiGiovanna?

12 DR. DiGIOVANNA: This is one of the more
13 difficult challenges. And from a philosophical
14 perspective, the fact that a drug can be abused but
15 is also necessary in certain circumstances -- I
16 don't believe it should not be available in life-
17 saving circumstances because other people may
18 choose to abuse it.

19 However, the difficulty here is that it may
20 not be available if it's needed. And
21 unfortunately, in a world that we are living in, it
22 very well may be needed on a very short-term basis

1 and a very emotionally-impacting basis. So I think
2 for those individuals who need it, it should be
3 available, and I certainly would limit it to in-
4 hospital intravenous use if that is in any way
5 possible.

6 DR. GULUR: Padma Gulur. I voted no. I
7 feel very strongly that it's needed as an
8 intravenous preparation having personally had to
9 use it once. It has an extremely important role to
10 play in severe arsenic poisoning, and it's the only
11 intravenous formulation that we have available.

12 However, I voted no because what I heard
13 here was that the incidence of mercury and arsenic
14 poisoning of that severity is really low. There's
15 very few people who are exposed to that.

16 It's true we are all under the terror -- we
17 feel the fact that people can take advantage of the
18 situation and poison the country. But in the
19 meantime, we also heard that to go through this
20 route, which is to rely on the compounding
21 pharmacies to provide this, we would have to make
22 sure that they could use it for other purposes so

1 it was economically viable for them.

2 It seems to me that the right way to do this
3 is this needs to have another avenue, that if there
4 is a drug that is that needed by this country, the
5 only way to get it is to also make it available for
6 potential abuse.

7 It does not seem to be the right way to do
8 things and I would hope that there are other
9 avenues that can be followed for these drugs to be
10 legitimately used for the purpose that they are
11 needed for.

12 As rightly pointed out, intravenous use,
13 hospital would be a great restriction, but if it
14 cannot be assured, then we are putting another
15 larger population at risk by putting it on the
16 list.

17 DR. VENITZ: Jurgen Venitz. I voted yes.
18 Just two comments to support that. Number one, we
19 had not only testimony today but also background
20 submissions that, I think, very strongly argued in
21 favor of keeping it on the 503A list.

22 Number two, in response to something, I

1 think, Dr. Day mentioned, I think implicitly or
2 not or explicitly or not, we do consider
3 alternative treatments, both the availability and
4 the comparative efficacy, if you like.

5 This is one of those cases where that
6 definitely went into my decision-making. I would
7 also strongly encourage the IV-use only.
8 Everything else, I don't think we can enforce. But
9 I do think we can make sure that it still can be
10 sterilely compounded.

11 MS. DAVIDSON: I voted yes and quickly just
12 would limit it to IV use in-hospital as has been
13 stated. And I also wanted to make a comment that
14 it wouldn't need to be made in anticipation at risk
15 of losing money.

16 USP 797 does have a provision for emergency
17 release of product prior to testing results within
18 certain parameters, so it is certainly possible to
19 make this within the hour that Mr. Mixon mentioned.

20 MR. HUMPHREY: William Humphrey. I voted
21 yes. I believe the toxicologists that there is a
22 clear indication for this drug in acute

1 life-threatening heavy metal toxicity. And I also
2 would recommend that it be used intravenously in
3 hospitals.

4 DR. HOAG: Steve Hoag. I voted yes. This
5 was a very difficult decision, but I figured the
6 risk-to-benefit ratio was in favor of keeping it on
7 the list.

8 MS. JUNGMAN: Elizabeth Jungman. I voted no
9 for many of the same reasons as Dr. Gulur. I am
10 very concerned about the acute toxicity situation
11 that has been discussed quite a bit here, but the
12 vast majority of the use is a use for which I
13 didn't see a lot of support and was just
14 uncomfortable exposing that significant majority of
15 patients, given where the data is on that.

16 DR. PHAM: Katherine Pham. I voted yes even
17 though every fiber of my being wanted to abstain,
18 but I don't believe in abstaining.

19 I didn't have time to make this comment in
20 previous discussion, but I did research a little
21 bit further. There had been a nomination for this
22 to go on the essential medicines list in the World

1 Health Organization back in 2010 and went through a
2 pretty decent independent clinician review that
3 brought it up for nomination there.

4 They ultimately decided that DMPS would not
5 be included due to insufficient evidence, and I
6 think that was back in 2011. Although that made me
7 feel like I should say no, at the end of the day,
8 it goes back to the criteria that we're all charged
9 with looking at, which is whether or not there are
10 alternative therapies available and there is not in
11 this route. So I kept it very practical, and I
12 said that it should be available only as IV.

13 DR. VAIDA: Allen Vaida. I voted no for all
14 the reasons that Dr. Gulur has already made.

15 DR. WALL: Donna Wall. I said yes because
16 of the severity of the poisoning. We really need
17 to have that kind of product. We know it's being
18 misused, but then we keep opioids on the
19 formularies and use them, and they're being misused
20 too.

21 The key is to having the medical communities
22 step up and make sure that they are working with

1 folks and that drugs are being used appropriately,
2 and if they're not, to sing out loud.

3 **Adjournment**

4 DR. VENITZ: Okay. Thank you. That doesn't
5 just conclude our vote, it also concludes the
6 meeting.

7 I want to thank everybody for what turned
8 out to be a very lively and productive meeting. I
9 hope you all have a safe trip home, and we'll see
10 each other again in November, I believe.

11 Thank you.

12 (Whereupon, at 5:08 p.m., the afternoon
13 session was adjourned.)

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