1	FOOD AND DRUG ADMINISTRATION
2	CENTER FOR DRUG EVALUATION AND RESEARCH
3	
4	
5	PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)
6	
7	
8	Morning Session
9	
10	
11	Virtual Meeting
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16	
17	Wednesday, June 9, 2021
18	10:35 a.m. to 2:40 p.m.
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22	

1	Meeting Roster
2	DESIGNATED FEDERAL OFFICER (Non-Voting)
3	Takyiah Stevenson, PharmD
4	Division of Advisory Committee and
5	Consultant Management
6	Office of Executive Programs, CDER, FDA
7	
8	PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS
9	(Voting)
10	Robin H. Bogner, PhD
11	Professor
12	University of Connecticut
13	School of Pharmacy
14	Department of Pharmaceutical Sciences
15	Storrs, Connecticut
16	
17	
18	
19	
20	
21	
22	

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Seemal R. Desai, MD, FAAD
1
      Founder & Medical Director
2
      Innovative Dermatology
3
4
      Clinical Assistant Professor
      Department of Dermatology
5
      University of Texas Southwestern Medical Center
6
7
      Dallas, Texas
8
      Timothy D. Fensky, RPh, DPh, FACA
9
      (National Association of Boards of Pharmacy
10
      Representative)
11
      Chief Pharmacy Operations Officer
12
      Sullivan's Pharmacy and Medical Supply, Inc.
13
      Sullivan's Health Care, Inc.
14
15
      Boston, Massachusetts
16
17
      Sandra J. Fusco-Walker
18
      (Consumer Representative)
19
      Allergy & Asthma Network
      Vienna, Virginia
20
21
22
```

1	Padma Gulur, MD, FASA
2	(Chairperson)
3	Professor of Anesthesiology
4	Executive Vice Chair for Performance and
5	Operations
6	Department of Anesthesiology
7	Director of Pain Management Strategy and
8	Opioid Surveillance
9	Medical Director Acute Pain Consult Service
10	Duke University Health System
11	Durham, North Carolina
12	
13	Anita Gupta, DO, MPP, PharmD
14	Head, Comprehensive Pain Center
15	Head, Interventional Pain Management
16	Departments of Medicine and Orthopedic Surgery
17	Scripps Clinic MD Anderson Cancer Center
18	Associate Professor
19	Johns Hopkins School of Medicine
20	Baltimore, Maryland
21	
22	

1	Kathleen M. Gura PharmD, BCNSP, FASHP, FASPEN
2	Assistant Professor of Pediatrics
3	Harvard Medical School
4	Manager, Pharmacy Clinical Research Program
5	Boston Children's Hospital
6	Boston, Massachusetts
7	
8	Linda F. McElhiney PharmD, RPh, MSP, FAPC,
9	FACA, FASHP, DPLA
10	Team Lead Compounding Pharmacist
11	Indiana University Health
12	Indianapolis, Indiana
13	
14	Kuldip R. Patel, PharmD, FASHP
15	Senior Associate Chief Pharmacy Officer
16	Duke University Hospital
17	Durham, North Carolina
18	
19	
20	
21	
22	

1	Elizabeth Rebello, RPh, MD, FASA, CPPS
2	Professor
3	Department of Anesthesiology and
4	Perioperative Medicine
5	University of Texas MD Anderson Cancer Center
6	Houston, Texas
7	
8	Jeanne H. Sun, PharmD, JD
9	(United States Pharmacopeia Representative)
10	Counsel
11	United States Pharmacopeial Convention
12	Rockville, Maryland
13	
14	Allen J. Vaida, BSc, PharmD, FASHP
15	Former Executive Vice President
16	Institute for Safe Medication Practices
17	Hatfield, Pennsylvania
18	
19	
20	
21	
22	

1	PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS
2	(Non-Voting)
3	Gus Bassani, PharmD
4	(Industry Representative, Neomycin Topic Only)
5	Chief Scientific Officer
6	Professional Compounding Centers of America
7	Houston, Texas
8	
9	Michael D. Bui, DDS, MPH, JD
10	(Industry Representative)
11	Senior Vice-President, Regulatory Affairs
12	Kadmon Pharmaceuticals
13	Cambridge, Massachusetts
14	
15	ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE
16	(Non-Voting)
17	Richard L. Green, BS Pharm, RPh, BCNP, FAPhA
18	(Melatonin, Methylcobalamin, Choline Chloride
19	and Oxitriptan Topics Only)
20	Director of Radiopharmacy Practice
21	Cardinal Health Nuclear & Precision Health
22	Butler, Tennessee

1	TEMPORARY MEMBERS (Voting)
2	Jonathan Emens, MD, FAASM, DFAPA
3	(Melatonin Topic Only)
4	Associate Professor of Psychiatry
5	Assistant Professor of Internal Medicine
6	Oregon Health and Science University
7	Oregon Institute of Occupational Health Sciences
8	Deputy Director of Mental Health
9	Veterans Affairs Portland Health Care System
10	Portland, Oregon
11	
12	Joanna Katzman, MD, MSPH
13	(Methylcobalamin Topic Only)
13 14	(Methylcobalamin Topic Only) Director of Public Health Initiatives, Project ECHO
14	Director of Public Health Initiatives, Project ECHO
14 15	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico
14 15 16	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico (UNM) Pain Center
14 15 16 17	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico (UNM) Pain Center Professor of Neurology
14 15 16 17 18	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico (UNM) Pain Center Professor of Neurology Department of Neurosurgery, UNM Pain Center
14 15 16 17 18	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico (UNM) Pain Center Professor of Neurology Department of Neurosurgery, UNM Pain Center UNM School of Medicine
14 15 16 17 18 19 20	Director of Public Health Initiatives, Project ECHO Executive Director of University of New Mexico (UNM) Pain Center Professor of Neurology Department of Neurosurgery, UNM Pain Center UNM School of Medicine

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Friedhelm Sandbrink, MD
1
      (Methylcobalamin Topic Only)
2
      National Program Director for Pain Management,
3
4
      Opioid Safety and Prescription Drug Monitoring
      Program, Specialty Care Program Office
5
     Veterans Health Administration
6
7
      Director for Pain Management Program
      Department of Neurology
8
     Washington Veterans Affairs Medical Center
9
     Washington, District of Columbia
10
11
      FDA PARTICIPANTS (Non-Voting)
12
     Frances Gail Bormel, RPh, JD
13
      Director
14
15
      Office of Compounding Quality and Compliance (OCQC)
      Office of Compliance (OC), CDER, FDA
16
17
18
      Gabrielle Cosel
19
      Director (Acting)
      Division of Compounding Policy and Outreach (DCPO)
20
21
      OCQC, OC, CDER, FDA
22
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Rosilend Lawson, VMD, JD
1
2
      Branch Chief (Acting)
      DCPO, OCQC, OC, CDER, FDA
3
4
      Charles Ganley, MD
5
      Director
6
      Office of Specialty Medicine (OSM)
7
      Office of New Drugs (OND), CDER, FDA
8
9
      Susan Johnson, PharmD, PhD
10
      Clinical Reviewer
11
      Pharmacy Compounding Review Team
12
      OSM, OND, CDER, FDA
13
14
15
      Suhail Kasim, MD, MPH
      Lead Physician
16
      Pharmacy Compounding Review Team
17
18
      OSM, OND, CDER, FDA
19
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PROCEEDINGS

(10:35 a.m.)

Call to Order

DR. GULUR: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Jeremy Kahn. His email and phone number are currently displayed.

My name is Padma Gulur and I will be chairing today's meeting. I will now call the June 9, 2021 meeting of the Pharmacy Compounding Advisory Committee to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Bogner?

DR. BOGNER: Good morning. This is Robin

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Bogner. I'm professor of pharmaceutics at the
1
     University of Connecticut, School of Pharmacy.
2
             DR. STEVENSON: Dr. Desai?
3
4
             DR. DESAI: Good morning. I'm Seemal Desai.
      I'm a board certified dermatologist in private and
5
      academic practice in Dallas, Texas, and clinical
6
      faculty at the University of Texas, Southwestern
7
     Medical Center.
8
             DR. STEVENSON: Dr. Fensky?
9
             DR. FENSKY: Good morning. I'm Tim Fensky.
10
      I'm the chief pharmacy officer for Sullivan's
11
      Pharmacy in Boston, Massachusetts.
12
             DR. STEVENSON: Ms. Fusco-Walker?
13
14
              (No response.)
             DR. STEVENSON: Ms. Fusco-Walker, you may be
15
     on mute. Please unmute your phone and introduce
16
     yourself.
17
18
              (No response.)
19
             DR. STEVENSON: Ms. Fusco-Walker, you may be
      on mute.
20
21
              (No response.)
             DR. STEVENSON: Okay. We'll come back.
22
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Dr. Gulur, please reintroduce yourself. 1 DR. GULUR: I'm Padma Gulur. I am professor 2 of anesthesiology and population health at Duke 3 4 University. DR. STEVENSON: Ms. Fusco-Walker, if you can 5 hear me now, please reintroduce yourself. 6 MS. FUSCO-WALKER: Yes. Sandra 7 Fusco-Walker. I'm a consumer representative for 8 the Allergy & Asthma Network. DR. STEVENSON: 10 Thank you. Dr. Gupta? 11 DR. GUPTA: Good morning. This is Dr. Anita 12 I'm the head of comprehensive pain 13 management at Scripps MD Anderson and the head of 14 interventional pain management at Scripps 15 MD Anderson, and also faculty at Johns Hopkins 16 School of Medicine in Baltimore Maryland. 17 18 you very much. 19 DR. STEVENSON: Dr. Gura? DR. GURA: Hi. I'm Kathy Gura. 20 21 clinical pharmacist at Boston Children's Hospital and an assistant professor of pediatrics at Harvard 22

Medical School in Boston. 1 DR. STEVENSON: Dr. McElhiney? 2 DR. McELHINEY: Hi. I'm Linda McElhiney. 3 4 I'm the team lead compounding pharmacist for Indiana University Health's health system in 5 Indianapolis, Indiana. 6 DR. STEVENSON: Dr. Patel? 7 DR. PATEL: Hey. Good morning, everyone. 8 This is Kuldip Patel. I'm the senior associate 9 chief pharmacy officer at Duke University Hospital. 10 DR. STEVENSON: Dr. Rebello? 11 DR. REBELLO: Good morning, everyone. 12 My name is Elizabeth Rebello, and I'm a professor of 13 anesthesiology and perioperative medicine at the 14 University of Texas MD Anderson Cancer Center. 15 DR. STEVENSON: Dr. Sun? 16 DR. SUN: Good morning. I'm Jeanne Sun. 17 18 I'm a pharmacist and counsel at the United States 19 Pharmacopeia. DR. STEVENSON: Dr. Vaida? 20 21 DR. VAIDA: Good morning. Allen Vaida. a pharmacist and former executive vice president at 22

the Institute for Safe Medication Practices. 1 DR. STEVENSON: Dr. Emens? 2 DR. EMENS: Good morning. I'm Jonathan 3 Emens. I'm an associate professor of psychiatry at 4 Oregon Health and Science University and the deputy 5 director of mental health and clinical 6 neurosciences at VA Portland Healthcare System. 7 DR. STEVENSON: Dr. Katzman? 8 DR. KATZMAN: Hi there. I'm a neurologist 9 at the University of New Mexico. I'm in the 10 Department of Neurosurgery and Psychiatry Nursing 11 in the College of Population Health. I direct the 12 UNM Pain Center and I direct the Public Health 13 Initiatives at Project ECHO. 14 DR. STEVENSON: Dr. Sandbrink? 15 DR. SANDBRINK: Good morning. This is 16 Friedhelm Sandbrink. I'm a neurologist and pain 17 18 physician and the director of pain management at 19 the Washington DC VA Medical Center, and national program director for Pain Management and Opioid 20 21 Safety and Prescription Drug Monitoring Programs in the Veterans Health Administration, and academic 22

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affiliation at Uniformed Services University in
1
     Bethesda and George Washington University in D.C.
2
             DR. STEVENSON: Dr. Bui?
3
             DR. BUI: Yes. I'm Dr. Michael Bui.
                                                     I'm
4
      senior VP of regulatory affairs at Kadmon
5
     Pharmaceuticals.
6
             DR. STEVENSON: Dr. Richard Green, if you
7
     can hear me.
8
             DR. GREEN: Yes, I can. Good morning.
9
      is Richard Green. I'm a board certified nuclear
10
     pharmacist, director of Radiopharmacy Practice at
11
     Cardinal Health Nuclear & Precision Health
12
     Solutions.
13
             DR. STEVENSON: I will now introduce the FDA
14
     participants.
15
             Dr. Bormel?
16
             MS. BORMEL: Hi. I'm Gail Bormel, the
17
18
      director of the Office of Compounding Quality and
19
     Compliance.
             DR. STEVENSON: Gabrielle Cosel?
20
             MS. COSEL: Hi. I'm Gabrielle Cosel. I'm
21
      the acting director of the Division of Compounding
22
```

Policy and Outreach in the Office of Compounding 1 Quality and Compliance. 2 DR. STEVENSON: Dr. Lawson? 3 4 DR. LAWSON: Hi. This is Rosilend Lawson. I'm acting branch chief in Compounding Policy and 5 Outreach in OCQC, Office of Compounding Quality and 6 Compliance. 7 DR. STEVENSON: Dr. Ganley? 8 DR. GANLEY: Yes. Hi. I'm Charley Ganley. 9 I'm the director of Office of Specialty Medicine in 10 the Office of New Drugs, FDA. 11 DR. STEVENSON: Dr. Johnson? 12 DR. JOHNSON: Hi. I'm clinical reviewer on 13 the Pharmacy Compounding Review Team in the Office 14 of Special Medicine in the Office of New Drugs. 15 DR. STEVENSON: Dr. Kasim? 16 DR. KASIM: Hi. I'm Suhail Kasim. I'm the 17 18 lead physician in the Pharmacy Compounding Review 19 Team in the Office of Specialty Medicine, in the Office of New Drugs. Thank you. 20 21 DR. STEVENSON: Thank you, everyone. I will hand it back to the chairperson, Dr. Gulur. 22

DR. GULUR: Thank you, Dr. Stevenson.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members

take care that their conversations about the topic

at hand take place in the open forum of the

meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during the break. Thank you.

Today we will discuss four bulk drug substances nominated for inclusion on the list of bulk substances that may be used to compound drugs in accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act, also known as the 503A Bulks List: melatonin, methylcobalamin, choline chloride, and oxitriptan.

For each of the four substances, we will hear presentations from the FDA, have the opportunity to ask clarifying questions; hear the nominators' presentations, with the exception of oxitriptan and melatonin; have the opportunity to ask clarifying questions; hold an open public hearing; and have committee discussion and voting.

The May 7, 2021 Federal Register notice identifies the uses FDA reviewed for each of the four bulk drug substances being discussed at this meeting. These uses reflect those for which adequate support was provided in the nomination.

In addition, the nominations and FDA's evaluations for the bulk drug substances, which are included in the briefing document posted on FDA's website, identify the proposed and reviewed uses, dosage forms, and routes of administration.

The nominators of these substances have been invited to make a short presentation supporting their nomination. To the extent that the nominators' presentations include information about additional uses, dosage forms, and routes of administration, I remind the committee that these additional uses, dosage forms, and routes of administration are not part of the agency's evaluation because the nominators either did not nominate those uses, dosage forms, and routes of administration, or they were not adequately supported.

The committee will also discuss a revision

FDA is considering to the list of drug products

that have been withdrawn or removed from the market

for reasons of safety or effectiveness, the

Withdrawn or Removed List. FDA now is considering

whether to amend the rule to add one more entry to the list, neomycin sulfate, all parenteral drug products containing neomycin sulfate, except when used for ophthalmic or otic use, or in combination with polymyxin B sulfate for irrigation of the intact bladder.

Let us begin. We will now have Dr. Takyiah Stevenson read the Conflict of Interest Statement for this meeting's 503A Bulks List topics.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug

Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of Boards of Pharmacy, NABP; the United States Pharmacopeia, USP; and the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

During the meeting, the committee will discuss four bulk drug substances nominated for inclusion on the 503A Bulks List. FDA will discuss the following nominated bulk drug substances and the uses that have been reviewed:

- 1) Choline chloride for liver diseases, including non-alcoholic fatty liver disease, and hepatic steatosis, atherosclerosis, fetal alcohol spectrum disorder, and supplementation in long-term total parenteral nutrition;
- 2) Melatonin for the treatment of sleep disorders in patients with autism spectrum disorder, specifically children and adolescents;

3) Methylcobalamin for amyotrophic lateral sclerosis, also known as ALS; pain management; peripheral neuropathy, including diabetic neuropathy; inborn errors of metabolism, also known as genetic metabolic disorders, including methylenetetrahydrofolate reductase deficiency, also known as MTHFR; hyperhomocysteinemia, including conjunctive therapy in hemodialysis patients; vitamin B12 deficiency; and autism spectrum disorder; and

4) Oxitriptan, also known as 5-HTP, for the treatment for patients with tetrahydrobiopterin BH4 deficiency.

The nominators of these substances or another interested party will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which specific matters related to the four bulk drug substances will be discussed. Based on the agenda for this meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have

been issued in accordance with 18 U.S.C. 1 Section 208(b)(3) to Drs. Kathleen Gura and Suthat 2 Liangpunsakul. 3 4 Dr. Gura's waiver involves stock holdings of an affected entity. The aggregate value of her 5 stock is between \$50,000 and \$100,000. 6 Dr. Liangpunsakul is only attending the 7 choline chloride topic, and his waiver involves 8 investment holdings in a healthcare sector mutual fund valued between \$250,000 and \$350,000. 10 The waivers allow these individuals to 11 participate fully in today's deliberations. FDA's 12 reasons for issuing the waivers are described in 13 the waiver documents, which are posted on FDA's 14 website at https://www.fda.gov/advisory-15 committees/committees-and-meeting-materials/human-16 drug-advisory-committees. 17 18 Copies of the waivers may also be obtained 19 by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers 20

Lane, Room 1035, Rockville, Maryland, 20857, or

requests may be sent via fax to 301-827-9267.

21

22

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the bulk drug substances at issue.

We would like to note that Dr. Timothy

Fensky is a representative member from the National

Association of Boards of Pharmacy, NABP, and

Dr. Jeanne Sun is a representative member from the

United States Pharmacopeia, USP.

Section 102 of the Drug Quality and Security
Act amended the Federal Food, Drug, and Cosmetic
Act with respect to the Advisory Committee on
Compounding to include representatives from the
NABP and the USP. Their role is to provide the
committee with the points of view of the NABP and
the USP.

Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue. Instead, they serve as the voice of the NABP and USP, entities with a financial or other stake in the particular

matters before the advisory committee.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Michael Bui and Mr. Richard Green are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Bui is employed by Kadmon Pharmaceuticals and Mr. Green is employed by Cardinal Health Nuclear and Precision Health Solutions.

We would like to remind members and temporary voting members that if the discussions involve any other bulk drug substances or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the topic at issue.

Thank you, and I will hand it back to the 1 2 chairperson, Dr. Gulur. DR. GULUR: Thank you. 3 We will now proceed with the FDA 4 introductory remarks from Dr. Frances Gail Bormel. 5 FDA Introductory Remarks - Frances Gail Bormel 6 MS. BORMEL: Thank you, Dr. Gulur. 7 I am Gail Bormel, the director of the newly 8 formed Office of Compounding Quality and 9 Compliance, the FDA office primarily responsible 10 for, among other initiatives, developing and 11 implementing policies and compliance strategies to 12 help assure the safety and quality of compounded 13 14 drugs. Our office aims to protect patients from the 15 risks of contaminated or otherwise harmful 16 compounded drugs while also preserving access to 17 18 compounded drugs for patients who have a medical need for them. 19 I would like to welcome you to the 20 21 10th meeting of the Pharmacy Compounding Advisory Committee. Today we will discuss four bulk drug 22

substances nominated for inclusion on the list of bulk drug substances that can be used in compounding human drug products under Section 503A of the Federal Food, Drug and Cosmetic Act, or FD&C Act.

This list is known as the 503A Bulks List, and as mentioned before, the substances that will be discussed are melatonin, choline chloride, methylcobalamin, and oxitriptan. Some of these substances may be available as dietary supplements.

As a reminder, the discussion today focuses on FDA's evaluation of these substances as bulk drug substances for use in human drug compounding under Section 503A of the FD&C Act and is not intended to inform FDA's regulation of these substances in dietary supplements.

We also note that the availability of a substance as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are regulated under a different part of the FD&C Act, and different considerations apply to

the regulation of dietary supplements and drugs, including drug products compounded using bulk drug substances under Section 503A.

For example, dietary supplements are intended for oral ingestion, while drugs may be intended for administration by numerous other routes of administration, such as topically, or by parenteral, or intrathecal injection. These different routes of administration raise very different considerations from a regulatory perspective, including safety considerations related to risk of contamination and considerations regarding systemic absorption.

The reviews conducted by the agency for bulk drug substances nominated for the 503A Bulks List follow the criteria described in FDA's regulations implementing Section 503A, which are separate and distinct from FDA's statutory and regulatory provisions governing the treatment of dietary supplements.

During this meeting, we will also discuss whether to add an entry for certain drug products

containing neomycin sulfate to the list of drug products that have been withdrawn or removed from the market because such drug products, or components of such drug products, have been found to be unsafe or not effective. This list, known as the Withdrawn or Removed List, implements conditions under both Section 503A and 503B of the FD&C Act.

As in previous committee meetings, we have scheduled time for the nominators to speak and time for an open public hearing after FDA's presentation on each of the four bulk drug substances. There will also be an open public hearing after the FDA presentation for neomycin sulfate.

I would also like to use this opportunity to provide you with an update on certain developments since the committee last met in September 2018.

Some of these actions affect compounders under Section 503A of the FD&C Act, such as state-licensed pharmacies, federal facilities, and licensed physicians. Other actions affect those compounders known as outsourcing facilities that

are regulated under Section 503B of the Act.

Finally, some of the actions affect compounders
under both sections 503A and 503B.

Since our last PCAC meeting in 2018, the agency has worked to establish and develop a 503A bulks list and a withdrawn and removed list under Section 503A and 503B. In December of 2019, FDA published a final rule that added two entries to the Withdrawn or Removed List. In February of 2019, FDA published a final rule establishing criteria for and placing six bulk drug substances on the 503A Bulks List. The February 2019 final rule also identified four bulk drug substances that FDA had considered and did not include on the 503A Bulks List.

In September of 2019, FDA published a proposed rule identifying five bulk drug substances that FDA has considered and proposed to include on the 503A Bulks List. FDA's proposed rule also identified 26 other bulk drug substances that FDA has considered and proposed not to include on the 503A Bulks List.

Another document that affects compounding under Section 503A was issued in October 2020. FDA issued a final standard memorandum of understanding addressing certain distributions of compounded human drug products were safe to consider and signed, pursuant to Section 503A(b)(3)(B).

The final standard MOU describes the responsibilities of a state board of pharmacy, or other appropriate state agency that chooses to sign an MOU, in investigating and responding to complaints related to drug products compounded in such state and distributed outside such state and in addressing the interest interstate distribution of inordinate amounts of compounded human drug products.

The agency has also been working on policy documents that affect compounders under

Section 503B of the Act, including those that advance their creation of the list of bulk drug substances for which there is a clinical need for use in compounding under Section 503B, which is known as the 503B Bulks List.

In March, 2019, the agency determined that two bulk substances would not be placed on the 503B list. In August 2019, the agency issued a Federal Register notice that proposed not including nine bulk drug substances on the 503B Bulks List. In July of 2020, FDA published a Federal Register notice proposing to place four bulk drug substances on the 503B Bulks List and proposing not to include 19 bulk drug substances on that list.

In March 2021, FDA published a Federal Register notice proposing to add one bulk drug substance to the 503B Bulks List and proposing not to add four bulk drug substances to that list. In January 2020, FDA published a revised draft guidance concerning current good manufacturing, practice requirements for compounders registered under Section 503B of the FD&C Act, which are known as outsourcing facilities.

In November 2020, FDA issued a final guidance on insanitary conditions at compounding facilities that compound drugs under Sections 503A and 503B. This guidance describes examples of

insanitary conditions FDA has observed, and specifically addresses drugs, including biological products, produced by pharmacies, federal facilities, and outsourcing facilities that compound or repackage drugs, or mix, dilute, or repackage biological products.

Notably, during the COVID-19 public health emergency, FDA published five temporary guidances, beginning in March and April 2020, for immediate implementation to provide guidance to states and compounders under Section 503A and 503B on issues associated with compounding drug products during the COVID-19 public health emergency.

These included guidances concerning

compounding of certain drugs or hospitalized

patients; compounding of certain alcohol-based hand

sanitizer products; repackaging or combining

propofol; and use of non-standard practices

regarding the use of personal protective equipment

for sterile pharmacy compounding by pharmacy

compounders not registered as outsourcing

facilities.

All of the FDA's compounding policy documents, including those just discussed, appear on the FDA's compounding website under the section titled, Regulatory Policy Information. Again, thank you for your participation on the Pharmacy Compounding Advisory committee. We look forward to a productive meeting and to continuing to work together.

DR. GULUR: Thank you, Dr. Bormel.

We will now proceed with the FDA presentation, starting with melatonin from Dr. Suhail Kasim.

FDA Presentation - Suhail Kasim

DR. KASIM: Good morning. I am Suhail Kasim from the Office of New Drugs. I will discuss the nomination for melatonin. This slide shows the review staff involved in the evaluation of melatonin.

Melatonin is a hormone nominated for inclusion on the list of bulk drug substances for use in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act, also called

the 503A Bulks List. It was proposed for the treatment of sleep disorders in patients with autism spectrum disorder, specifically children and adolescents in doses ranging from 0.2 milligrams up to 5 milligrams for oral administration, although the dosage forms to be compounded were not specified.

Please note that the discussions of the use of melatonin in the other pediatric populations and in certain adult populations were included in the appendix section of the briefing document, which included the evaluation of melatonin as background information. However, the other uses were not considered for the overall assessment and recommendation.

In conducting the 503 evaluation, FDA reviewed publicly available information to assess melatonin based on four criteria. Information assessed for each of the four criteria will be discussed.

The first criteria applied was the information considered regarding the physical and

chemical characterization of melatonin. Melatonin is well characterized physically and chemically and is likely to be stable under ordinary storage conditions in the solid dosage form. However, it has limited stability in water. Aqueous based liquid melatonin products should have corresponding stability data to support their claimed expiry.

Before discussing the other three criteria, the next few slides will go through the general pharmacology of melatonin. Melatonin is a neurohormone that plays a key role in regulating the sleep-wake circadian rhythm, and its synthesis is associated with circadian rhythms controlled primarily by the light-dark cycle. During daylight hours, the levels of melatonin are low. During nighttime conditions, plasma melatonin levels rise rapidly. Circulating melatonin levels can impact sleep patterns.

The figure illustrates the circadian profile and the timing of endogenous melatonin synthesis influenced by the light-dark cycle. Melatonin production peaks in the middle of the night between

2 a.m. and 4 a.m. in the morning from about 10 to 20 picograms per mL during daylight hours to 100 to 200 picograms per mL during the hours after sundown.

Melatonin secretion is age-dependent. As shown in the right side of figure, the peak nocturnal melatonin levels in most 70 year olds are only a quarter or less of what they are in young adults. Therefore, melatonin secretion varies by age and depends on the time of day for peak secretions; whereas children with autism spectrum disorders and other neurodevelopmental disorders do not have normal physiological production of melatonin.

Therefore, the pharmacological effects of exogenous melatonin on the pharmacodynamic aspects of sleep in populations with neurodevelopment disorders may not be the same as populations experiencing other primary pediatric sleep disorders.

The next two slides discuss the clinical pharmacology of exogenous melatonin. Most of the

melatonin in the circulation is inactivated in the liver after it undergoes first-pass metabolism. It is primarily metabolized by CYP1A2 and CYP2C19, so inhibitors of CYP1A2 enzyme may increase melatonin concentrations.

Exogenous melatonin has low bioavailability, approximately 15 percent, and it is variable as a consequence of hepatic first-pass extraction.

Because the different dosage forms have different effects on absorption, distribution, metabolism, and excretion, melatonin metabolism affects the PK based on the dosage form.

Next, we will discuss the safety. With regard to nonclinical safety, no major toxicities were observed in short-term acute toxicity studies. Several repeat-dose toxicities have been conducted with melatonin, which did not show major toxicities. The longest study reported consists of a 26-week chronic toxicity study in rats, which showed some minor findings. These nonclinical toxicities were at much higher doses than proposed for clinical use.

In a 70-day juvenile toxicity study in rats, no toxicities were seen at much higher doses than proposed for clinical use. The standard panel of genotoxicity assays did not show genetic toxicity activity and melatonin did not have genotoxic adverse effects. In terms of the reproductive and developmental toxicity testing, some malformations were noticed in the rabbit when dams were dosed with much higher doses of melatonin than proposed for clinical use.

Carcinogenicity testing has been conducted for melatonin in the rat, and increased incidence of pituitary adenomas and thyroid tumors were seen among animals treated with the highest dose when compared to control vehicles. Overall, the nonclinical testing program for melatonin was extensive and has been shown to have high safety margins at the proposed clinical doses.

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Event

Reporting System for reports of adverse events for melatonin in addition to a review of the medical

literature for potential safety signals reported of melatonin. The FAERS reported adverse events were consistent with the known safety profile of melatonin, including information that is discussed in the literature. The reports included cases in children with autism spectrum disorder, and we will elaborate on these adverse event profiles in the subsequent slides.

The FAERS reported adverse events also are primarily consistent of acute reactions to short-term exposure rather than exposure data for longer term effects. For few serious FAERS events identified, the information was confounded by use of melatonin with other concomitantly used medications, comorbid disease state, possible drug-drug interactions, or it lacked enough details precluding the ability to determine a drug event association.

Three patients reported using melatonin for sleep disorder in autism spectrum disorder or neurodevelopmental disorder. Melatonin was used to manage sleep that was a reaction to the drug used

to manage a comorbidity in children with autism spectrum disorder. These three FAERS cases highlight the medical complexities, including polypharmacy in children and adolescents with autism spectrum disorder or neurodevelopmental disorder.

The figure shows single-substance melatonin exposure cases documented by the United States poison and control centers per year, from 2008 to 2020. There is a trend for a rising number of reports to the American Association of Poison Control Center's National Poison Data System. The observed trend may be secondary to the increased use of melatonin.

The most commonly reported reasons for all calls to U.S. poison control centers were for general unintentional exposure, which accounted for 82 percent, and therapeutic error, which accounted for 9 percent. Overall, poison center calls related to general unintentional exposure were predominantly comprised of younger children with 91 percent being reported with children under the

age of 5 years.

CAERS data included 238 spontaneously reported cases that included at least one adverse event in association with the use of melatonin.

Some cases listed as many as 73 different ingredients in the suspect product containing melatonin.

In most of the CAERS cases, there was insufficient information reported, and it was not possible to determine whether a causal connection existed between the use of melatonin and the adverse events reported because of the considerable number of other ingredients in the suspect melatonin product or that melatonin was used with other concomitant medications.

The table shows pooled adverse events in controlled clinical trials associated with melatonin for primary or secondary sleep disorders in children and in adults. The daily melatonin doses reviewed in these systematically reviewed studies range from 0.15 milligrams up to 12 milligrams.

Adverse events were characterized as generally infrequent, mild, or moderate in severity and were either self-limiting or resolved on withdrawal of treatment. These included daytime sleepiness, dizziness, hypothermia, decreased appetite, and restlessness. The first column shows the number of studies these events were noted in, and the second and third columns show the events that were recorded for these particular adverse events.

This table shows safety data from the double-blind, randomized, placebo-controlled study in patients with autism spectrum disorder who have not shown improvement after standard sleep behavioral intervention.

For the pooled melatonin doses,

2 milligrams, 5 milligrams, or 10 milligrams,
during the double-blind period, the AE rate
compared to placebo, for somnolence there was

28 percent event rates reported versus 12 percent;
for fatigue, 25 percent versus 19 percent; and for
agitation, 18 percent versus 10 percent. These

were some of the events reported in the doubleblind controlled studies shown in the first two columns over here.

During the 91-week long term safety

follow-up on study, shown in the columns on the

right side of the table, similar types of adverse

events that were reported during the double-blind

study were also observed during that open-label

study period.

The treatment-related somnolence and fatigue were considered to reflect the pharmacological effect of residual data in melatonin most probably secondary to a higher dose. It was also possible that some of these participants had a differential response and were poor metabolizers of CYP1A2 enzyme, developing daytime somnolence or fatigue owing to melatonin accumulation.

Because endogenous melatonin levels in humans sharply decline just before the onset of puberty, there may be a potential risk of delayed sexual maturity with gonadal development in prepubertal children taking melatonin over extended

periods, and animal studies have supported this theory. Although, in the long-term study that was discussed in the previous slide, in a subset of those children and adolescents with autism spectrum disorder, there was no reported delay in sexual maturation or pubertal development with orally administered prolonged release or controlled-release melatonin after two years of continuous use.

Melatonin appears to be relatively safe and well tolerated for oral administration at the nominators' proposed dose, 0.2 milligrams up to 5 milligrams in children and adolescents with autism spectrum disorders.

Before discussing the effectiveness data for melatonin that is the third criteria in the 503 evaluation, I'll spend a few minutes on the next two slides.

Disorders of sleep are one of the co-occurring medical conditions in patients with autism spectrum disorder, and it can also worsen the core symptoms of autism spectrum disorders.

Sleep disorders are common and severe in children with neurodevelopment disorders like autism spectrum disorders compared with typically developing children.

Sleep disorders in children and adolescents with autism spectrum disorders include difficulties initiating and maintaining sleep; frequent and prolonged night awakenings; irregular sleep-wake patterns; short sleep duration; and early morning awakenings. For the evaluation of effectiveness of melatonin on sleep disorders in pediatric patients with autism spectrum disorders, the following sleep outcomes are considered: sleep onset latency; night awakenings, and total sleep time.

The middle section of the forest plot figure shown here, that is a meta-analysis of the controlled trials in the systematic review, show that the treatment effect estimate were all in the direction showing benefit with melatonin in the patients with autism spectrum disorders who experienced sleep disorders for the sleep diary reported sleep onset latency outcomes, regardless

of the dosage form of melatonin, when used in the short term. Melatonin decreased sleep onset latency with median duration of 28 minutes and a pooled mean difference reduction of by 35 minutes.

Similarly, in the upper section of the forest plot figure shown here, melatonin increased sleep duration or total sleep time with medium duration of 33 minutes and pooled mean difference, 64 minutes. Please note that in this figure, the studies that favor the outcome for melatonin are on the right side.

The improvements in total sleep time while on melatonin treatment appear to be due to earlier sleep onset. Although not shown here, there was no improvement in the number of awakenings per night. Adding behavioral intervention to melatonin treatment resulted in a better treatment response on the outcomes.

In conclusion, melatonin may be effective for the short-term treatment of sleep disorders in children and adolescents with autism spectrum disorder under the supervision and care of a

healthcare practitioner. The treatment response in favor of melatonin for the pharmacodynamic sleep outcomes evaluated may vary based on the melatonin dose, the timing of administration, and the dosage form.

Lastly, we apply the fourth criterion that is the historical use of melatonin compounded drug products. Melatonin has been used in pharmacy compounding since at least 2009 and has been compounded in a variety of dosage forms. According to the Johns Hopkins University CERSI report, melatonin is sometimes used as a sleep aid in patients with autism spectrum disorder in the United States. Melatonin is approved for use in Europe, Australia, and Japan.

We have balanced the four criteria that was discussed to evaluate melatonin for the 503A Bulks List. Based on the information that we have considered, a balancing of the four evaluation criteria weighs in favor of melatonin for oral administration being added to the 503A Bulks List. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Kasim.

We will now take clarifying questions for FDA presenters. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

With this, I would like to invite the question. I see Dr. Emens has raised his hand; if you could speak.

DR. EMENS: Hi. This is Jonathan Emens.

Thank you, Dr. Kasim. My only question

is -- and I don't know if you are prepared to

comment on this, but could you talk about the 1 magnitude of the fact in terms of increases in 2 total sleep time and decreases in sleep latency 3 4 relative to other treatments for insomnia? DR. KASIM: Dr. Gulur, can I respond to the 5 question? 6 7 DR. GULUR: Yes, please. DR. KASIM: Dr. Emens, thank you for that 8 First of all, I have to acknowledge, as question. 10 you may be aware, there are no FDA-approved products for pediatric use. There are products 11 that are being used off label; that is FDA-approved 12 products that are being used off label for use in 13 14 the pediatric population. But in terms of comparative efficacy that 15 have been used along with melatonin, I was not able 16 to come across any data to indicate -- except from 17 the recommendations for the Academy of Neurology 18 19 and the Academy of Pediatrics, which made

22 information that was specific in relation to other

recommendations, including discussions for

melatonin. But I did not come across any

20

21

products that are being used for managing sleep 1 disorders. 2 I hope that answers your question. 3 4 you. 5 DR. GULUR: Thank you, Dr. Kasim. Dr. Emens, I see your hand is not raised 6 anymore and will assume that you have no further 7 questions. 8 Thank you. No further 9 DR. EMENS: questions. 10 Committee Discussion and Vote 11 DR. GULUR: I do not see any other raised 12 hands, so with that we will conclude this section 13 on clarifying questions for the presenters. 14 15 I would like to state into the record that we do not have a nominator presentation for this 16 topic. I would also like to state into the record 17 that there are no open public hearing speakers for 18 19 this topic. With that, the open public hearing portion 20 21 of this meeting has now concluded and we will no

longer take comments from the audience.

22

We will now give another opportunity for remaining clarifying questions for all the melatonin presenters. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked your question.

Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

At this time, I do not see any raised hands for further clarifying questions. With that, we will move into the panel discussion question part of the meeting.

Would the panel members like to discuss the topic and present their views?

(No response.)

DR. GULUR: Seeing there is no discussion, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments, which were not present for this particular in the open public hearing.

We will proceed with the question to the committee and panel discussions for melatonin. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Today's question is a voting question.

Dr. Takyiah Stevenson will provide instructions for the voting.

DR. STEVENSON: Question 1 is a voting question. Voting members will use the Adobe

Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote

question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster, and each voting member will state their name and their vote into the record.

You can also state the reason why you voted as you 1 did, if you want to. 2 Are there any questions about the voting 3 process before we begin? 4 (No response.) 5 DR. GULUR: As there are no questions, I 6 will now read the question at hand. 7 FDA is proposing that melatonin for oral 8 administration be included on the 503A Bulks List. 9 Should melatonin for oral administration be placed 10 on the list? 11 Do voting panel members have any questions 12 about the wording of the question itself? 13 14 (No response.) DR. GULUR: Seeing none, if you vote no, you 15 are recommending FDA not place the bulk drug 16 substance on the 503A Bulks List. If the substance 17 18 is not on the list when the final rule is 19 promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes 20 21 subject of an applicable USP or NF monograph, or a component of an FDA-approved drug. 22

If there are no questions or comments 1 concerning the wording of the question, we will now 2 begin the voting on question for melatonin. 3 4 Dr. Vaida, I see you have a question. DR. VAIDA: Yes. My only question is, this 5 is just for oral administration, correct? 6 DR. GULUR: Correct. That is what the 7 question states, only oral administration. 8 Does that answer your question, Dr. Vaida? 9 DR. VAIDA: Yes, it does. Thank you. 10 DR. GULUR: Thank you. 11 Do you have any other questions? 12 13 (No response.) DR. GULUR: Since there are no questions or 14 comments concerning the wording of the question, we 15 will now begin the voting on the question for 16 melatonin. 17 18 DR. STEVENSON: We will now move voting 19 members to the voting breakout room to vote only. There will be no discussion in the voting breakout 20 21 room. (Voting.) 22

DR. STEVENSON: The voting has closed and is 1 now complete. Once the vote results display, I 2 will read the vote result into the record. 3 4 (Pause.) DR. STEVENSON: Voting has closed and is now 5 complete. The vote results are displayed. 6 read the vote totals into the record. 7 chairperson will go down the list and each voting 8 member will state their name and their vote into 9 the record. You can also state the reason why you 10 voted as you did, if you want to. 11 12 There are 13 yeses, zero noes, zero abstentions. 13 14 DR. GULUR: Thank you. We will now go down the list and have everyone who voted state their 15 name and vote into the record. You may also 16 provide justification for your vote, if you wish 17 18 to. 19 We'll start with Dr. Gura. DR. GURA: Hi. Kathleen Gura. 20 I vote yes. 21 DR. GULUR: Dr. McElhiney? DR. McELHINEY: Linda McElhiney. I vote 22

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1
      yes.
             DR. GULUR:
2
                          Thank you.
             Dr. Desai?
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             DR. DESAI: Hi. Seemal Desai. I voted yes,
5
     and I appreciate the FDA's clear presentation on
     the data.
6
7
             DR. GULUR:
                          Thank you, Dr. Desai.
             Padma Gulur. I voted yes.
8
             Dr. Rebello?
9
             DR. REBELLO: Elizabeth Rebello. I voted
10
      yes.
11
             DR. GULUR: Dr. Fensky?
12
13
             DR. FENSKY: Tim Fensky. I voted yes.
14
             DR. GULUR:
                          Dr. Bogner?
15
             DR. BOGNER: Robin Bogner. I voted yes.
             DR. GULUR: Dr. Sun?
16
             DR. SUN:
                       Jeanne Sun. I voted yes.
17
18
             DR. GULUR: Dr. Emens?
19
             DR. EMENS:
                          Jonathan Emens. I voted yes.
             DR. GULUR:
                          Dr. Vaida?
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21
             DR. VAIDA: Allen Vaida. I voted yes.
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             DR. GULUR: Dr. Patel?
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DR. PATEL: Kuldip Patel. I voted yes,
1
     based on the data presented by the FDA.
2
             DR. GULUR:
                          Thank you.
3
             Dr. Gupta?
4
             DR. GUPTA:
                          Anita Gupta. I voted yes.
5
             DR. GULUR: Ms. Fusco-Walker?
6
             MS. FUSCO-WALKER: Sandra Fusco-Walker.
7
                                                        Ι
     voted yes.
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9
             DR. GULUR:
                          Thank you, everyone.
             We will now take a 15-minute break.
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                                                   We will
      reconvene at 11:55 Eastern time for the
11
     methylcobalamin topic. Panel members, please
12
      remember that there should be no chatting or
13
     discussion of the meeting topics with other panel
14
     members during the break. Thank you.
15
              (Whereupon, at 11:39 a.m., a recess was
16
     taken.)
17
18
             DR. GULUR: Welcome back, everyone.
19
             We will now proceed with the FDA
     presentation on methylcobalamin from Dr. Susan
20
21
      Johnson.
             DR. JOHNSON: Hello? Can you hear me?
22
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DR. GULUR: Yes, we can hear you now. 1 DR. JOHNSON: Thank you. 2 FDA Presentation - Susan Johnson 3 DR. JOHNSON: Good morning, just. My name 4 is Susan Johnson, and I'm a clinical reviewer in 5 the Pharmacy Compounding Review Team. I'll be 6 discussing the FDA review of methylcobalamin. 7 I'd like to thank the methylcobalamin 8 primary review team and give special thanks to the 9 clinical review staff in several therapeutic review 10 divisions in the Office of New Drugs. 11 Representatives of each division listed on this 12 slide have joined us to help should questions arise 13 about their medical specialty. 14 Methylcobalamin has been nominated for 15 inclusion on the list of bulk drug substances for 16 use in compounding under Section 503A of the 17 18 FD&C Act. It was reviewed for use in the treatment 19 of vitamin B12 deficiency, various inborn errors of metabolism, hyperhomocysteinemia, autism spectrum 20 21 disorder, amyotrophic lateral sclerosis, and various peripheral neuropathies and pain 22

conditions. The proposed dosage forms include oral, sublingual, nasal spray, and injectable solution for subcutaneous or infusion administration.

Turning now to the physical and chemical characterization of methylcobalamin, methylcobalamin is one of four structurally related vitamers of vitamin B12. Each vitamer has a different ligand attached to the same cobalamin base.

This is a table for reference comparing selected features of the various cobalamins.

Methylcobalamin is a naturally occurring substance in human and animal protein. Methylcobalamin is not a component of FDA-approved products.

The B12 vitamers, hydroxocobalamin and cyanocobalamin, both are in FDA-approved products primarily for use via intramuscular injection, although there is an approved nasal spray product. Each of the vitamers is available in oral dietary supplements, and as we heard earlier, today's discussion does not address dietary supplement

products.

Methylcobalamin is stable at room

temperature and solid formulations when protected

from light. An aqueous solution is stable when

protected from light and stored at a controlled

temperature with a controlled pH. We conclude that

methylcobalamin is well characterized, and if

formulated and stored appropriately, would be

stable in solid and liquid dosage forms.

Moving now to safety, beginning with general pharmacology, when orally ingested, all the cobalamins are initially separated from proteins to which they may be naturally bound and then attached to the protein haptocorrin. As they move to the duodenum and ileum, they are dissociated from haptocorrin and become attached to a second protein commonly referred to as intrinsic factor.

The complex is then moved into ileal enterocytes via a receptor-mediated, calcium-dependent endocytosis. Once absorbed into the systemic circulation, all cobalamins are transported through the plasma in an inactive state

attached to transcobalamin or haptocorrin. Passive absorption of cobalamin also occurs throughout the gastrointestinal tract.

The model on this slide was compiled by its authors from a literature review of the pharmacokinetics of cobalamin. It shows that each type of cobalamin, including methylcobalamin, reaches the cell wall in an inactive state.

Cobalamins are then absorbed into the cytosol, where the unique ligands are removed and each is reduced to the base cobalamin molecule. The overall process to reduce each to the base molecule is the same for each cobalamin, although the kinetics and enzymes involved are specific to each.

From the base cobalamin molecule, active methylcobalamin and adenosylcobalamin are formed. The multiple metabolic steps in this diagram are controlled by enzymes and cofactors whose actions may be altered due to inborn errors of metabolism that we will discuss later.

In the center of this diagram, B12 represents active methylcobalamin. Active

methylcobalamin is a cofactor from methionine synthase in the reaction that methylates homocysteine, converting it to methionine.

Methionine is in turn important in generating S-adenosylmethionine, or SAM, and then SAM-e that are critical to DNA and RNA synthesis.

Nonclinical pharmacokinetics suggest a saturable absorption process and renal excretion, which are consistent with human pharmacology.

Acute toxicity studies show it safe to be given at high doses for short periods of time, but other elements of a full, nonclinical safety program were not found in the literature.

We found limited clinical pharmacokinetic data for methylcobalamin. Oral bioavailability is inversely proportional to the consumed dose. A small amount of cobalamin from dietary intake amounting to several milligrams is stored in the liver, and only 0.1 to 0.2 percent of that is lost per day due to metabolic activity.

Turning to clinical safety information, the clinical studies of methylcobalamin that we

reviewed provided limited adverse event information, but several studies included reports of non-serious adverse events. We looked at the labeling of the FDA-approved cobalamin products, as they may provide safety information that is relevant to methylcobalamin based on the apparent comparability of their pharmacologic action.

Although the most common reactions seen in labeling for hydroxocobalamin and cyanocobalamin products are non-serious, the approved drugs have been associated with serious and fatal events, and we find that these may occur with methylcobalamin as well.

FAERS data showed 174 reports of serious adverse events. Two cases reported use of methylcobalamin alone, including one of apparent jaundice in a 3 year old receiving methylcobalamin. Neither case reported sufficient information to establish causality.

CAERS data regarding use of dietary supplement products and included 384 reports and, among these, there were 6 deaths reported. No

reports appear to have sufficient information to assess causality, and most are confounded by use of multiple ingredient products or multiple concomitant products. There were two cases in which methylcobalamin was the only product reported to have been used.

In conclusion regarding safety,
methylcobalamin is found in food, and its use
orally as a dietary supplement does not appear to
be associated with serious adverse events. Serious
adverse events that are listed in FDA-approved
labeling for injectable hydroxocobalamin and
cyanocobalamin products could occur with
methylcobalamin based on the comparability of
mechanism of action. Overall, we have a concern
regarding lack of available safety data with
methylcobalamin, particularly for intravenous
injections and infusions.

Turning now to the effectiveness factor in the review, the first use we looked at was vitamin B12 deficiency. This condition used to be commonly associated with causing pernicious anemia,

but methyl B12 deficiency is now seen mainly in older patients with age-related changes in the function of gastric parietal cells, or intrinsic factor, or in individuals with low B12 intake levels such as vegans.

One observational study of the use of oral methylcobalamin in children was found from India where methylcobalamin is more commonly used than the cobalamins approved in the U.S. This study reported the correction of low cobalamin levels in 27 of the 28 children dosed orally for one month with methylcobalamin.

In conclusion regarding the effectiveness of methylcobalamin for the treatment of vitamin B12 deficiency, the pharmacologic mechanism of methylcobalamin appears comparable to that of FDA-approved cobalamin products, and we find that it's likely to be effective in treating vitamin B12 deficiency.

We also found limited clinical data to support its use in oral form to treat vitamin B12 deficiency. However, no data were found that show

hydroxocobalamin or cyanocobalamin injectable products are insufficient to provide treatment for vitamin B12 deficiency when an injectable product is required.

We next reviewed the use of methylcobalamin to treat inborn errors of metabolism. These are caused by genetic mutations. There are numerous inborn errors of metabolism that affect absorption, transport in the blood, intracellular metabolism, or physiologic actions of the cobalamins. Some of these disorders, such as methylmalonic aciduria, are responsive to chronic supplemental administration of hydroxocobalamin or cyanocobalamin. No studies of the use of methylcobalamin in these disorders were found.

Methylene-tetrahydrofolate reductase, MTHFR, deficiency, and MTHF dehydrogenase deficiency are inborn errors of the folate cycle. They are treated with folic acid and betaine. Classic homocystinuria is an inborn error of metabolism that decreases the conversion of homocysteine to cysteine. It's treated with hydroxocobalamin. No

clinical studies were found that support the use of methylcobalamin in the treatment of these inborn errors of metabolism.

The next use we reviewed is

hyperhomocysteinemia. This is not an inborn error

of metabolism and can result from a variety of

causes, including the use of certain drugs such as

metformin. Eighty-five percent of patients with

chronic kidney disease have hyperhomocysteinemia.

Current practice guidelines for these patients do

not recommend routine use of folate or vitamin B12,

except in cases of deficiency. We found no

specific data to support the effectiveness of

methylcobalamin to treat hyperhomocysteinemia.

Looking at the use of methylcobalamin to treat autism spectrum disorder, or ASD, we found four published studies. Two studies were uncontrolled and each included approximately 40 patients. Due to lack of a control arm, neither provide substantive information about whether methylcobalamin is effective in ASD.

In the first of two controlled studies, no

the methylcobalamin and placebo groups. In the second controlled study, there was a statistically significant difference between methylcobalamin and placebo on a non-specific measure of clinical improvement, but this finding was not associated with differences between the treatment groups with respect to behavioral scales specific to ASD symptoms. These studies do not support the effectiveness of methylcobalamin to treat ASD.

The Johns Hopkins CERSI study will be discussed again later with respect to use of methylcobalamin in ASD patients. To assess effectiveness, key opinion leaders were queried and responded that B12 would have no effect in ASD unless being used to treat a dietary deficiency. We conclude that we found no specific data to support the effectiveness of methylcobalamin in treating ASD.

The next use that we reviewed was amyotrophic lateral sclerosis or ALS. Based on the results of a post hoc analysis of a phase 2/3 study

conducted by a Japanese pharmaceutical firm, the same firm decided to undertake another study. We have not found that the results of the second study have been published. We conclude that we were unable to identify studies that show methylcobalamin is effective in the treatment of ALS.

Studies of the use of methylcobalamin, in the treatment of various types of neuropathy, analyzed for within rather than between group responses, were subject to bias per the author or failed to show statistically significant differences between methylcobalamin and placebo. The available data do not support methylcobalamin's effectiveness in the treatment of peripheral neuropathy.

Studies of methylcobalamin to treat pain either failed to show differences between treatments or did not analyze differences between active and placebo groups. Available data do not support methylcobalamin effectiveness in the treatment of pain.

In conclusion regarding effectiveness, the pharmacologic mechanism of methylcobalamin suggests that like FDA-approved cobalamin products, methylcobalamin is likely to be effective in treating vitamin B12 deficiency, but we found no data regarding clinical situations in which the FDA approved cobalamin products are insufficient to provide treatment when an injectable treatment is needed. We found negligible or no specific information to support effectiveness of methylcobalamin to treat inborn errors of metabolism, hyperhomocysteinemia, ASD, ALS, peripheral neuropathy, or pain.

Turning to the fourth factor of use in compounding, FDA requested a review from the University of Maryland CERSI. They found little information to characterize methylcobalamin's use. Johns Hopkins CERSI was asked to look at methylcobalamin use in patients with autism spectrum disorder. Data were derived from a clinical sample of nearly 1800 patients at the Kennedy Krieger Institute, a registry population

sample, and a Medicaid claims search. Estimates of the portion of ASD patients who used methylcobalamin ranged from less than 1 percent to 6 percent of ASD patients.

FDA found online promotions from compounding pharmacies and treatment clinics promoting methylcobalamin for a wide variety of conditions and diseases, such as depression, Alzheimer's disease, AIDS, and ASD. A number of different routes of administration were described, including intravenous infusions.

In summary, we consider methylcobalamin to be physically and chemically well characterized if formulated and stored properly. I want to highlight considerations related to the other factors.

Methylcobalamin is a vitamer of vitamin B12, so based on pharmacology and the use of FDA-approved cobalamin products, methylcobalamin would be expected to be effective in treating vitamin B12 deficiency, however, it's unclear that methylcobalamin provides a unique benefit over the

other vitamers of B12 that are available in FDA-approved products.

It is also unclear that the treatment of vitamin B12 deficiency is currently the primary use of compounded injectable methylcobalamin in the United States. It appears that the primary use is to treat patients with conditions, in some cases serious, for which there is little evidence to support the effectiveness of methylcobalamin. In these situations, we do not have information on the range of doses used or the frequency of administration, and we find that we cannot make a judgment regarding the safety of the current use of injectable products in patients.

Therefore, we find that a balancing of the four evaluation criteria weighs against methylcobalamin being added to the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act. Thank you.

I'm happy to take questions.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Johnson.

We will now take clarifying questions for 1 FDA presenters. Please use the raised-hand icon to 2 indicate that you have a question and remember to 3 4 clear the icon after you have asked your question. When acknowledged, please remember to state your 5 name for the record before you speak and direct 6 your questions to a specific presenter, if you can. 7 If you wish for a specific slide to be 8 displayed, please let us know the slide number, if 9 possible. Finally, it would be helpful to 10 acknowledge the end of your question with a thank 11 you and the end of your follow-up question with, 12 "That is all for my questions," so we can move on 13 to the next panel member. 14 With that, I would request that the summary 15 slide for methylcobalamin that was just presented 16 be displayed. 17 18 (Pause.) 19 DR. GULUR: Thank you. If we could display slide 30, and once that is done, I would request 20 21 Dr. Patel, who has a question, to speak.

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DR. PATEL: Hello. This is Kuldip Patel.

Thank you, Dr. Johnson, for that 1 presentation. I just wanted to better understand a 2 little bit more of the two controlled studies that 3 4 were summarized. I believe it was mentioned that the difference was not statistically significant, 5 so I just wanted to know a little more in depth of 6 what -- at least one of the two controlled, it 7 seemed like there might have been equivalency, but 8 we didn't get a chance to understand the details of 10 what was being compared and what were the endpoints that were being looked at. Thank you. 11 DR. JOHNSON: Sure. Do we want to pull up 12 slide 22, please? 13 14 (Pause.) DR. STEVENSON: Susan, I can operate your 15 slides for you. This is Takyiah Stevenson 16 speaking. I can move your slides for you; just one 17 18 moment. I got it; one moment. 19 Go ahead, Susan. You can speak. DR. JOHNSON: Thanks. 20 21 DR. STEVENSON: Sure. DR. JOHNSON: Great. Thanks very much. 22

So let's look at the details. One of the things that I would point out about these studies is that they're relatively small, and had they found a lot of effects in ASD, it was still pretty, perhaps, hard to judge whether they were generalizable to the entire ASD population.

In the Bertoglio study -- I think we have folks who are connected with these studies in the nominator presentation, so we may be able to ask more questions about the actual occurrence that maybe are argued in the publications.

But I would point out that the Bertoglio study was a double-blind, placebo-controlled, crossover study of 30 children aged 3 to 8. They received 6 weeks of treatment with 64.5 micrograms per kilogram of methylcobalamin, and they received it subcutaneously every 3 days, and then they received the alternate treatment.

So there were multiple endpoints studied, including a fairly commonly administered Clinical Global Impression-Improvement scale. I can list for you the other scales. I'm not sure if that's

something that you would be interested in.

The second study was a double-blind placebo-controlled study in 57 children ages 3 to 7. They were treated for 8 weeks with 75 micrograms per kilogram or placebo every 3 days. There was a within-group improvement in CGI-I that was statistically higher for the methylcobalamin group than placebo, but no difference on two other behavior scales that assess the ASD specific aspects; and those were the parent-rated ABC or the Social Responsiveness Scale.

I'm not an expert on these scales, and we have subject matter experts in ASD who could perhaps comment further if there were specific questions about what was looked at or what was found.

DR. PATEL: This is Kuldip Patel. It would be helpful to know if that improvement scale is a standard measure that is used for better understanding effectiveness of treatment options in this disorder.

DR. JOHNSON: Sure. We have online Dr. Hong

and Dr. Rasetti from the Division of Psychiatry, 1 and Dr. Rasetti would like to speak to this 2 question. 3 4 DR. RASETTI: Yes. Can you hear me? DR. JOHNSON: Yes, we can. Thank you. 5 DR. RASETTI: Alright. 6 I'm Dr. Rasetti from the Division of 7 Yes. Psychiatry. Regarding the first study of Bertoglio 8 from 2010, they used as outcome measures, besides 9 the CGI-I, the Clinical Global Impression-10 Improvement, they used the Aberrant Behavior 11 Checklist, the ABC. This is the usual scale that 12 we use also in the agency. 13 Plus we use the other four different scales, 14 the Parent Interview for Autism-Clinical Version; 15 then the Peabody Picture Vocabulary Test; and then 16 the MacArthur Communication Development Inventory. 17 18 When they looked at this scale and all the behavior 19 scales and improvement scales, they were not able to identify any difference compared to placebo, as 20 21 Dr. Johnson said. The second study, the Hendren study from 22

2016, they used three outcome measures. One was the Clinical Global Impression-Improvement scale, and the other two were, again, the Aberrant Behavior Checklist scale and also the Social Responsiveness Scale. They were not able to find any significant difference between placebo and the methylcobalamin in the behavioral scales.

Regarding the CGI-I scale, when they look at that, there is a percentage of improvement, so they treat it like a categorical variable -- this is usually what we do -- and they did not find any significant difference. When they look at it as a continuous variable, they were able to find a significant difference of 0.7 points. It actually is less than 1 point. This is what is required to move from one category to the other one; taken from the CGI, 4 is no improvement and 3 would be mild improvement.

Did I answer your question?

DR. PATEL: Yes, ma'am. Thank you.

DR. RASETTI: Thank you.

DR. GULUR: Thank you, Dr. Patel. Does that

answer your question? Do you have any further 1 2 questions? DR. PATEL: No, that was very helpful. 3 4 Thank you. DR. GULUR: Thank you. 5 I do have a question for the specialist who 6 was just speaking about this very scale as a 7 follow-through. Again, not being an expert, but 8 looking up the CGI and how it's conducted, it appears there's no universally accepted scoring 10 guidelines for the 7 points. Rather, it sounds 11 like it was based solely on clinical judgment, and 12 it seems to go with clinical gut sense about how 13 14 the patient is doing. How is it used in research in a standard way 15 to compare between, considering that there could be 16 clinician bias? 17 18 DR. RASETTI: Okay. Thank you for the 19 question. This is a very important point, and we agree with you. Usually, for example, the two 20 21 drugs that have been approved by the FDA for autism spectrum disorder, it is a combination of the ABC 22

scale and the CGI-I scale; only the CGI-I scale is 1 not enough. 2 Did that answer your question? 3 DR. GULUR: Yes, it does. Thank you very 4 I appreciate it. 5 much. We do have Dr. Desai who has a question. 6 you would speak. 7 DR. DESAI: Thank you, Dr. Gulur. 8 appreciate the FDA's thorough presentation and 9 walking us through this, as well as the input from 10 our specialist on the call. 11 My question is more related back to the 12 beginning of Dr. Johnson's presentation and the 13 stability. It seemed like one of the concerns, 14 based on what was presented, was the IV 15 formulations. I'm just trying to get a sense of 16 when would these factors have been presented. 17 18 Was the stability one of the major concerns 19 from the FDA team when reviewing this? DR. JOHNSON: This is Sue Johnson. It was 20 21 not a primary concern for us largely because we think that this is a manageable formulation issue, 22

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and that if proper steps were taken in terms of
1
      light, pH and temperature, a formulation that could
2
     work could be generated by compounding pharmacies.
3
4
             We can talk a little bit more [inaudible -
     audio lost] --
5
             DR. DESAI: Did we lose Dr. Johnson?
6
             DR. GULUR: Dr. Johnson, we're not able to
7
     hear you.
8
9
              (No response.)
             DR. GULUR: Dr. Johnson, are you on mute?
10
             (No response.)
11
             DR. GULUR: We will give Dr. Johnson a few
12
     minutes to reconnect.
13
14
             (Pause.)
             DR. JOHNSON: Dr. Johnson, are you
15
     reconnected?
16
             DR. JOHNSON: Yes? Hi. I've changed
17
18
     phones. Dr. Ganley's letting me use his setup.
19
     don't know why it flipped me out, but it wouldn't
      let me dial back in with the same number.
20
21
             DR. GULUR: Not a problem. We're glad to
     have you back.
22
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DR. JOHNSON: We're back.

The main point about the formulation issues is that we did not find that to be a significant consideration in recommending that methylcobalamin not be added to the 503A list. We think that the formulation issues could be overcome by compounding pharmacies.

DR. DESAI: Thank you, Dr. Johnson. I think what I'm just trying to ascertain, because there was such a large breadth of points made in your very nice presentation, is what would you say is the main concern for this not to be included?

DR. JOHNSON: Thanks for that question.

Yes. There were a lot of nominated conditions and a lot of different types of data sets, so it is difficult to coalesce into one recommendation.

But I think our primary concern is that while we do feel that methylcobalamin should act in the same pharmacologic manner as the other cobalamins and therefore be effective for treating vitamin B12 deficiency, its use -- and I think we'll hear some more about this in the nominator

presentations -- does not seem to be related to 1 treatment of vitamin B12 deficiency primarily. 2 Ιt seems to be being used in a number of other 3 4 conditions, and not as an oral product but as an injectable product, as subcutaneous, IM, 5 intravenous, and intravenous infusion. Those we 6 just feel we don't have a lot of safety information 7 on; practically none. 8 One of the things that you'll find in the literature is that methylcobalamin is used much 10 more in Asia and Australia. It just isn't used as 11 much as the other FDA-approved cobalamins, so we 12 have more data on those. But the main 13 14 consideration is the way it's being used is something that we do not have a lot of safety 15 information about. 16 DR. DESAI: Thank you, Dr. Johnson. 17 18 DR. JOHNSON: And I would just add such as 19 the range of doses, frequency of doses, exactly what treatments people are receiving. 20 21 DR. GULUR: Thank you, Dr. Johnson.

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Dr. Desai, did that answer your question?

DR. DESAI: Yes. Thank you, Dr. Gulur. 1 Dr. Ganley, I see that your hand DR. GULUR: 2 is raised. Would you like to speak? 3 DR. JOHNSON: Oh. He raised his hand so he 4 would be recognized for me to get back in. 5 DR. GULUR: I see. Thank you very much. 6 I do not see any other hands -- well, I just 7 see Dr. Katzman. I see your hand is raised. 8 DR. KATZMAN: Yes. Thank you. Yes. 9 This is Joanna Katzman here. 10 Dr. Johnson, thank you so much for your 11 great presentation. Your last comment about the 12 uses of methylcobalamin for indications outside of 13 the United States, predominantly studies done in 14 Asia for neurological conditions, was very helpful. 15 In fact, I've seen some recent studies for subacute 16 postherpetic neuralgia and more remote studies for 17 18 chronic post-thoracotomy pain that actually looks 19 fairly decent, although, like you said, they need more data and they haven't really been done here in 20 21 the U.S. My question to you, Dr. Johnson, is wanting 22

to know if you've seen any studies looking at comparing methylcobalamin with the other types of cobalamins, any kind of crossover studies with the conditions listed, to look for any efficacy or safety issues that might prohibit the use of methylcobalamin for low B12 or effectiveness in any of the indicated conditions.

DR. JOHNSON: That's an interesting question. Part of where our review started was to find out if, in fact, methylcobalamin added to the armamentarium for B12 products.

DR. KATZMAN: Right.

DR. JOHNSON: And we did not find comparative information that will allow us -- and I think the point of the presentation is we don't have information that shows the FDA-approved products are insufficient, and we did not find comparative information that showed that methylcobalamin, with the exception of the vitamin B12 deficiency, would be effective for the same indications that the approved cobalamins are used for.

Does that answer your question? We had 1 hoped to find that as well, but we did not. 2 DR. KATZMAN: Right. Right. 3 Can I just ask one more question in a little 4 bit of a different way, Dr. Johnson? Are there any 5 contraindications to using methylcobalamin for 6 nutritional repletion in patients with vitamin B12 7 deficiency, in addition to the other two 8 cobalamins? 9 DR. JOHNSON: I'm going to let our expert 10 speak on this. My understanding is if one treats 11 pernicious anemia too aggressively, one can cause 12 permanent neurologic damage. That is the only 13 significant treatment caution that I have seen 14 associated with it. 15 But I'm going to ask from the Division of 16 Non-Malignant Hematology, Dr. Ryan or 17 18 Dr. Deisseroth, if you'd like to add to any 19 limitations to the use of methylcobalamin in treating vitamin B12 deficiency. 20 21 DR. KATZMAN: Thank you. (Pause.) 22

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             DR. JOHNSON: I think Dr. Ryan is allowed to
     participate as a responder.
2
             DR. GULUR: Dr. Ryan, the chair recognizes
3
4
     you if you'd like to speak.
              (No response.)
5
             DR. GULUR: Dr. Ryan, are you on mute?
6
7
              (No response.)
             DR. JOHNSON: I think we can work behind the
8
9
      scenes to get an answer and come back, perhaps.
             DR. GULUR: That will be fine, Dr. Johnson.
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             We will move on to the next panel member
11
     with questions, unless, Dr. Katzman, you have
12
      further questions.
13
14
             DR. KATZMAN: No. Thank you so much,
     Dr. Johnson.
15
             DR. JOHNSON: We'll try to get Dr. Ryan
16
      online and have her address the question.
17
18
             DR. GULUR: Wonderful.
19
             Thank you, Dr. Johnson. Takyiah will let me
     know, and we will recognize Dr. Ryan when ready.
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21
             The next panelist who has their hand raised
      for a question, Ms. Fusco-Walker, would you like to
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1 speak? MS. FUSCO-WALKER: Yes. Thank you very 2 much. 3 4 Dr. Johnson, I'm wondering if you can explain what the different risk would be for a 5 person who would use a compounded injectable 6 version of the methylcobalamin instead of an FDA-7 approved product. 8 9 DR. JOHNSON: Just to be clear, 10 methylcobalamin is not in any FDA-approved products. 11 MS. FUSCO-WALKER: Right; one of the other 12 13 two, I mean. I'm sorry. DR. JOHNSON: I think I'm going to ask Gail 14 Bormel to talk in general about FDA's viewpoint 15 16 about using FDA-approved products versus compounding products, but again, to keep in mind 17 18 that we wouldn't be talking about products that 19 contain the same active ingredients. So Gail Bormel, would you like to comment? 20 21 MS. BORMEL: Sure. Is that ok, Dr. Gulur? DR. GULUR: Yes, of course, yes. 22

MS. BORMEL: As Dr. Johnson said, we're just talking about, in general, FDA-approved drugs versus compounded drugs by state-licensed pharmacies, federal facilities, or licensed physicians.

So generally, FDA-approved drugs are subject to premarket review, so they're looked at in terms of safety and efficacy before they are marketed, and also FDA-approved drugs are made according to CGMP conditions, the CGMP regulations.

In contrast, compounded drugs are not reviewed for safety and efficacy prior to marketing, and the compounded drugs are made in accordance with Section 503A of the Act. They're not subject to current good manufacturing conditions.

So there are differences in review and in the quality conditions that compounded drugs under Section 503A are subject to versus FDA-approved drugs.

 ${\tt MS.}$ ${\tt BORMEL:}$ ${\tt Does}$ that answer the question?

MS. FUSCO-WALKER: Yes. Thank you for

1 clarifying that. I have no more questions. Thank you, Dr. Bormel, and thank DR. GULUR: 2 you, Ms. Fusco-Walker. I understand you have no 3 4 more questions. We will move on to Dr. Fensky who had his 5 hand raised. 6 Would you like to speak? 7 DR. FENSKY: Thank you. Tim Fensky. 8 Dr. Johnson, thank you for the presentation. 9 I just need to clarify one thing that I heard, 10 whether you can clarify it or the expert to clarify 11 this for me. 12 Basically, when we're talking about the ASD 13 and the studies that were being held, I heard 14 something about the CGI-I scale is not the only 15 scale that needs to be assessed when doing 16 this -- and correct me if I'm wrong -- and that's 17 18 why the other scales are being used. 19 If that's the case, does the FDA identify any products that do make a significant improvement 20 21 for these scales, for the core symptoms of ASD? DR. RASETTI: I can answer you. I'm Dr. 22

Rasetti, Division of Psychiatry. 1 DR. FENSKY: Yes, thank you. 2 DR RASETTI: We have two drugs that have 3 4 been approved so far for autism spectrum disorder, and one is risperidone, Risperdal, and the other 5 one is aripiprazole. They are not approved for 6 core symptoms of ASD. They've been approved for 7 irritability. 8 The scales that have been used are two. One is CGI-I and the second one is the ABC, the 10 Aberrant Behavior Checklist. This is a 56-item 11 scale that has a different items, including 12 irritability, social withdrawal, stereotypic 13 14 behavior, hyperactive non-compliance, and inappropriate speech. 15 For the risperidone and for the 16 aripriprazole, this scale showed significant 17 18 improvement than in the subscale of irritability. 19 For the risperidone, I think there were three double-blind, placebo-controlled studies, and for 20 21 the aripriprazole, there were two double-blind,

placebo-controlled studies, and part of them showed

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a significant difference in this case.
1
              Did I answer your question?
2
              DR. FENSKY: Yes. Thank you very much.
3
4
     have no further questions.
             DR. RASETTI: Thank you.
5
             DR. GULUR: Thank you both.
6
              Dr. Fensky, you have no further questions,
7
     and I see that your hand has been lowered.
8
             With this, at this time, I do not see any
9
      further panel member questions, clarifying
10
     questions, so we will move on.
11
             DR. JOHNSON: I think we might have Dr. Ryan
12
     on the phone.
13
14
              Dr. Ryan, are you available now?
              (No response.)
15
             DR. JOHNSON: Dr. Ryan?
16
              (No response.)
17
18
              DR. GULUR: Dr. Johnson, we will have an
19
      opportunity after the nominator presentations for
      further questions and during the discussion.
20
21
      Perhaps we can have her join us then.
             DR. JOHNSON: Certainly. Thanks very much.
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DR. GULUR: Thank you. 1 We will now proceed with the nominator 2 presentations. We have two presentations, Dr. Ajay 3 4 Day, who is speaking on behalf of National Community Pharmacists Association and Alliance for 5 Pharmacy Compounding, followed by Dr. Richard Frye, 6 who is speaking on behalf of Professional 7 Compounding Centers of America. 8 Dr. Day? 9 10 Nominator Presentation - A.J. Day DR. DAY: Good morning or good afternoon, 11 depending on where you're listening in from. 12 not have the red bar that gives me control over the 13 slides. 14 (Pause.) 15 DR. DAY: Okay. Thank you very much. 16 Well, good day, and thank you for inviting 17 18 me to speak to this committee today. My name is 19 A.J. Day. I'm the vice president of clinical services at PCCA. I serve on the board of the 20 21 Alliance for Pharmacy Compounding and with the NCPA

Compounding Committee. And I'd like to express my

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gratitude, to begin with, to the FDA for hosting this virtual meeting, which in this format allows for greater participation from stakeholders, particularly physicians, than we have had in the past.

Our nomination is specifically focused on patients with autism spectrum disorders. We will not be presenting on other nominated uses. I'd like to start by addressing this excerpt from the FDA's analysis, stating that it is not clear that methylcobalamin provides a unique benefit over other vitamers of B12 that are FDA approved.

This statement should actually be flipped around. There is no evidence that other vitamers of B12 are safe or effective in patients with autism spectrum disorders. All clinical literature for the use of B12 in patients with ASD focus on the use of methylcobalamin.

To remove this option and suggest that patients and providers should use cyanocobalamin or hydroxocobalamin, which, as Dr. Johnson pointed out, are not naturally occurring in humans, while

methylcobalamin is, will force clinicians to experiment on these patients. There is no data to guide dosing, no data on safety, no data on clinical outcomes using these other vitamers, not even anecdotal data.

FDA discusses the process for activating exogenously administered cobalamins. This process relies on fully functioning gastrointestinal lining, transport proteins, and intrinsic factor. Dr. Johnson did an excellent job of walking us through all of that process.

A hallmark feature for many patients with ASD is compromised gut and intestinal health, and sensitivity to proteins and foods. Therefore, oral absorption of cobalamins may not be the same in ASD patients.

Data assessed by Paul and Brady 2017, as referenced by FDA, as well as their referenced citations, does not explore altered gastrointestinal health or function in patients with ASD. Now, Paul and Brady actually acknowledged that very point in their paper, shown

in this excerpt on your screen, where patients with impaired production of intrinsic factor such as autoimmune, pernicious anemia, or atropic gastritis, and/or a compromised intestinal absorptive function as in celiac disease, ulcerative colitis, Crohn's disease, or tropical sprue, may greatly impair B12 absorption by endocytosis.

The research provided by Johns Hopkins
University acknowledges their perspective of only
using methylcobalamin to address vitamin deficiency
and therefore predominantly utilizing oral dosing.
Given the altered GI status of this patient
population, it is unsurprising that patients
generally do not show significant improvement in
that environment.

Presentations by Dr. Frye and Dr. Neubrander later today will address the biochemical and clinical reasons for subcutaneous dosing of methylcobalamin is preferred for patients with ASD. It is also important to acknowledge that detailed reviews by FDA and Johns Hopkins did not identify

significant safety concerns. There are many trials published for various potential uses, including ASD, and FDA states that adverse events reported with methylcobalamin use are infrequent and non-serious.

Methylcobalamin is an approved product as an injection in both Japan and Australia. Safety data from the Japanese product indicates an adverse reaction rate of 0.45 percent. The product warns of potential anaphylactoid reactions, though no such reactions have been documented.

Similar data is on the Australian product label. Additionally Australia's Therapeutic Goods Administration has a searchable database of adverse event notifications for medicines. Searching for oral, single-ingredient methylcobalamin reactions, from January 1, 1991 through March 1, 2021, there are no results for adverse reactions related to the injectable product. There are four non-serious case reports related to oral formulations with no details provided for other health conditions or medications that patients may have had, therefore,

causality cannot be determined

Several publications are available which report adverse events. This first portion of the table lists articles which assessed subcutaneous methylcobalamin in patients with ASD.

This next slide includes other indications that were studied. This data is included as extra data on the safety profile of injected methylcobalamin, even when used IV at relatively high doses at a frequency that exceeds the commonly utilized dosing schedule for ASD. Articles highlighted in yellow were not included in FDA's bibliography. Dosing in blue highlights milligram as opposed to microgram dosing protocols.

Here we have additional studies, and when we look at the totality of the data from all of these trials in these three slides, with their combined 531 weeks of trial data, the only serious adverse events were identified in the trial for ALS, and those were not attributed to the methylcobalamin therapy.

When we consider therapies for patients with

ASD, we must remember that these patients receive high frequency, in-depth medical supervision with a multimodal care approach. Current clinical trial designs are generally ill-suited to measure changes in core symptoms of ASD.

This article from the National Institute of Mental Health states that the gold standard diagnostic instruments were not created to measure severity or improvement of the disorder, and they do not holistically and comprehensively measure changes in core symptom domains.

FDA does point out that there are no approved drugs to treat the core symptoms of ASD, and the only two drugs approved to treat symptoms of irritability associated with autism have significant adverse events, including EPS.

An informal survey of compounders two weeks ago reports that 24 pharmacies responded as dispensing compounded methylcobalamin to a combined 27,565 patients in the last 12 months.

662,000 milliliters of compounded methylcobalamin was dispensed by those pharmacies to those patients

in that 12-month time period, keeping in mind that the typical dose is 0.1 mLs. This request in the survey was specific for data representing patients with ASD.

Medicaid data on utilization of
methylcobalamin provided by Johns Hopkins research
is not informative. Prescription claims for
compounded methylcobalamin are unlikely to be
submitted to CMS because CMS generally does not
reimburse for it. Surveys by University of
Maryland and JHU key opinion leaders are severely
limited, and no physicians that we have spoken with
were contacted by either research organization. We
have no information about how physicians were
selected to participate or why the number of
physicians selected were so few.

In May of 2017, FDA hosted a patient-focused drug development meeting for autism. This URL listed on the slide takes you directly to the transcript of that meeting where FDA officials, physicians, family, and caretakers of patients with autism and autism spectrum disorders discussed the

shortfalls of clinical trial designs for this patient population, the impact of methylcobalamin injections, and various FDA-approved products and therapies.

Here we have a screenshot of a comment that is submitted to the public docket from a physician specializing in chronic illness in children and adults with ASD. I hope you will all have the opportunity to read this and the multitudes, hundreds, of other comments that were submitted.

This is simply highlighting a specific comment within the previous slide that discusses the biochemical pathways that injected methylcobalamin addresses in the patients that he treats. I'm limited on time for this presentation, so I will not be reading the specific comments in the details of that.

Similarly, Dr. Buckley points out specific clinical outcomes achieved with this injected methylcobalamin. Additionally, the Medical Academy of Pediatric Special Needs identifies compounded injectable methylcobalamin as a standard of care.

In conclusion, injectable methylcobalamin is commercially available in Japan and Australia.

There are no significant adverse events identified from global literature searches, and FDA states that adverse events reported with methylcobalamin use are infrequent and non-serious. It has been compounded since at least 2005.

There are no alternative options for patients with ASD. Denying methylcobalamin from the 503A Bulks List will eliminate therapy for thousands of patients, where no significant safety risk has been identified. There are no products, FDA-approved or otherwise, that address the core symptoms of ASD to even the same degree as compounded methylcobalamin reported in the presentation from Dr. Johnson.

As Ms. Bormel stated in her introductory remarks, the goal of this process is to protect the public from unsafe compounded drugs while maintaining patient access to needed compounded therapies. No evidence has been presented to establish compounding methylcobalamin as unsafe,

and there are significant numbers of patients who need continued access to this therapy.

Dr. Frye will address the clinical and biochemical assessment. Thank you very much.

DR. GULUR: Thank you, Dr. Day.

Dr. Frye, if you'd like to start your presentation.

Nominator Presentation - Richard Frye

DR. FRYE: Thank you very much for inviting me to talk here. I'm presenting on behalf of PCCA.

I'm chief of neurodevelopmental disorders and director of the autism program at Phoenix

Children's Hospital. I have been treating children with autism almost exclusively for the past

15 years, mostly from a biochemical point of view, another medical point of view.

I'd just like to say that methylcobalamin injections I've found as one of the most effective treatments for some children with autism, with some having very significant positive response to the treatment. So today I'll talk a little bit about methylcobalamin treatments for autism spectrum

disorder.

Just my disclosures, several research grants, industry funding, and advisory boards disclosed, and my disclaimer, of course, that this is not an FDA-approved treatment when we talk of it as treatment.

I have put some key points here and not enough time to go through them all, but in general what I'd like to talk about is biochemical pathways that are abnormal in children with autism and how methylcobalamin appears to be very therapeutic in helping fix these pathways; and how when we talk about the double-blind, placebo-controlled studies that there was some discussion about, we see that there is evidence in those studies that the children that did have response biochemically did improve their behavior and symptoms.

What we find in children with autism is very interesting. We find abnormalities in these four interconnected pathways; that is, problems with methylation, redox metabolism, folate metabolism, and tetrahydrobiopterin metabolism. We find these

are all connected, and there are many groups that have studied this.

What I've highlighted in red in this diagram are the metabolites and the enzymes that have been shown to be abnormal in multiple studies from multiple groups, so it's been verified. What I also have here are these green boxes which show us where we can intervene into these biochemical pathways. And we can see that B12 is very key for intervening into methionine synthase.

One of the first people to really identify these biochemical abnormalities was Jill James at Arkansas Research Institute, and she was able to find in multiple studies, and confirm this, that children with autism had abnormalities in both methylation and redox metabolism. And at that point, she suggested it was a subgroup of children with autism.

Studies have looked at this data, and there is a nice meta-analysis and systematic review in Free Radical Biology and Medicine, for those that are interested, that shows that these abnormalities

are repeatable and shown by many groups. What's also been shown is that there are abnormalities in glutathione, the major antioxidants of the body, as a result of these abnormalities in multiple tissues of the body, including the brain. Also what's been shown is that these redox abnormalities result in oxidative damage to DNA proteins and lipids in children with ASD.

These abnormalities seem to be pretty
pervasive, and recently Dr. Jill James teamed up
with Juergen Hahn at the Rensselaer Polytechnic
Institute, where they used discriminate analysis to
ask whether this is a signature of autism, these
abnormalities of methylation and oxidative stress.
And indeed they found in their first study that
looking at these metabolites of abnormal
methylation and oxidative stress, that you can
actually discriminate children with autism, for
those that are typically developing, with about a
98 percent accuracy.

So Dr. James was really the first one to show that this simple treatment of injected

methylcobalamin 3 times a week and oral folinic acid daily improved these biochemical markers of methylation metabolism and oxidative stress, including improvement in the production of glutathione. In that study -- it was an open-label study -- it was shown that the glutathione redox ratio, which is shown in B, improved in many but not all of the children.

In this study, the Vineland Adaptive

Behavior scale was performed at the beginning and
at the end of this 3-month study. We took that
data to ask if there were any improvements
associated with this treatment, and we found that
the change in months in development ranged anywhere
from 2 months to 12 months on average, and many
skills actually improved anywhere from 6 to
12 months in 3 months of the treatment with
methylcobalamin. And these were kids that were not
making progress, so it wouldn't even be expected to
change much on these scales.

Of course this was an open-label study, so one of the things that we wanted to see is whether

the biochemical changes correlated with the behavioral changes, and we did find that for 6 of the 9 subscales, that there was a significant association with improvement in biochemical pathways with improvement in behavior and symptoms.

This is the double-blind, placebo-controlled study done by Dr. Robert Hendren, one of the two double-blind, placebo-controlled studies of methyl B12. This study did not use folinic acid or folate with the methyl B12, which I think could be a significant difference from the previous study.

They randomized 57 children, and as mentioned before, there was a significant improvement overall in the Clinical Global Impression-Improvement scale at the point 0.005 level. The other scales did not show improvement in those that were treated, however, it should be noted that both the Social Responsiveness Scale and the ABC, the Aberrant Behavior Checklist, as just previously noted in this paper by Palmer, are parent-reported scales. And what we found in clinical trials with individuals with autism is

that parent-reported scales are very much open to large placebo effects.

But one of the things that I think is very important about the Hendren study, even though not all of the outcomes were positive, is that the change in the CGI, the Clinical Global Impression scale, was correlated with improvements in the methylation capacity; that is the SAM/SAH ratio.

So again, improvements in the biochemical pathways were correlated with improvement in the Clinical Global Impression scale. This was also true of the previous double-blind, placebo-controlled study, where overall there was no significant effects, but in a subgroup that did improve, there were biochemical changes.

One of the things that we know about children with autism is that the disorder is very heterogeneous and that there may be certain subgroups that respond to certain treatments and have certain ideologies. So it's very important to understand, when you're looking at autism spectrum disorder, that there are many subgroups that we

have to find that will respond to different treatments, most likely. And I believe that the studies that we've shown here suggest that there may be the subgroup, which may be significant, that responds to methyl B12.

Overall, the clinical studies, again, there are two double-blind, placebo-controlled studies, there are two prospective open-label studies, and there are several case reports. All of them show improvement in ASD symptoms. Again, the double-blind, placebo-controlled studies and one of the open-label studies show that these improvements are correlated with changes in biochemistry. And there were few adverse effects, and when they occurred, they were very mild.

How does B12 work? Well, we talked about improving the function of these biochemical pathways, particularly to improve methylation and glutathione production. But one of the other ways that we know that improving this pathway helps the brain is that glutathione is made of glutamate, and one of the things that is a theme in autism is

there's too much hyperexcitability and too much glutamate in the brain of children with autism, And by reducing glutamate, you can rebalance the excitatory-inhibitory ratio.

Other evidence from this study, for example by Jill James, demonstrated that there were certain polymorphisms that are associated with autism within these pathways, particularly the transcobalamin B12 binding protein. And if an individual has a polymorphism in the B12 binding protein and in COMT, they are at significant risk for having autism with an odds ratio of 7. There have also been case reports or case series of four patients with a novel TCN2 mutation -- this is a B12 binding protein -- and two of them had autism.

Interestingly, in these cases of children with autism, when they were treated with cyanocobalamin, they actually developed acute anemia, which was only improved when they were given methylcobalamin, and methylcobalamin was shown to improve their symptoms. Also, there's evidence of decreased levels of B12 in the brain of

children with autism, and methylcobalamin in particular was 3.1 times lower in the brain of individuals with autism as compared to controls.

We also find that the biochemical abnormalities that would be associated with a decrease in B12, that has been also found in individuals with autism, were also found in the brain, including changes in methylation and glutathione metabolism.

In addition, we find that there's decreased expression of the mRNA from methionine synthase in the cerebral cortex of those with autism, and then it decreases much faster with age than typically developing populations. Also, there is evidence that dietarily there is lower B12 intake in children with autism spectrum disorder, as shown in this meta-analysis.

This is another letter that you did see, which I'll highlight, from the Medical Academy, their special needs president that states that this is a treatment that is considered standard of care for children with autism through their training

program, and they find that it's extremely effective. This is an organization of over a thousand physicians that treat children with autism.

I would say that one of the problems with getting funding -- I am an academic researcher and trying to get funding for researching B12. One of the comments on two of the grants that were not funded was that methylcobalamin was standard of care and widely used, so it wasn't seen to be novel to actually fund for further clinical research because it was already something that was already widely used.

With that, I will thank you for giving me the time to present this to you.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Frye.

We will now take clarifying questions for nominator presenters. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember

to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I would actually like to start the questions, and I do see we have other interested panel members as well.

This question is for you, Dr. Frye, if you could answer. You have stated that the downside, shall we say, of vitamin B12 injections are minimal and that there are no real known side effects. I'm curious as to your view on the 2010 paper by Geier, an autism cohort study, where they found cobalt levels following vitamin B12 injections were significantly high.

Just to stress, the dose was 75 micrograms

per kilogram, and what they summarize over here is that methylcobalamin injections significantly increased the mean levels of plasma cobalt 6.83-fold and urinary cobalt 51-fold in comparison to unexposed subjects, and significant positive correlations were found between the frequency of methylcobalamin injections and the levels of plasma and urinary cobalt; our concern of course being that cobalt toxicity affects the heart and a few other things, cardiomyopathy.

I'd also, as a follow-up, like to clarify that Dr. Day presented one patient with an MI, where it was considered not related to the methylcobalamin.

So we'll start with Dr. Frye; if you could comment on that study and your thoughts on the cobalt toxicity with injectables.

DR. FRYE: So again, I have patients that have been on methylcobalamin injections for long periods of time, and I have not seen any toxic effects that would be linked to cobalt, although I understand your concern.

The fact that there's elevated levels -- and sometimes we see even elevated levels of B12 in the blood, and we actually found this was linked to something called the folate receptor autoantibody in one of our studies -- one of the things that we take as kind of an overarching notion is that children with autism have metabolic systems that are under stress, so they need higher levels of these vitamins for those systems to work properly.

So the fact that they are elevated in the blood just in general is not concerning because we're treating a disorder, and the levels for normal individuals may not be relevant as much to individuals with autism.

For example, one of the other areas that we've made a lot of progress in is that we find that folate has trouble getting into the brain, and we know the mechanisms behind this. One of the things that we can do is increase folate levels in the blood to actually push the folate through the reduced folate carrier into the brain and restore levels. And this has been measured --

DR. GULUR: Dr. Frye, I apologize for interrupting, but my question was very specific to cobalt toxicity and increased cobalt levels with 75 micrograms per kilogram of vitamin B12 being injected. I'm summarizing that your response was that you have anecdotally not seen this in the study, in the patients that you treated per se, but that you would also be concerned that cobalt toxicity could be a possibility?

DR. FRYE: I think that it's something of further study, but I don't see any evidence that it seems to be harmful to my patients. In fact, I see many positive effects. And when we stop the B12 injections, as sometimes we do, to see if they're necessary after certain amounts of treatment, you find that children start to lose skills, they feel tired, and they regress a bit.

So it seems like the treatment seems to give them more benefit than side effects, and I have not seen any side effects of cobalt. Although being an academician, I would think that anything is important to study because that's something that we

have a question about.

I think the question is very insightful and valid, but I don't see, and I haven't heard from any of my colleagues, this concern or any symptoms that would make me think that there's cobalt toxicity.

DR. GULUR: Thank you, Dr. Frye.

Just to summarize my read on this study, which included 72 patients -- so it was not as large as some of the other studies presented so far on the benefits -- the other question was there was a paper that I would appreciate your comment on, which was on speech disorders in autism patients. They reviewed multiple substances that could help in that arena.

A summary report that was done -- I apologize; I'm going to pull the reference up for you in just a second. But essentially, that paper on speech disorders, which reviewed multiple substances, close to 12, that could help patients with autism spectrum disorder, summarized that the oral formulations were safe and effective, which

seems contrary to what we've just heard, where oral formulations of drugs are less useful in autism spectrum disorder.

So I would appreciate your view on the fact that there's a published review with multiple other experts who seem to feel like oral formulations are safe, and that anything else would require a larger clinical study to ensure a safe and efficacious dosage, which is similar to the cobalt side-effect study, which also states that larger studies are required to establish the safe dosage of intravenous methylcobalamin.

DR. FRYE: Okay. Well first, this isn't intravenous; this is subcutaneous.

DR. GULUR: Subcutaneous.

DR. FRYE: Yes. So if the cobalt study was intravenous, that would definitely be a difference. But the studies that have used methylcobalamin orally have all been combined with other supplements, and they do show that there is some benefit overall of multivitamins that include cobalamin.

However, I would caution that many children with autism don't tolerate, first of all, anything oral. They are very restricted, so we can't give them anything oral. And two, many children have severe GI problems, including inflammation in the gut, which may limit the ability to absorb B12 and produce intrinsic factor probably. So they may not be absorbing it if we give it orally.

Just in general, what's associated with autism is severe food restriction, so we need these other compounds injected and other formulations so that these substances can be given to children with autism and they can receive it. And I have that issue with many patients.

DR. GULUR: Thank you. I do appreciate your difficulty as an academician in obtaining research funding for this. That said, it appears that at least a few papers in this arena all call for larger translational medicine studies be performed so safe new protocols to treat ASD disabilities can be introduced.

Would you agree that there is a need for

controlled studies on a larger scale?

DR. FRYE: I do. Oh, most definitely, and that's what we're currently doing with leucovorin right now because it seems to be so helpful for some children. We have gained funding for doing multicenter clinical trials, and I completely agree that that would be great.

The problem, as a practical matter, is this area of research in autism is very underfunded, and I don't know that people realize how underfunded and how much impact we could make if we were able to research these substances.

Just briefly, one of the comments of the first grant I submitted was your exact questions about the oral form and whether it was superior; that is, injected versus superior. So in the second grant, we actually included a separate arm that included the oral form of methyl B12, and I think the reviewers were a little bit confused on the noninferiority analysis, and it was a little bit too complex for them at that point. So that, with the idea that they thought this was kind of

standard of care, I think prevented us from getting 1 funding. 2 Dr. Frye, thank you very much 3 DR. GULUR: 4 for your detailed answers. I much appreciate it. With that, I would like to request Dr. Vaida 5 to speak on his question. 6 DR. VAIDA: Yes. Thank you very much, and 7 thank you, Dr. Day and Dr. Frye for those 8 presentations. 10 I just had a quick question. So the FDA did have an issue with lack of reports on safety, and 11 unfortunately that's because the 503A's don't have 12 to report adverse events, yet it seems like the 13 drug is being compounded. 14 First for Dr. Day, you said there were 15 27,000 patients that were treated with 0.1 mL. The 16 other question that the FDA had was the range of 17 18 doses. So for both of you, what was the common 19 dose with those 27,000 patients, or do you know? DR. DAY: This is A.J. Day. The most common 20 21 concentrations of the compound is going to be 25 milligrams per mL with a dose of 0.1 mL per 22

dose. That is most common. There are going to be 1 some intrapatient variabilities, and Dr. Frye, as 2 well as our speaker in the open public hearing, I 3 4 believe, will address some of those as well. Dr. Frye? 5 DR. FRYE: Yes. I think that, yes, you're 6 7 absolutely correct. It is very variable, and that's a real area where we need to study more the 8 clinical trials used, anywhere from about 60 to 75 micrograms per kilogram. But I find in my 10 clinical practice that it varies considerably, and 11 many times you have to titrate the dosing anywhere 12 from about 1500 to probably 3000 micrograms every 13 other day to every 3 days as far as injectables. 14 DR. VAIDA: Alright. Thank you. No further 15 questions. 16 DR. GULUR: 17 Thank you. 18 Dr. Gura? 19 DR. GURA: Thank you. This question is directed to Dr. Frye. 20 21 First, an excellent overview of the situation. My question is, with the fact that 22

there are products available from Japan and Australia, are you aware of any attempts of anybody trying to import them to do studies rather than using a compounded product? And is there any sort of registry for autistic patients to record their responses to therapy so we can get that data that asked about common doses and adverse events? Thank you.

DR. FRYE: Yes. That's such a great question. No, I'm not aware of anybody trying to get the formulations from outside the states. And the question about the registry is very good.

There have been several attempts and several, where we would say, surveys of the use of certain treatments in autism to see which ones seem to be the most effective with the least side effects.

They have all pointed to methyl B12 as being one of the most effective treatments with the lowest amount of side effects.

Right now, we're working on a national survey that Dr. Jim Adams did with, I believe, about somewhere of about 5,000 respondents, and we

injectables, they had a significant improvement over time in the parent-rated severity of their disorder compared to children that didn't take that treatment. It's one of the treatments that was perceived as most effective by parents. Of course, most of these surveys are retrospective, which is unfortunate because there are limitations in that type of research, and unfortunately there's no prospective registry.

At this point, I know that there are several groups, including Autism Speaks, who's trying to develop a network where we standardize the way we see patients so at least clinically we can record their improvements over time, as well as any types of changes that they may have received from therapies, both positives and negatives.

DR. GURA: Thank you. No further questions.

Open Public Hearing

DR. GULUR: Thank you.

We will now begin the open public hearing session.

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

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

For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant --

(Reverberation.)

DR. GULUR: I apologize. I think there are technical difficulties. I will repeat the last sentence.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore,

please speak only when recognized by the chair. 1 Thank you for your cooperation. 2 Speaker number 1, your audio is connected 3 4 now. Will speaker number 1 begin and introduce yourself? Please state your name and organization 5 you are representing for the record. 6 DR. NEUBRANDER: This is this 7 Dr. Neubrander. Can you hear me? 8 DR. GULUR: We can hear you, Dr. Neubrander. 9 I apologize. I think there are some technical 10 echoes. 11 DR. NEUBRANDER: It's feeding back. I don't 12 think it's my phone. 13 DR. STEVENSON: Dr. Neubrander, this is 14 Takyiah Stevenson speaking. Can you hear me? 15 (No response.) 16 DR. STEVENSON: Dr. Neubrander, can you hear 17 18 me? 19 DR. NEUBRANDER: Can you hear me now? DR. STEVENSON: Yes. We can hear you now. 20 21 DR. NEUBRANDER: I don't know why it's feeding back. Is there something that you know how 22

to do on your side? 1 DR. STEVENSON: May I ask you, you might 2 have to mute your computer speakers and speak just 3 4 into the phone only. That might get rid of the echo. 5 DR. NEUBRANDER: I've muted my computer 6 speakers. Can you hear me now? 7 DR. STEVENSON: Yes. That is much better. 8 Thank you. 9 DR. NEUBRANDER: Great. 10 I'm Dr. Neubrander from New Jersey. I have 11 no financial interests, or nobody paid me for 12 anything, which is sad. Anyhow, that's a joke. 13 Nobody paid for me for my trips, or me to prescribe 14 this, or anything else, so I have no financial 15 interests. 16 Let me say this, though. I was trained as a 17 18 pathologist. In that study on the cobalt 19 toxicity -- this has nothing to do with my 7 minutes, and I'm going to talk, but it came 20 21 up -- the problem is when you test for cobalt, in cobalamin, the cobalt is in the center of 22

cobalamin. It's tied in there; it's not biologically active. And when you have the test to see what cobalamin is, you have to burn it off, and it goes through, and it comes off.

So when you put it in, when you take the bladder, or the urine, or whatever you take and you put it into the instrument, you have to burn it off, and now you expose that it's there, but biologically it's inactive. So that's the answer to that.

Alright. Let me just do this. Will you advance the slide for me? Because I have no ways to do that.

Okay. Keep on this slide. The first slide said that the FDA has what we've been hearing about, questions about safety, effectiveness, adverse effects, and dosing.

On this second slide, it's extremely important. This is the 2016 Brain TISSUE study by Zhang and Deth, and it shows that methyl B12 is present in much higher amounts during the early stages of development and the reproductive years.

Here you can see that children with autism had one-third the amount of methyl B12 as did those from infancy to 20 years of age. So this amount that the children with autism has is essentially that of a 50 year old.

Dr. Richard Deth, a well-known researcher in the field of methylation, he shared the importance of continuing injectable methyl B12 for children with autism. First, he discussed that methylation is impaired in autism and associated with oxidative stress, and monitoring these identifies ASD with 98 percent accuracy of those with autism. Dr. Frye mentioned that also.

Next, Dr. Deth reiterated that methyl B12 is only one third that of normal levels and that normalizing brain levels can improve neurodevelopment in ASD. And he stated that the other forms of B12, like cyanocobalamin, are not efficiently converted to methylcobalamin.

He ended his discussion by saying the blood-brain barrier restricts entry of cobalamin into the brain, indicating high dosage levels are

needed to augment brain levels of methylcobalamin.

He went on to say clinical trials have demonstrated injectable methyl B12 produces benefits very quickly; the example shown being a significant drop in the ATEC score after only 8 weeks. He concluded by stating that high doses of methyl B12 may be adding clinical benefits beyond its cofactor role.

Currently, only risperidone and aripiprazole are approved medications for autism, specifically to decrease irritability. By contrast, methyl B12 improves many autistic symptoms.

On May 26th and again June 7th, I provided the FDA with the list of 83 of the commonly observed symptom improvements we see; 197 pages of parental quotations in my practice; 541 pages from the evaluation tool I used in my clinic that documents undeniable symptom improvements from injectable methyl B12.

I have estimated that over the years, I have received, after taking away placebo effect,

33 percent. After taking away that, I have estimated I have over 6 million words from parents

documenting what methyl B12 has done for them and what's different in my clinic within the first 6 to 9 weeks with no changes.

Since May 2002, when I discovered the effect of methyl B12 for autism, I have personally prescribed and monitored, for at least 3500 children, more than 1.5 million doses with excellent results in a few weeks, with no serious adverse effects; a very conservative estimate.

I just gave an estimate here, but Dr. Day gave better criteria. I said at least 25 million doses have been done without significant effects, and his is higher than that, which that's good.

This early study from my clinic documented that the ATEC scores improved significantly, within 6 to 9 weeks, when the children did not make any other changes to anything they were doing for any treatment other than methyl B12 injections.

A later study from my clinic with an N of 321 and a p-value of less than 0.0001 again showed excellent clinical improvements in just 8 weeks when the children did not make any other changes to

anything they were doing whatsoever, other than methyl B12 injections.

Here you will see a form I use. In addition to ATEC, the Parent Designed Report Form shown here is an additional evaluation tool I use in my clinic. It does not replace ATEC, but for some symptoms, many symptoms really, it is more sensitive to changes in a child.

One of the major differences in what I do in my clinic in the evaluation tools is parents have to document, in detail, with examples, what the child was like before they started every 3-day shots and what the child is like after they started the shots. And again, they have to give detailed examples and whatever. By giving before and after with detailed examples, it takes away the placebo effect.

Basically here, from this list of 83 symptoms for methyl B12, those above are the ones that more than 40 percent of the parents have observed in 6 to 9 weeks after making no changes to anything they were doing other than methyl B12

injections.

Side effects are misunderstood. Many of the side effects from methyl B12 are because the processing speeds in the autistic brain are considerably slower. By studying the graph in the 2009 publication by Thatcher, that studied 54 autistic children from my clinic, the processing speeds in autistic children's brains were slowed 150 percent in the central region, 185 percent in the frontal region, and 275 percent in the occipital-parietal region of the brain.

The precuenus and cuneus in the parietal region are involved in organization, sensory integration, synthesis, and manipulation of auditory, visual, and kinesthetic input, and it slowed 275 percent in autism. These proportions in the parietal lobe are involved in memory and quick decisions in crisis situations, and again slowed 275 percent in kids with autism. The occipital cortex is involved with memory encoding with semantic tasks and visual association, and again, it slowed 275 percent in autism.

symptom improvement has generated new brain waves that must be processed near the center of the parietal [indiscernible]. And it slowed down 275 percent, so parents see sensory issues there. However, the remaining overflow unprocessed excess stimuli has to go to the motor cortex, and it slowed down 150 percent, so the parents see hyperactivity and stimming. The additional unprocessed excess stimuli overflow to the frontal cortex, it slowed down a 185 percent, so parents see irritability and worse behaviors.

These types of side effects are not bad but part of the process; no different than the pain of an operation -- I didn't tell you to advance your slide. I'm so sorry. Please advance the slide.

Oh, I'm sorry.

Those are the 80-some symptoms. That was where I said it slowed down. Please advance it again to the next one. That one's the precuenus; that's where it is. This is where it has that.

I'm so sorry; one more slide.

DR. GULUR: That's ok. Just a reminder that it's been 8 minutes of your time.

DR. NEUBRANDER: I know. Okay. Let me just go through this really quickly.

This is the side effects. Let me advance another one real quickly. That's what I was talking about, and advance again to the side effects. These are the net side effects; you can look at them. I've given you all this information in detail with my script, the type of side effects. They're several, and they're very uncommon, so go ahead. Next slide. I'm almost finished. This one is important, though.

Basically, here you'll see this is the dependency, et cetera. Serum levels for B12 in autism are not the pattern of the B12 deficiency; rather a B12 dependency. Zhang's paper documented one-third less methyl B12 in the brains of autistic children. These alluded to autistic children having high-dose serum B12 dependency when he said high-dose treatment with methylcobalamin may reflect additional beneficial actions beyond its

cofactor effect.

I only got a couple of more real fast slides, real fast. Next one.

Basically, subcutaneous, we've done all of them. People come to me from literally 80 countries and I've seen over 3500 kids. When they come to me on oral -- a lot of them come on oral methyl B12. It hasn't done anything to any significant degree. We put them on the subcutaneous and it does great.

Two more slides real fast, for real. Next one, the calculated dose, you can read about that in here. Basically, I believe that as a group, Dr. Day, Dr. Frye, and myself have established that there is safety, that there is effectiveness, that there is a lack of medication for these kids, and that methyl B12 can fill that void.

So therefore, all my patients, we all hope that we've established that it would be unconscionable to take methyl B12 injections away from children on this spectrum and their families. Thank you.

DR. GULUR: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. VOLK: Hello. My name is Heather Volk.

I'm an associate professor in the Department of

Mental Health from the Johns Hopkins University

Bloomberg School of Public Health. I have nothing
to disclose regarding relationships with

methylcobalamin, or B12, or related substances.

The data that I'm going to verbally present you today -- and I apologize for my scratchy voice; I'm a bit under the weather and a late addition to the agenda, so I have not sent slides -- is all available publicly on the Johns Hopkins University Center for Excellence and Regulatory Innovation or the Johns Hopkins CERSI center website. The report is posted there.

Briefly, over the past two years, we conducted a study to examine current and historical use of several substances, including on the

403 bulk compounding list, including methylcobalamin, and that's the compound and results I will speak to today.

In our study evaluating current and historical use, we first examined data coming from over 1700 individuals with autism spectrum disorder diagnosed in the Center for Autism Related
Disorders at the Kennedy Krieger Institute. These individuals, upon intake at the Center for Autism and Related Disorders at Kennedy Krieger, were asked to complete a patient intake research questionnaire, upon which a list of any medication that they had been taking, or had been prescribed and taken, for their autism spectrum disorder was included.

Among those on the list was included B12, and notably about 1 percent of individuals, or 20 of the 1700 individuals seen at Kennedy Krieger, reported taking methyl B12 for their ASD-related symptoms, and all of those administrations were oral. We further then linked those individual records, when possible, to the Kennedy Krieger

Pharmacy database and found that only 0.5 percent, or half a percent, of those individuals actually had a valid prescription filled at Kennedy Krieger.

We realize that clinical data is not really representative of the population of the true use of these substances among individuals with autism spectrum disorder, and as a result thought to further validate and understand use of this substance in individuals with ASD for treatment specifically of symptoms related to autism spectrum disorder.

As a result, we conducted a study then using Medicaid claims files gathered from 2010 through 2014. This included over 369,000 individuals between the ages of 2 and 17 with autism spectrum disorder. They were all required to have an ICD-9 code of autism more than twice or at least on two non-consecutive visits to confirm their diagnosis.

We then linked those diagnostic codes to drug administration codes available through the National Drug Code, as well as the Healthcare Common Procedure Coding System and the current

procedural technology codes, the document infusions of a substance in a medical setting.

So based on the linkages of these three drug mechanisms, we were able to see through the Medicaid claims data what the actual prevalence of many substances, including methyl B12, was among individuals with autism spectrum disorder over a period of four years across the United States.

Overall, we found the prevalence of about

1 percent of use of methylcobalamin in this

data set and, in particular, relative to children

with autism spectrum disorder. Notably, this

prevalence did not differ from that which we saw in

the general population sample from which we

compared them to.

Most often, injection or solution

administrations were seen in the Medicaid data.

However, the use of claims data, while

population-based and giving us a broad sense of use

across the country for treatment of autism can help

us expand upon our findings from clinical settings,

we are unable at that point in time to really have

a sense of individual motivations for use and what particular symptoms might have been treated, or perhaps perceived effectiveness.

Following up to that, we conducted a population-based study, working with Simons Foundation Powering Autism Research for Knowledge or the SPARK consortia. We conducted an online survey from December of 2019 through February of 2020, where SPARK participants and their parent or guardian were asked to respond to a series of questions regarding complementary and alternative medicines, as well as FDA-approved pharmaceuticals for a range of psychiatric disorders, including autism spectrum disorder.

We had over 1400 respondents during that short time period. Most often the mother responded on behalf of her child with autism spectrum disorder. And overall from this data, we found that nearly 50 percent of individuals had tried a complementary or alternative medication for treatment of autism symptoms. Specifically in regard to methyl B12, about 6 percent of

individuals in this data set reported they had used it, and most predominantly oral or injection routes of administration were seen.

Parents reported, or most often the mother reported, that they tried or attempted B12 therapy as a result of language difficulties in their child with autism spectrum disorder, not specifically or necessarily a symptom related specifically to autism related impairment. Additionally, they report most often that there was no change in that symptomatology for which they had primarily tried the B12 medication or that perhaps there was a slight change in that data.

Based on these three data sources, we are led to believe that in the population overall for individuals with autism spectrum disorder, the use of methyl B12, as well as other B vitamins, is relatively rare, and appears that it may have on the population level limited impact in regard to improving ASD-related symptoms. Thank you.

Clarifying Questions (continued)

DR. GULUR: Thank you.

We will now take remaining clarifying 1 questions for all the methylcobalamin presenters. 2 Please use the raised-hand icon to indicate that 3 4 you have a question and remember to put your hand down after you have asked your question. Please 5 remember to state your name for the record before 6 you speak and direct your question to a specific 7 presenter, if you can. 8 If you wish for a specific slide to be 9 displayed, please let us know the slide number, if 10 possible. As a gentle reminder, it would be 11 helpful to acknowledge the end of your question 12 with a thank you and the end of your follow-up 13 question with, "That is all for my questions" so we 14

Do we have any questions for our presenters?

Dr. Sandbrink?

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can move on to the next panel member.

DR. SANDBRINK: Yes. Friedhelm Sandbrink, Washington, D.C. This is a question I think for Dr. Frye, but also for speaker 1 in the public presentation.

What I'm really trying to understand a

little bit better -- as before, this evidence and 1 the many data that you presented so well about 2 methylcobalamin, what about the other injectables 3 4 and approved vitamin B12 preparations that we have on the market here? 5 I know there was reference in there, but 6 maybe you can explain a little bit more why they 7 may not be used, or why they shouldn't be used, or 8 what is the evidence in regard to any treatment with those products? Thank you. 10 DR. GULUR: Dr. Frye, if you would like to 11 12 respond. This is Dr. Day. Dr. Frye had to 13 DR. DAY: 14 sign off of the meeting to go see patients. 15 DR. GULUR: Thank you, Dr. Day. Speaker number 1? 16 DR. DAY: I'm not sure if Dr. Neubrander is 17 18 still available. 19 DR. GULUR: Dr. Neubrander, would you be available to answer this question? 20 21 (No response.) DR. GULUR: Dr. Neubrander, are you on hold? 22

(No response.) 1 DR. GULUR: Thank you. 2 With that, we will end the time for 3 4 clarifying questions and move on to the panel discussion questions. 5 Dr. Vaida, would you like to comment? 6 DR. VAIDA: Yes, and this is I guess a 7 comment before we're voting in that it seems that 8 part of the issues with this methylcobalamin is the number and variety of uses that have been put 10 forward. But a lot of the discussion, at least in 11 the last hour or so, has been on autism syndrome 12 disorder. 13 Is there any way to look at this as was done 14 with oxitriptan, in that it would just be for 15 subcutaneous use for ASD with indications that the 16 FDA has done before? 17 18 DR. GULUR: For the FDA, Dr. Johnson, 19 Dr. Bormel, would you like to answer? DR. GANLEY: This is Dr. Ganley. I'm able 20 21 to answer that. DR. GULUR: Thank you, Dr. Ganley. 22

DR. GANLEY: Yes. I'm not sure what the question is because if the ingredient is placed on the 503A list, there's no restriction with regard to how it may be used. In the past, we have placed limits on the route of administration, but we're not able to restrict how a prescriber may prescribe that.

So for just taking methylcobalamin into account here, if there was a reason -- if you believe it should be added to list, it would have to be clear as to why you would restrict oral use versus parenteral use, for example.

DR. VAIDA: Okay. So with oxitriptan, it seems you did make an exception.

DR. GANLEY: The oxitriptan will be discussed this afternoon. And although the reason -- I don't want to really get into a prolonged discussion of that, but if it was added to the 503A list for that use, we recommended it only be for oral. That's how generally it is used if you look at those reviews, and there's not evidence of it being administered parenterally, and

there's obviously safety issues.

If it is added to the list, it does not prevent oxitriptan from being used for any condition out there.

DR. VAIDA: Okay. I'm sorry. I must have been misreading your guidance that you put out for oxitriptan.

DR. GANLEY: Generally, the previous evaluation in 2015 was for different uses, and there was not evidence of effectiveness for those conditions. So the risk-benefit assessment is not in favor of adding it to the list. But all it really takes for the 503A list is to find a condition for which we do think there's a benefit-risk assessment in favor of benefit over risk, and if it gets on the list, that doesn't prevent a prescriber to use it for anything.

But all we have done is limited the route of administration. For example, if it was a drug that would be topically administered, we can limit it to topical so that it would not be given orally or by parenteral administration. So those are the

caveats related to this. 1 DR. VAIDA: Alright. Thank you. 2 DR. GULUR: Thank you, Dr. Vaida. 3 We'll ask Dr. Fensky at this time to ask his 4 question. 5 DR. FENSKY: Thank you. I just need to get 6 something clarified by the FDA. Three of the four 7 medications that we're discussing today being 8 compounded, I think one was since 2005, another one was 2009, and another one was 2011. 10 Why is it now that these medications are 11 just coming up for review versus being done 12 previously? It seems to me that, basically, there 13 may not be -- the study's out there, but I haven't 14 really seen a lot, especially with the 15 methylcobalamin, of adverse effects with 16 compounding methylcobalamin. Thank you. 17 18 MS. BORMEL: This is Gail Bormel. 19 really sure I understood the question. DR. FENSKY: So Gail, what I'm asking, so 20 21 basically, if these products have been out there and been compounded since 2005, why is it just now 22

that we're coming up for them to put on this bulk 1 list? 2 MS. BORMEL: This is Gail. We've only 3 started this process since probably about 2015, to 4 take bulk substances that were nominated for the 5 503A Bulks List to the advisory committee. 6 We had a process whereby bulk drug 7 substances were nominated for inclusion on the 503A 8 Bulks List, and we had those bulk substances, and we then took them and have been, since that time, 10 reviewing them, preparing the evaluations, and 11 taking them to the advisory committee. We've done 12 a number of bulk drug substances already, and we're 13 just now bringing four more. 14 The timing really has to do with when we 15 started the nominations for the 503A Bulks List, 16 and then the reviews and the evaluations, and then 17 18 setting up the advisory committee meeting. 19 DR. FENSKY: Okay. That's helpful, Gail. This is my first meeting, so I just need 20 21 clarification on that. That's all. Thank you. MS. BORMEL: Sure. 22

DR. FENSKY: No more questions. 1 DR. GULUR: Thank you, Dr. Fensky. 2 I do have a question for the FDA presenters. 3 4 Could you comment on the cobalt-related side effects, the cobalt levels, et cetera, that paper 5 that was out there? Based on your review, were 6 there any concerns? 7 I did hear Dr. Neubrander state that it was 8 a testing error from LabCorp that causes that 9 to -- but it's not physiologically present. But if 10 you read that paper in detail, it is in excess of 11 Lab Corp's maximal occupational exposure levels; 12 assuming that they have accounted for that in their 13 14 testing methodology, as well as they had done some in vitro studies that showed tissue damage, organ 15 tissue damage, with exposure to cobalt at those 16 levels for neurons, et cetera. 17 18 Would an expert on the FDA side be able to 19 comment on that? DR. GANLEY: Yes. This is Dr. Ganley. 20 21 not sure if we've seen that paper or looked at it. I don't know if Dr. Johnson's able to answer that. 22

She's more familiar with the data that's available. 1 DR. GULUR: It's May 2010, Autism Cohort 2 Study of Cobalt Levels Following Vitamin B12 -3 4 Injections. It's David Geier, G-E-I-E-R, published in Toxicological and Environmental Chemistry. 5 (No response.) 6 DR. GULUR: While I recognize that there 7 seems to be a general sense that side effects with 8 methylcobalamin are not high --DR. JOHNSON: Hi. This is Sue Johnson. 10 Unfortunately, the technical gremlins got me again 11 and it bounced me out. 12 We do not have that paper in our review. 13 That's part of what we're trying to do, is gather 14 any more information that's relevant on safety and 15 efficacy, and we will definitely look into safety 16 associated with cobalamin, which sounds like it 17 18 could very well affect any of the cobalamins. 19 It is not something that's in the labeling for the approved products, so we will just have to 20 21 investigate it further. We appreciate you bringing

it to our attention.

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DR. GULUR: Alright. Thank you. 1 Dr. Fensky, is your hand still raised or do 2 I see that you've lowered it? Have we ensured that 3 4 you've had an opportunity to ask all your questions? 5 DR. FENSKY: Yes. I forgot to lower it. 6 7 Thank you. DR. GULUR: Alright. 8 Are there any further questions? 9 10 (No response.) Committee Discussion and Vote 11 DR. GULUR: Seeing none, the committee will 12 now turn its attention to address the task at hand, 13 the careful consideration of the data before the 14 committee, as well as the public comments. We will 15 proceed with the question to the committee and 16 panel discussions for methylcobalamin. 17 18 I would like to remind public observers that 19 while this meeting is open for public observation, public attendees may not participate except at the 20 21 specific request of the panel. Today's question is

a voting question. Dr. Takyiah Stevenson will

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provide the instructions for the voting.

DR. STEVENSON: Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that the voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed. Once all

voting members have selected their vote, I will 1 announce that the vote is closed. 2 Next, the vote results will be displayed on 3 4 the screen. I will read the vote results from the screen into the record. Next, the chairperson will 5 go down the roster and each voting member will 6 state their name and their vote into the record. 7 You can also state the reason why you voted as you 8 did, if you want to. 10 Are there any questions about the voting process before we begin? 11 DR. DESAI: I do have a question. 12 Dr. Desai. I was trying to unmute. I guess this 13 is a question, if the chair would allow. When you 14 were asking for committee discussion, I know that 15

Am I allowed to make a comment for the committee?

time has closed, but I was trying to unmute.

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DR. GULUR: Dr. Desai, I will allow that at this point. If you have difficulty unmuting, please raise your hand. That will give me an indication that you wish to ask a question.

DR. DESAI: Yes. You're right, Dr. Gulur. 1 I did raise my hand in the chat, so thank you. 2 DR. GULUR: Go ahead and ask your question. 3 DR. DESAI: My comment related to something 4 that I don't think we've talked about as a 5 committee, which are the number of comments that 6 were received in the open public docket on the 7 regulations.gov website. I was reading through all 8 the materials prior to the meeting, and there are over a thousand comments, many from patients and 10 other physicians, related to this issue. 11 Obviously, there's a lot of concern about 12 this from multiple different sides. The FDA gave 13 14 us a very comprehensive presentation, our nominators gave us a very comprehensive 15 presentation, and then we had the OPH. 16 My question is more, procedurally, do we 17 18 need to have an opportunity to discuss the public 19 consensus that has been submitted, or is there an opportunity to discuss that now, or was this simply 20

meant for us as committee members to review prior

to the meeting and use that in our decision making?

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DR. GULUR: Dr. Desai, if there's some particular point from that that you would like to bring up for discussion with the panel, please do. That is what the panel discussion time is for, if there are certain comments or points that you found particularly worth sharing.

DR. DESAI: Sure. What I found is I read through these, and as I said, there was over a thousand. I'm sure all of my fellow committee members did as well as part of the pre-work. I was struck by the number of patients, particularly parents of children, who commented about their own journey with autism spectrum disease and how methylcobalamin really helped them with their process of navigating the disease and suffering from it.

There were several also physician comments that talked about how these are used in the injectable forms in their practice, and I know that we talked about the data concern. But I still think that these public comments are very important for us to keep in mind, and I just wanted to make

sure the committee was aware of that and uses it in 1 their weighing of their decision. Thank you. 2 DR. GULUR: Thank you, Dr. Desai. 3 stated, there are four criteria, as we saw at the 4 end of the FDA discussion, that must be taken into 5 account while making your decision: the safety, 6 the efficacy, use, et cetera, so I'm sure all of 7 this informs the process. 8 Did you have any other comments, Dr. Desai? 9 DR. DESAI: No. Thank you. I just wanted 10 to go on record as making sure that we acknowledged 11 the comments that came in on the docket. Thank 12 you. 13 14 DR. GULUR: Thank you, Dr. Desai. Again, it's unusual, but I do see another 15 raised hand. 16 Ms. Fusco-Walker, do you have a question or 17 18 a comment? 19 (No response.) DR. GULUR: Ms. Fusco-Walker, are you muted? 20 21 MS. FUSCO-WALKER: Thank you very much for turning it on. I'm having difficulty here. 22

tried to ask a question before we moved to this part of the session.

I agree with the previous speaker. I read through a lot of the comments that were made online, and I do have concerns about parents and their experience with using this product. But I had a question directly related to the product that I wanted to ask the last speaker.

This product has been available for quite some time because FDA has a guidance that allows these compounds to be used until a decision is made about 503A, whether they're on the bulk list or not. And these products are being used by compounded pharmacies and physicians, and they're being distributed and used subcutaneously by injection, et cetera.

I know that compounding pharmacies do not have to report adverse events -- that's 503A; that's not a requirement -- but are there any adverse reports being picked up over the last 16 years that this product has been used? Is anybody compiling that anywhere to see the effects

of all these people that are writing online, these parents that are saying this has made such a difference for them?

DR. JOHNSON: Hi. This is Sue Johnson again from FDA. We've talked about the FAERS and CAERS data, which are voluntary reporting systems for both dietary supplements and drugs. It's difficult to tell most of the time from submissions what type of product has been used, because the reports are generally very attenuated.

But we have to surmise that from a dietary supplement oral standpoint -- I'm sorry, from an oral product standpoint, there are dietary supplements available, and that is likely that products that are used in any reports about dietary supplements are in the CAERS database.

The FAERS database is a little bit

different. Some of those could be about compounded products, but we really don't have a way to reassure ourselves of that. We do know that they're not approved products, at least in the U.S., but the U.S. number of cases was relatively

small compared to the total number of cases, which includes foreign data.

mechanisms where the adverse events can be reported if the investigator, clinician, or patient/user chooses to. It's sometimes difficult to assess exactly what product is used. Keep in mind that each compounding pharmacy makes their own formulation, so they could differ between or among pharmacies. Not everything is a standardized product like an NDA product, and it is difficult to surmise exactly what the experience has been.

We would very much like to encourage additional data that's been categorized and clarified to be submitted. I know some of it has come in with the comments, and we would continue to encourage the receipt of that kind of information. That helps us very much to receive voluntary reports.

MS. FUSCO-WALKER: Thank you. Thank you very much. I have no further questions.

DR. GULUR: Thank you.

Thank you, Dr. Johnson. Just to close out that last comment from you, just to be clear, the removal of methylcobalamin from the 503A Bulks List would only prevent compounding. It would not remove access to patients with autism spectrum disorder to use oral dietary supplements, which a majority of them seem to be currently consuming. It would limit the injectable availability of methylcobalamin.

Is that a reasonable assumption here?

DR. JOHNSON: Yes.

DR. GULUR: Sorry. Just to clarify, I'm just confirming that methylcobalamin will continue to be available in an oral formulation to anyone who wishes to use it like they do today, whichever indication, under the dietary supplement. By not being on the compounding list, it would limit it for injectables, which based on the John Hopkins' open public speaker is a very small proportion of patients who use the injectable formulation?

DR. JOHNSON: So there were among the nominations a number of dosage forms proposed,

including oral nasal spray -- oh goodness, I don't have the list. But there were dosage forms proposed in addition to injectable products. All compounding with methylcobalamin would cease to be allowed if methylcobalamin were not put on the 503A list.

I'm going to ask Gail Bormel if she would like to add anything to that. Am I missing a perspective there?

MS. BORMEL: Sure. This is Gail Bormel. If methylcobalamin is not placed on the 503A Bulks

List, it would not be available for compounding under 503A, period, and that is separate and apart from methylcobalamin's availability as a dietary supplement. Our vote today and our decision today does not affect the availability of methylcobalamin as a dietary supplement.

But what it would do if methylcobalamin is not placed on the 503A Bulks List, that means that compounders under Section 503A, like state-licensed pharmacies, would no longer be able to use methylcobalamin as a bulk drug substance to make a

compounded drug product. 1 2 DR. GULUR: Thank you, Dr. Bormel. That was very helpful. 3 4 I see some hands raised still for the open discussion. We'll allow a couple of minutes more, 5 but we'll have to close this at some point. 6 Dr. Fensky? 7 DR. FENSKY: Thank you. I just wanted to 8 make a comment about the reporting of adverse 9 events. From a board of pharmacy perspective, most 10 boards of pharmacy across the United States are 11 actually gathering adverse effects when it comes to 12 compounding through their board, so that may be a 13 possibility in the future, to be getting those 14 adverse effects reported into some type of 15 database. 16 I just wanted to bring it up since we were 17 18 talking about where these things were being 19 reported, but I know boards of pharmacy are starting to collect this data. 20 21 DR. GULUR: Thank you, Dr. Fensky. I see, Ms. Fusco-Walker, you have your hand 22

Is that because you have a further 1 raised. question or have you just forgotten to retract it? 2 (No audible response.) 3 DR. GULUR: Thanks. 4 With that, we will move on. I will read the 5 question that we will be voting on into the record. 6 FDA is proposing that methylcobalamin not be 7 included on the 503A Bulks List. Should --8 DR. STEVENSON: I do apologize. This is 9 Takyiah Stevenson speaking. Just before we read 10 the question into the record, I see the Dr. Gail 11 Bormel has a comment or question. 12 Dr. Bormel, you can start, and then --13 DR. GULUR: Go ahead, Dr. Bormel. 14 MS. BORMEL: Yes. Thank you. 15 I just wanted to make it clear that there 16 are no reporting requirements, as was mentioned 17 18 before, for compounders operating under Section 503A of the Act. So even if there are 19 adverse events that occur with some of these 20 21 compounded products, even if they're reported to the Boards of Pharmacy, as it stands currently, 22

there's no mandatory reporting for these comments 1 to come into FDA. 2 We always look at our FAERS system, as well 3 4 as our CAERS system. But FAERS has to do with our drug adverse event reporting system, and that 5 reporting system for compounded drug products is 6 purely voluntary. 7 So we don't really get an idea of -- we 8 could never tell you the denominator of compounded 9 products made and what types of adverse events were 10 sustained, because it is a voluntary reporting 11 system. It's not mandatory for these adverse 12 events to be reported by compounders under 13 Section 503A. 14 DR. GULUR: Thank you, Dr. Bormel. 15 I will take this moment, because this has 16 been slightly unusual, and give everybody one more 17 18 chance. Is there anyone else who has a comment or

(No response.)

a question before we move to the vote?

for a robust discussion on this topic.

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DR. GULUR: Dr. Bormel, I still see your

Thank you

hand raised. Would you have another comment? 1 MS. BORMEL: No. Thank you. 2 DR. GULUR: Thank you, Dr. Bormel. 3 Alright. Seeing as how we have concluded 4 our discussion on this topic, I will attempt one 5 more time to read the question into the record. 6 FDA is proposing that methylcobalamin not be 7 included on the 503A Bulks List. Should 8 methylcobalamin be placed on the list? 9 Does anyone have any questions about the 10 wording of this question? 11 Dr. Katzman? 12 DR. KATZMAN: Yes. I just have a 13 clarification about the wording of this. Depending 14 on how we vote, if we vote yes, that means that 15 we're voting that we agree that it should not be 16 included. If we vote no, then we're saying that it 17 18 should be included. 19 Is that correct? DR. GULUR: Yes, I was going to read this 20 21 part after, but I'll read it now. If you vote no, you are recommending FDA not 22

place the bulk drug substance on the 503A Bulks 1 List. If the substance is not on the list when the 2 final rule is promulgated, compounders may not use 3 4 the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF 5 monograph, or a component of an FDA-approved drug. 6 Does that help answer your question? 7 DR. KATZMAN: So if I vote no, then I'm 8 recommending it not be put on the list. 9 DR. GULUR: Correct. 10 DR. KATZMAN: Okay. 11 DR. GULUR: Does that answer all your 12 questions, Dr. Katzman? 13 14 DR. KATZMAN: Yes, thank you. Thank you so much. 15 DR. GULUR: You're very welcome. 16 Are there any other raised hands? 17 Dr. Sandbrink, I don't see your hand raised 18 19 at this time, though it may have been earlier. just want to ensure we've given you an opportunity 20 21 to ask a question. DR. SANDBRINK: Yes. This is Friedhelm 22

Sandbrink, Washington, D.C. I had the same 1 clarifying question. So saying it the other way 2 around in regard to the wording, if we vote yes, 3 4 that means it will remain on the list and remains available as it is currently. 5 DR. GULUR: Correct. 6 And just for further clarification for 7 everyone, I will repeat the clarification. 8 If you vote no, you are recommending FDA not place the bulk drug substance on the 503A Bulks 10 List. If the substance is not on the list when the 11 final rule is promulgated, compounders may not use 12 the drug for compounding under Section 503A unless 13 it becomes the subject of an applicable USP or NF 14

Dr. Katzman, I see your hand is still raised. Is that because you have a question?

(No response.)

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monograph, or a component of an FDA-approved drug.

DR. GULUR: If there are no questions or comments concerning the wording of the question, we will now begin the voting on the question for methylcobalamin.

DR. STEVENSON: We will now move voting 1 members to the voting breakout room to vote only. 2 There will be no discussion in the voting breakout 3 4 room. (Voting.) 5 DR. STEVENSON: The voting has closed and is 6 now complete. Once the vote results display, I 7 will read the vote result into the record. 8 (Pause.) 9 DR. STEVENSON: The voting has closed and is 10 now complete. The vote results are displayed. 11 will read the vote totals into the record. 12 chairperson will go down the list, and each voting 13 member will state their name and their vote into 14 the record. You can also state the reason why you 15 voted as you did, if you want to. 16 There are 9 yeses, 5 noes, and zero 17 18 abstentions. 19 DR. GULUR: Thank you. We will now go down the list and have 20 21 everyone who voted state their name and vote into the record. You may also provide justification for 22

your vote, if you wish to. 1 We'll start with Ms. Fusco-Walker. 2 MS. FUSCO-WALKER: Yes. Sandra 3 4 Fusco-Walker. I voted no based on the information provided, but I hope this compound can be addressed 5 again with more data. 6 DR. GULUR: Dr. Desai? 7 DR. DESAI: Hi. Seemal Desai. I voted yes. 8 This was a very interesting and very dynamic 9 I very much appreciated all of the 10 discussion. science presented by the FDA, the nominators, and 11 12 our public speakers. For me, one of the most important things is 13 access to care for medications for our patients, 14 and the overwhelming number of responses in the 15 public docket related to access of this compound is 16 what influenced me to vote yes, in addition to the 17 18 data presented during the OPH. Thank you. 19 DR. GULUR: Dr. McElhiney? DR. McELHINEY: Linda McElhiney. 20 I voted 21 yes, mainly because I want these patients to have access to care so that they have quality of life. 22

Also, it's standard of practice in two medical 1 professional organizations, so I think that we 2 should support the experts that actually deal with 3 these patients. Thank you. 4 Dr. Fensky? 5 DR. GULUR: DR. FENSKY: Tim Fensky. I voted yes. 6 DR. GULUR: Dr. Rebello? 7 DR. REBELLO: Elizabeth Rebello. I voted no 8 based on the lack of adequate scientific evidence. 9 DR. GULUR: Dr. Bogner? 10 DR. BOGNER: Robin Bogner. I voted yes 11 based on the number and compelling stories from 12 many of the comments, the hundreds of comments. 13 DR. GULUR: Dr. Katzman? 14 DR. KATZMAN: I voted yes for all the 15 reasons stated before me, including access to care 16 and benefits for the thousands of patients with 17 18 ASD, as well as the minimal risks described today 19 as well. Thank you. DR. GULUR: Dr. Sun? 20 21 DR. SUN: This is Jeanne Sun. I voted yes, [inaudible - audio feedback] -- access to these 22

medications and based on the testimony, and the 1 briefing materials, and the presentations that were 2 given, and just the number of patients that are 3 4 relying on this medication. DR. GULUR: Dr. Gupta? 5 DR. GUPTA: Thank you. I voted no. First 6 off, I think this was a very difficult decision. 7 believe that although this is a very important 8 medication, first of all for access, I do think it's very important that we address patient safety 10 as well. 11 I do think that although the presentation 12 from the FDA was compelling, the presentation for 13 patient access was also very compelling, and we do 14 have to find better evidence to ensure that there 15 is patient safety. That also was very strong. 16 So I did vote no at this time and hope that 17 18 we can overturn that decision very soon. Thank 19 you. DR. GULUR: Dr. Vaida? 20 21 DR. VAIDA: Yes. Allen Vaida. I voted yes. Actually, I voted yes because I wasn't convinced 22

that there was a lot of information to show that the drug was unsafe. It seemed that it was just because of the number of uses that it came up. But I would like to qualify my vote also -- not that it would mean anything -- that it would just be for oral and subcutaneous. Thank you.

DR. GULUR: Dr. Sandbrink?

DR. SANDBRINK: Friedhelm Sandbrink. I voted yes. I want to mention that I was left quite frustrated with the lack of comparison data between the different B12 products that are commercially available and that FDA approved in the proposed methylcobalamin. But at the same time, I also felt that there was insufficient evidence to take that option away at this point.

DR. GULUR: Dr. Patel?

DR. PATEL: Hi. Kuldip Patel. I voted no.

I agree with all of the sentiments described by the committee members here; a really, really difficult decision given its existing use. Though, after hearing all of the various different presentations and also appreciating the importance of having the

therapeutic option available, I just didn't see the level of objective clinical effectiveness that's needed to conclusively vote yes.

I'd like to also go back to was important from Dr. Vaida with regards to how this committee gets to vote. And it really would have been nice to have it be stratified where you can isolate a particular indication as opposed to broadly deciding on a bulk substance to make it available or not. Thank you.

DR. GULUR: Thank you, Dr. Patel.

Padma Gulur, and my vote was no. I balanced, similar to as you've heard from the other panel members, clinical effectiveness. There was soft information for most of the indications for the value of methylcobalamin compounded over anything that is currently available.

Specific, we discussed autism spectrum disorder in much detail, and that is actually where my [inaudible - audio gap] stands. This is a population that is sick, and they are unable to

advocate for themselves. Fortunately, their parents do advocate for them. However, patient safety being where it should be, if there were side effects from this, it wouldn't be easy to discern in patients who already have chronic disease. So this more than ever is a need and a cry for science and appropriate studies.

I would hope that Dr. Frye's request for funding, et cetera, though this is not the forum, be recognized and how important it is that the people who are taking care of these patients have an opportunity to truly study this in a balanced manner.

But that said, today there are risks potentially there, and while I accept that some of the risk papers that are out there haven't been fully looked at, those were my concerns in moving this.

As far as access, the fact that the oral formulation, which is already for [inaudible - audio gap] -- autism spectrum disorder, including the patient comments that have come in, a majority

that seem to be using, and they would not be 1 limited from access to that is what influenced my 2 Thank you. 3 vote. 4 We will now take a break. I just wanted to commend our panel members, the FDA, our presenters, 5 and the public for their patience and dedication as 6 we discussed this important topic, and it has 7 undoubtedly delayed our lunch break. 8 We will, given the time, only take a 9 20-minute break at this time, and we'll reconvene 10 at 3 p.m. 11 Is someone trying to speak? 12 I'm sorry. DR. GURA: Yes. Hi. This is Kathleen Gura. 13 14 You skipped over me during the roll call for the vote. 15 I am sincerely sorry, Dr. Gura. DR. GULUR: 16 Let me get you back on record. 17 18 Dr. Gura? 19 DR. GURA: Okay. I voted yes. And the reason for my answer is if we take this option 20 21 away, we're going to be forcing patients to go into the supplement world, and at that point, we may not 22

really know what the quality is of the products 1 they're going to use to compensate for the lack of 2 access. So I wanted to go on record for that. 3 4 Thank you. Thank you, Dr. Gura, and I 5 DR. GULUR: apologize for having missed you in the roll call. 6 Takyiah, have we covered everyone else? 7 DR. STEVENSON: Yes, Dr. Gulur. I believe 8 9 we have. Adjournment 10 DR. GULUR: Thank you very much. 11 As we were saying, we're going to take a 12 break for 20 minutes, and we'll reconvene at 3 p.m. 13 Panel members, please remember that there should be 14 no chatting or discussion of the meeting topics 15 with other panel members. Additionally, those 16 panel members participating in the remaining topic 17 discussions should plan to rejoin at 3 p.m. to 18 19 ensure you're connected before we reconvene. Thank 20 you. 21 (Whereupon, at 2:40 p.m., the morning

session was adjourned.)

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