

UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Bethesda, Maryland

Wednesday, September 14, 2016

1 PARTICIPANTS:

2 Welcome and Introductory Remarks:

3 MARK HUDAK, MD
4 Chair of Pediatric Advisory Committee (PAC)
5 Chief, Division of Neonatology
6 University of Florida, College of Medicine
7 Assistant Medical Director
8 National Intensive Care Unit
9 Wolfson Children's Hospital
10 Jacksonville, Florida

11 Introduction of New Designated Federal Official
12 and Award Presentation:

13 MARIEANN R. BRILL, MBA, RAC, MT (ASCP)
14 Designed Federal Official, PAC
15 Office of Pediatric Therapeutics
16 Office of the Commissioner
17 Food and Drug Administration
18 Silver Spring, Maryland

19 Opening Statement:

20 MARIEANN R. BRILL, MBA, RAC, MT (ASCP)
21 Designed Federal Official, PAC
22 Office of Pediatric Therapeutics
23 Office of the Commissioner
24 Food and Drug Administration
25 Silver Spring, Maryland

26 Center for Drug Evaluation and Research (CDER)
27 (Sustiva):

28 CAROLYN YANCEY, MD
29 Division of Pediatric and Maternal Health
30 Center for Drug Evaluation and Research
31 Food and Drug Administration

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1 PARTICIPANTS (CONT'D):

2 Update on Exjade (deferasirox):

3 PETER WALDRON, MD
4 Division of Pharmacovigilance
5 Office of the Commissioner
6 Center for Drug Evaluation and Research
7 Food and Drug Administration

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Abbreviated Presentations:

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8 MENVEO (Meningococcal(groups A, C, Y and W-135)
9 Oligosaccharide Diphtheria CRM197 Conjugate
10 Vaccine

9

10 JUDITH U. COPE, MD, MPH
11 Office of Pediatric Therapeutics
12 Office of the Commissioner
13 Food and Drug Administration

12 IXIARO(Japanese encephalitis vaccine):

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14 Office of Pediatric Therapeutics
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16 Topamax (topiramate):

16

17 MONA KHURANA, MD
18 Division of Pediatric & Maternal Health
19 Office of New Drugs
20 Center for Drug Evaluation and Research
21 Food and Drug Administration

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20 Asacol & Asacol HD, and Delzicol (mesalamine):

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21 LCDR ERICA RADDEN, MD
22 Division of Pediatric & Maternal Health
Office of New Drugs
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1 PARTICIPANTS (CONT'D):

2 Kepivance (palifermin):

3 LCDR ERICA RADDEN, MD
4 Division of Pediatric & Maternal Health
5 Office of New Drugs
6 Center for Drug Evaluation and Research
7 Food and Drug Administration

8 Bloxiverz (neostigmine methylsulfate):

9 AMY TAYLOR, MD

10 Division of Pediatric & Maternal Health

11 4 Office of New Drugs
12 Center for Drug Evaluation and Research
13 5 Food and Drug Administration 9
14 Doryx (doxycycline hyclate):

15

16 AMY TAYLOR, MD

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18 Division of Pediatric & Maternal Health

19 4 Office of New Drugs
20 Center for Drug Evaluation and Research
21 5 Food and Drug Administration
22 13 Xolair (omalizumab):

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24 AMY TAYLOR, MD

25 Division of Pediatric & Maternal Health

26 4 Office of New Drugs
27 Center for Drug Evaluation and Research
28 5 Food and Drug Administration 16
29 Karbinal ER (carbinoxamine maleate):

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31 ETHAN HAUSMAN, MD

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33 Division of Pediatric and Maternal Health
34 Center for Drug Evaluation and Research
35 19 Food and Drug Administration

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37 Pregnancy and Lactation Labeling Rule (PLLR):

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39 MIRIAM DINATALE, D.O.

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41 Division of Pediatric and Maternal Health
42 Center for Drug Evaluation and Research
43 Food and Drug Administration

1 PARTICIPANTS (CONT'D):

2 Tutorial - Review postings of the web:

3 LCDR KENNETH QUINTO, MD, MPH
4 Office of Pediatric Therapeutics
5 Office of the Commissioner
6 Food and Drug Administration

7 Annual Post-Market HDE Reviews:

8 Berlin Health EXCOR Pediatric Ventricular Assist
9 Device (VAD):

10 REBECCA WARD, MPH
11 Product Evaluation Branch 1
12 Division of Postmarket Surveillance
13 Office of Surveillance and Biometrics
14 Center for Diseases and Radiological Health
15 Food and Drug Administration

16 CONTEGRA Pulmonary Valved Conduit:

17 GEORGE AGGREY, MD
18 Epidemiology Evaluation and Research Branch I
19 Division of Epidemiology
20 Office of Surveillance and Biometrics
21 Center for Diseases and Radiological Health
22 Food and Drug Administration

23 Pleximmune:

24 KELLIE KELM, PhD
25 Cardio-Renal Diagnostics Branch
26 Division of Chemistry and Toxicology Devices
27 Office of In Vitro Diagnostics Devices and
28 Radiological Health
29 Center for Diseases and Radiological Health
30 Food and Drug Administration

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1 PARTICIPANTS (CONT'D):

2 Enterra Therapy System:

3 CATHERINE RICKETTS, RN, BSN
4 Product Evaluation Branch II
5 Division of Postmarket Surveillance
6 Office of Surveillance and Biometrics
7 Center for Diseases and Radiological Health
8 Food and Drug Administration

9 Elana Surgical Kit (HUD):

10 COLIN ANDERSON-SMITS, MPH
11 Epidemiology Evaluation and Research Branch II
12 Division of Epidemiology
13 Office of Surveillance and Biometrics
14 Center for Diseases and Radiological Health
15 Food and Drug Administration

16 Wrap-Up and Adjournment:

17 MARK HUDAK, MD
18 Chair of Pediatric Advisory Committee (PAC)
19 Chief, Division of Neonatology
20 University of Florida, College of Medicine
21 Assistant Medical Director
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Other Participants:

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Office of Pediatric Therapeutics
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Silver Spring, Maryland

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5 Mineola, New York
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8 Stony Brook, New York

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11 Center for Clinical and Community Research
12 Children's Research Institute
13 Children's National Medical Center
14 Washington, D.C.

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16 Medical Director
17 Palliative Medicine Service
18 Le Bonheur Children's Hospital
19 Associate Professor of Pediatrics
20 University of Tennessee, Medical School
21 Memphis, Tennessee

22 ROBERT DRACKER, MD, MHA, MBA, CPI
23 Medical Director, Summerwood Pediatrics
24 Founder, Infusacare Medical Services, P.C.
25 Liverpool, New York
26 Chief of Service, Department of Pediatrics
27 Community General Hospital
28 Syracuse, New York

29 PETER HAVENS, MD, MS
30 Director, Pediatric HIV Care Program
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32 Professor, Pediatrics
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34 Milwaukee, Wisconsin

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2 SARAH HOEHN, MD, MBE, FAAP
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3 University of Kansas School of Medicine
Attending, Pediatric Intensive Care Unit
4 University of Kansas Medical Center
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5 BRIDGETTE JONES, MD
6 Associate Professor of Pediatrics
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7 Associate Program Director, Children's Mercy
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8 KELLY WADE, MD, PHD, MSCE
9 Attending Neonatologist
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12 Pediatric Cardiologist
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13 New Orleans, Louisiana

14 Consultants:

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16 Division of Pediatric and Maternal Health
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17 PREMCHAND ANNE, MD, MPH, FACC
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1 PARTICIPANTS (CONT'D):

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4 Nemours/Alfred I. DuPont Hospital for Children
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4 National Institute of Mental Health
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6 Bethesda, Maryland

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11 Fellowship
12 UT Southwestern and Children's Medical Center
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1 P R O C E E D I N G S

2 (8:02 a.m.)

3 DR. HUDAK: I'm Mark Hudak. I'm the
4 Chair of this committee and will be chairing most
5 of this meeting. I'd like to welcome everybody
6 today. Our usual order of business to start with
7 is we have a number of new members. Some people
8 who are new and official, but they've been here
9 before.

10 So maybe we can go around the table and
11 introduce ourselves? Thanks.

12 DR. FISCHER: Thank you. Gwen Fischer
13 from the University of Minnesota. Pediatric
14 Critical Care and this is my first meeting.

15 MS. JONES: Hi. I'm Bridgette Jones.
16 I'm the pediatric healthcare representative from
17 the AAP.

18 DR. MOON: Hi. I'm Mark Moon. I'm a
19 cardiothoracic surgeon from Wash U in Saint Louis.

20 DR. SAVEI: Hi. I'm Dr. Wael Savei,
21 pediatric gastroenterologist from the University
22 of Connecticut.

1 DR. HAVENS: Peter Havens, pediatric
2 infectious diseases from Medical College of
3 Wisconsin.

4 DR. Turer: Christy Turer, primary
5 care from University of Texas Southwestern.

6 DR. SHWAYDER: Tor Shwayder, pediatric
7 dermatology, Henry Ford Hospital in beautiful,
8 downtown Detroit.

9 DR. CNAAN: Avital Cnaan, statistician,
10 Children's National. From beautiful D.C.

11 DR. CATALETTO: Mary Cataletto,
12 pediatric pulmonology and sleep medicine, Winthrop
13 University Hospital in New York.

14 DR. CAMPBELL: Jeff Campbell, pediatric
15 neurosurgeon from Nemours, A.I. DuPont in
16 Wilmington, Delaware.

17 DR. CUNNINGHAM: Melody Cunningham,
18 pediatric palliative care, University of Tennessee
19 in Memphis.

20 DR. HUEHN: Sarah Huehn, pediatric
21 critical care, palliative care, University of
22 Kansas.

1 DR. DRACKER: Bob Dracker, pediatric
2 hematology and transfusion medicine, Syracuse, New
3 York.

4 DR. BRILL: Marieann Brill, DFO, OPT.

5 DR. WHITE: Michael White, Oschsner
6 Health System and University of Queensland
7 Clinical School in New Orleans.

8 DR. WADE: Kelly Wade, Neonatologist,
9 Children's Hospital of Philadelphia in
10 Philadelphia.

11 DR. ANNE: Premchand Anne. I'm a
12 pediatric cardiologist from Saint John Providence
13 Children's Hospital in Detroit.

14 DR. COPE: Judy Cope. I head up the
15 safety team for the Office of Pediatric
16 Therapeutics at FDA.

17 DR. NELSON: Skip Nelson, Deputy
18 Director, Office of Pediatric Therapeutics, FDA.

19 DR. HAUSMAN: Ethan Hausman, division of
20 pediatric and maternal health, FDA.

21 DR. ALEXANDER: John Alexander, Deputy
22 Director, Division of Pediatric and Maternal

1 Health, FDA.

2 DR. HUDAK: Okay. Welcome to all the
3 new members and we hope to have an on-time
4 meeting. As at this point I'll turn it over to
5 Marieann as our DFO to read the required
6 statements.

7 DR. BRILL: Thank you, Dr. Hudak, and
8 good morning everyone. The following announcement
9 is made to address the issues of conflict of
10 interest with regards to today's discussion of
11 reports by the agency as mandated by the Best
12 Pharmaceuticals for Children Act and Pediatric
13 Research Equity Act.

14 Based on the submitted agenda for
15 today's meeting and all financial interests
16 reported by the committee participants it has been
17 determined that those individuals who will be
18 participating in each topic do not have a conflict
19 of interest for the following products: Exjade,
20 Asacol, and Asacol HD, Bloxiverz, Delzicol, Doryx,
21 Karbinal ER, Kepivance, Sustiva, Topamax, Xolair,
22 MENVEO, IXIARO, Pleximmune, Elana, CONTEGRA,

1 Enterra Therapy System, and Berlin Heart.

2 In general, the committee participants
3 are aware of the need to exclude themselves from
4 involvement in the discussion of topics if their
5 interests would be affected and their exclusion
6 would be noted for the record.

7 In order to provide the scientific and
8 latego perspectives required to adequately address
9 the products covered in today's meeting. The
10 following individuals were invited to participate
11 as expert consultants and are considered temporary
12 voting members on the committee: Dr. Mark Moon,
13 Dr. Ken Towbin, who will be joining us via phone,
14 Dr. Gwen Fisher, Dr. Premchand Anne, Dr. Jeffrey
15 Campbell, Dr. Wael Savel, and Dr. Tor Shwayder.

16 Dr. Bridgette Jones will serve as the
17 healthcare representative and that is a non-voting
18 position. Dr. Maldonado who is our industry rep,
19 will not be able to join us today since he is
20 traveling from London. Therefore, based on an
21 analysis of all the reported interests that we
22 received prior to this meeting we have the

1 following recusals: Dr. Mark Moon will be recused
2 from the discussion of Enterra Therapy System. Dr.
3 Bridgette Jones will be recused from the
4 discussion of Karbinal ER.

5 Dr. Mark Hudak will be recused from
6 discussion of Sustiva. Dr. Gwen Fisher will be
7 recused from the discussion of Berlin Heart. At
8 the time the product comes up for discussion,
9 these individuals will simply step away from the
10 table. With respect to all other participants we
11 ask, in the fairness -- in the interest of
12 fairness that they state any current or previous
13 financial involvement with any firm whose product
14 they may wish to comment on.

15 In addition, I'd like to remind the
16 audience that the final version of the materials
17 that will be presented at today's meeting will be
18 posted on the Pediatric Advisory Committee
19 website. So any copies of slides that you have
20 that appear different from the ones that are on
21 the screen will be updated and provided on the
22 website.

1 As a reminder to the committee and those
2 around the table, this meeting is being
3 transcribed, and as such, when you are
4 acknowledged to make a statement or have a
5 question, if you would please press the button on
6 your microphone and state your name prior to the
7 beginning of your statement.

8 I would also like to remind the members
9 of the committee and audience to please silence
10 your cell phones to minimize interruptions during
11 the meeting. One last thing I'd like to point out
12 of due to a business schedule ahead of us today we
13 may need to make some time adjustments to the
14 agenda. We ask the speakers to please be mindful
15 of the duration of their discussion or their
16 presentation so that we stay in the target for the
17 agenda.

18 One last announcement, for those
19 Pediatric Advisory Committee members who are
20 joining the meeting tomorrow, Euneka will be here.
21 She will meet you in the lobby by 6:30 tomorrow
22 morning and she will procure four cabs to bring

1 you to White Oak for the off period meetings.

2 Please look out for an email from Euneka as well.

3 At this time I'd like to turn the
4 attention over to Dr. Hudak.

5 DR. HUDAK: Okay. We have one other
6 significant point of business in the introductions
7 today. We do have a significant absence this
8 morning due to conflicting schedule, but Dr.
9 Dianne Murphy who is the director of the Office of
10 Pediatric Therapeutics is not here today.

11 She has been the guiding light for this
12 pediatric therapeutics development since she came
13 to the FDA in 1998. She's been here through all
14 of the abbreviations that have taken place,
15 FDAAA, PDUFA, and PREA, and BPCA, and FDASIA.
16 She was in place when this committee first came
17 into being, actually as a subcommittee to the
18 pediatric infectious disease, I think, committee.

19 So she has done remarkable work. She's
20 been recognized nationally and internationally.
21 She received a very prestigious award from the
22 American Academy of Pediatrics in 2013 called the

1 Excellence in Public Service Award. Past
2 recipients of that award have included people like
3 Michelle Obama, David Kessler, the late Senator
4 Edward Kennedy, Henry Waxman, and so forth. So
5 she's in a very elite group with that award, well
6 recognized by her home organization the AAP.

7 She also, last year, 2004, I guess,
8 received the Francis Kelsey Award from the FDA
9 which was inaugurated in 2010. So her staff
10 actually selected an award here for her. This is
11 one that will be presented to her, I'm sure, in
12 another ceremony. But I think on behalf of the
13 staff and all of the current and prior members of
14 all former committees I'm very happy to announce
15 this award here.

16 It's to Dianne Murphy for her
17 unrelenting support and dedication to the health
18 and well-being of children. So there will be a
19 separate ceremony, I'm sure, for Dianne, and for
20 those of you who don't know, Dianne is leaving the
21 agency, retiring, to do other things. Somewhere
22 around the end of October of this year. I'm

1 dubious about that because in talking to Dianne
2 she says that she has so much work to do that I'm
3 not sure she's going to get it done by the time,
4 end of October, so we'll see what happens.

5 Moving on to business here. We thought
6 we would move up Dr. Towbin's presentation which
7 is scheduled for a little later in the afternoon,
8 since we have some extra time here before the open
9 public hearing. So, Dr. Towbin.

10 SPEAKER: Quinto.

11 DR. HUDAK: Quinto, sorry. Kenneth.
12 Stick with first names.

13 DR. QUINTO: Good morning. I'm
14 Lieutenant Commander Ken Quinto, a medical officer
15 in epidemiology and the Office of Pediatric
16 Therapeutics, OPT, and I'll be presenting the
17 Pediatric Advisory Committee Risk Base Assessment
18 Review procedure.

19 Our presentation will follow the outline
20 noted in this slide. First I'll present a brief
21 review of the risk based assessment. Next I will
22 provide an overview of the procedure to review web

1 posted safety reviews, and submit comments to the
2 open docket.

3 First, a brief review. During the April
4 2016 PAC meeting I first present the risk base
5 assessment to the Pediatric Advisory Committee.
6 In essence, the risk base assessment is a
7 modification to PAC review for certain CDER
8 products that are designated low safety risk.

9 The factors that determine low safety
10 risk CDER products were built from previous
11 criteria, used for abbreviated presentations to
12 the PAC. This is a timeline for the risk based
13 assessment process. After the data collection for
14 the FDA adverse event reporting system, FAERS,
15 collects adverse event reports, the internal
16 review team, consisting of members from OPT, the
17 Division of Pediatrics and Maternal Health, the
18 Office of Surveillance and Epidemiology, and the
19 appropriate CDER division attend meeting one.

20 During this meeting, the team discusses
21 a plan to review FAERS cases and drug utilization
22 data. Prior to meeting two, the Pediatric

1 Post-Marketing Pharmacovigilance and Drug Utilization
2 Draft Review is circulated. During this meeting
3 the team discusses a draft review of the FAERS
4 cases, and of the results of a drug utilization
5 data analysis.

6 Near the conclusion of this meeting the
7 team will decide whether a product is a low safety
8 risk product or not. If the product is designated
9 as a low safety risk product it follows a process,
10 noted in green, to the top portion of the slide.
11 If the product is not designated as a low safety
12 risk produce it follows a process noted in red in
13 the bottom portion of the slide.

14 During meeting two the review team
15 considers the following factors in determining
16 whether to designate the produce below safety
17 risk. Number one, no pediatric deaths or
18 pediatric deaths likely attributable to disease
19 progression. Number two, no or few serious
20 adverse events, SAEs attributable to the produce.

21 Number three, no new safety signals
22 identified by FDA through literature review, FAERS

1 case review, drug utilization data review, and
2 ongoing track safety issues for product or class
3 of products. Number four, product adequately
4 labeled for pediatric use, including dosing
5 information, and adverse events included on
6 product label. Number five, there is little
7 pediatric use or the number of adverse events
8 relative to use it not concerning.

9 As I previously stated, the factors that
10 determine low safety risk CDER products were built
11 from previous existing criteria used to determine
12 abbreviated presentations to the PAC.

13 This is a timeline for the low safety
14 risk product. As of two days ago we are now in
15 the last phase of the low safety risk product
16 timeline. Reviews for the four CDER products have
17 been posted to the FDA website, and the docket is
18 open to receive comments until Friday, September
19 23.

20 I will not explain the procedure for
21 reviewing the web posted product safety reviews
22 and submitting comments to the docket. The first

1 address noted here is the direct link to the web
2 posted safety reviews page. This address is an
3 address that we use for all current and future web
4 posted safety reviews.

5 It is fairly simple to find the direct
6 address of the web posted safety reviews by going
7 to www.fda.gov/pediatrics which brings you to the
8 OPT homepage or you can also search, 'FDA
9 pediatrics'. This is the OPT homepage. Scrolling
10 down to the bottom of the OPT homepage you will
11 find a direct link to the web posted safety
12 reviews under the advisory committee meeting
13 subheading. The link is appropriately names, 'web
14 posted pediatric safety reviews', and noted in the
15 red box of this screenshot.

16 This is the web posted pediatric safety
17 review page. It has a product name on the left
18 column, the link to the safety review in the
19 middle column, and the link to the open docket in
20 the right column. When you click on the product
21 safety review link in the middle column you bring
22 up the products pediatric post-marketing

1 pharmacovigilance and drug utilization review.

2 When you click on the docket link on the
3 right column you arrive at the open docket at
4 regulations.gov where you can submit your
5 comments. After clicking the comment now box,
6 which is noted in red you will arrive at the
7 comment forum where you insert your comments,
8 upload any files, if necessary, and include your
9 name and contact information. Then click
10 continue.

11 You'll be then be able to preview your
12 comment and obtain a receipt of your comment after
13 submission. The docket will remain open for
14 comments until Friday, September 23. Thank you
15 for your attention.

16 DR. HUDAK: Can I have one question?
17 Are these comments that come in available and
18 archived for the public for past September 23 or
19 just accessible to FDA?

20 DR. QUINTO: So we will be receiving,
21 from what I understand, we will be receiving
22 comments and logging the comments. We will be

1 looking specifically for data relative to the
2 reviews that will make us reconsider our
3 conclusions to the reviews, so opinions that are
4 not supported with data will be logged, but we
5 review any specific data or evidence that comes in
6 to take a look at the reviews, and to make sure
7 that in evidence of light new data that we should
8 consider bringing the product to the PAC in
9 collaboration with the internal review team to be
10 making that decision.

11 DR. HUDAK: Any other comments,
12 questions around the table? I think this is a
13 nice evolution of the process. It does become
14 much more efficient. We have a huge backload, I
15 think still, of products to assess and review, so
16 I think this does help. Thanks very much.

17 DR. QUINTO: Thank you.

18 DR. HUDAK: Okay. I think we will move
19 on to the open public hearing. We have one
20 speaker who has registered. Craig Butler who's
21 the national executive director of the Cooley's
22 Anemia Foundation. Is Mr. Butler here? Yes.

1 Good morning. Mic is yours.

2 MR. BUTLER: Good morning. My name is
3 Craig Butler and I am the national executive
4 director of the Cooley's Anemia Foundation. I
5 would like to thank you for the opportunity to
6 address the committee this morning. I'm here
7 today because I know that this meeting will
8 include an update on the FDA's ongoing analysis of
9 a possible safety signal regarding the use of
10 Exjade or deferasirox in children with fever.

11 This is a matter that we first raised
12 with this committee at the last year's meeting on
13 September 16, 2015, and we are pleased that an
14 update will be given today and are anxious to hear
15 the details of the FDA analysis. As you know from
16 our previous testimony, we hope for a
17 recommendation for a label change for the drug
18 concerning interruption during times of febrile
19 illness, and for the need for continued monitoring
20 of this medication among the pediatric population.

21 As representative from the Foundation
22 related during their appearance here last fall, we

1 were motivated to request these actions due to the
2 tragic passing in January of 2015 of Zana
3 Connelly, a **thalassemia** patient, shortly before her
4 third birthday. While the circumstances which
5 brought about this sudden death are complicated.
6 The fact that a high fever was present during a
7 period when the child was receiving chelation
8 therapy via Exjade is troubling, and has raised
9 significant concern among the **thalassemia**
10 community, especially among parents of young
11 children.

12 Many patients and parents express
13 concern about remaining on Exjade after Zana's
14 passing, but may have felt that other options are
15 not viable for them. At our recent patient/family
16 conference in San Diego in July this issue was
17 mentioned to me several times.

18 I was able to tell them that the
19 Foundation's medical advisory board, which
20 consists of **thalassemia** experts from the major
21 **thalassemia** treatment centers in the United States
22 recommends cessation of Exjade and Jadenu, the more

1 recent formulation of deferasirox whenever fever
2 is present, but that the labels for Exjade and
3 Jadenu do not provide this recommendation.

4 Many patients and parents find this
5 troubling. Not least, because a significant
6 portion of our patient population is treated by
7 hematologists who are not associated with a major
8 treatment center, and who therefore, may not have
9 had experience with **thalassemia** and its treatment.
10 As a result, they may rely heavily on information
11 from the drug label. Absent any mention of what
12 to do in case of a fever, a doctor with little
13 experience with the chelator might continue
14 recommending use of the drug which could result in
15 unwanted complications.

16 We know that this committee has listened
17 to our request for guidance and we appreciate the
18 commitment to action in this area. Please know
19 that the Foundation is thankful for your attention
20 and response. Your willingness to recommend that
21 the FDA investigate an appropriate course of
22 action is appreciated by the Foundation and by the

1 patients we represent.

2 We also gratefully acknowledge the work
3 of Dr. Judith Cope, Dr. Peter Waldron, and
4 members of the FDA in this area, and look forward
5 to hearing the report later in this meeting.
6 Thank you for listening.

7 DR. HUDAK: Thank you, Mr. Butler. As
8 you point out, there will be an update somewhere
9 around 11:15 this morning by Dr. Peter Waldron,
10 medical officer with Division of Pharmacovigilance
11 to talk about that.

12 Are there any other members who have not
13 officially signed up for public comment? Okay.
14 Seeing none, I will mention that there is one
15 other comment which we received online which will
16 be posted by the FDA at some point soon for people
17 to see.

18 Okay. So we are at the point where we
19 can begin our program. I think, Dr. Cope, you're
20 up next, are you? For abbreviated presentations
21 on Menveo and Ixiaro. I may be butchering that
22 pronunciation.

1 DR. COPE: Okay. As I'm starting off
2 I'm like to announce that we have representatives
3 from the Center for Biologics
4 Evaluation and Research sitting at the table. If
5 you both would introduce yourself, please.

6 DR. ZINDERMAN: Captain Craig Zinderman.
7 I'm the associate director of the Division of
8 Epidemiology in the Office of Biostatistics and
9 Epidemiology in CBER.

10 DR. BAYER: Bethany Bayer, medical
11 officer in the Office of Biostatistics and
12 Epidemiology.

13 DR. COPE: Thank you. So as we're
14 starting off, I wanted to say for these two
15 vaccines that we'll be discussing, Menveo and
16 Ixiaro, that basically we're making them
17 abbreviated presentations. Before I get started
18 with that, I just want to clarify. We're
19 basically going to put up one slide for each
20 vaccine and very briefly discuss.

21 The reason is this is a process that
22 we've been working on over the last few years, and

1 so I just wanted to start off by reminding people
2 you got the background materials. But you'll see
3 that the CBER reviews are very comprehensive.
4 They include the adverse event reviews using the
5 FAERS database, the post-market surveillance, the
6 passive surveillance system that both CDC and FDA
7 use.

8 Also, it is looking at the periodic
9 adverse event reports that sponsors submit. Also,
10 the FDA team looks at data mining to be sure
11 there's not maybe a safety signal that emerges
12 with the disproportional adverse event. Also,
13 uses the utilization data and performs a
14 literature review.

15 All of those, for these two vaccines
16 show that really there were no new safety issues
17 and basically that if there were any deaths at all
18 they were not related to the vaccine, and that the
19 product is appropriate label. So I just wanted to
20 do that before we got to the two slides.

21 So I'm ready to show the first slide for
22 Menveo. So Menveo is basically an active

1 immunization for the prevent of invasive
2 meningococcal disease, and for the types of
3 neisseria meningitis groups that are shown here on
4 the title of the slide.

5 As I mentioned, or actually this product
6 was licensed in 2010 and approved for ages 11
7 years to 55 years of age. Then in 2011 it was
8 approved to be used in children two years and
9 older. What's important on that was it actually
10 came to this Pediatric Advisory Committee
11 following that for safety review in 2012. The
12 PAC, at that point, felt it should go back to
13 routine monitoring or continue the routine
14 monitoring that was done.

15 Now, for this pediatric meeting. What
16 prompted this is a new labeling that takes the
17 age group all the way down to 2 months. So
18 that's what prompted this safety review. Now,
19 you've got the full safety drug utilization review
20 that's in your background materials. But, again,
21 FDA did not see any new safety issues, felt that
22 the product was labeled appropriately, and

1 actually this product had one death, but it was
2 felt to be not related at all to the vaccination.

3 So FDA recommends, and they will
4 continue for standard ongoing safety monitoring
5 and we ask, you the committee, if you concur.

6 DR. HUDAK: Okay. So we'll open it up
7 for any questions from the committee, having read
8 the materials that were provided on this product.
9 If no comments, I guess we will maybe just best to
10 go around the table and get a vote. Why don't we
11 do that?

12 DR. DRACKER: Bob Dracker in Syracuse.
13 Just one question, has it been in any suggestion
14 that indications or age for use is going to be
15 changed at all? You know, what we're doing right
16 now?

17 DR. ZINDERMAN: I'm sorry. I don't
18 follow. Is your suggestion that the indication
19 for use would be changed?

20 DR. DRACKER: There's been no
21 recommendation yet as to change of vaccination
22 date. Typically we use the vaccine, you know, at

1 11 to 12 years of age. There's no suggestion to give
2 it at that younger age group yet, correct? To
3 cover the smaller, you know, the initial --
4 because those two peaks of disease almost,
5 obviously, are exposure. So I didn't know if
6 there was any current consideration regarding
7 early recommendations for administration?

8 DR. BOYER: So the recommendations are
9 determined by the ACIP, the Advisory Committee on
10 Immunization Practices, and they are the ones that
11 have reviewed it several times, and the current
12 recommendations are 11 years and then a booster
13 dose at 15 to 16 years, so that's actually a
14 different group through the ACIP and the CDC that
15 discuss that.

16 But the current recommendations are just
17 for high risk children between 2 months and up to
18 55 years.

19 DR. DRACKER: You understand my
20 reasoning for questioning that, though? You know,
21 with the early recommendation I wonder if we're
22 going to ultimately use the vaccine at an earlier

1 age to carry that high risk group earlier on.

2 That's why.

3 DR. BOYER: So I know that's been a
4 point of discussion and it is approved down to 2
5 months if that is raised. That is reconsidered on
6 a regular basis by the ACIP.

7 DR. HAVENS: And it's recommended in
8 high risk groups down to age 2 months, so it is
9 recommended in high risk groups because of their
10 concerns.

11 DR. HUDAK: Okay. So to return to the
12 question, the question for the committee is based
13 on the information the FDA has compiled in its
14 review looking at safety. Whether the FDA should
15 continue the standard safety monitoring process or
16 elevate it to some other level.

17 So the recommendation is to continue the
18 standard ongoing monitoring and we'll take a vote
19 on that.

20 DR. FISCHER: This is Gwen Fisher. I
21 concur.

22 DR. MOON: You don't vote.

1 DR. JONES: Okay.

2 DR. MOON: Mark Moon. I concur.

3 DR. SAVEL: Wael Savel. I concur.

4 DR. HAVENS: Peter Havens. I concur.

5 DR. TURRER: Christy Turer. I concur.

6 DR. SHWAYDER: Tor Shwayder. I concur

7 and I'm glad that you've brought it down to 2

8 months.

9 DR. CNAAN: Avital Cnaan, I concur.

10 DR. CATALETTO: Mary Cataletto. I

11 concur.

12 DR. CAMPBELL: Jeff Campbell. I concur.

13 DR. CUNNINGHAM: Melody Cunningham. I

14 concur.

15 DR. HOEHN: Sarah Hoehn. I concur.

16 DR. DRACKER: Bob Dracker. I concur.

17 DR. WHITE: Michael White. I agree.

18 DR. WADE: Kelly Wade. I concur.

19 DR. ANNE: Premchand Anne. I concur.

20 DR. HUDAK: Okay. So we'll go on to the

21 second product which is the vaccine for Japanese

22 encephalitis.

1 DR. COPE: Okay. Ixiaro is
2 indicated for active immunization for the
3 prevention of disease caused by the Japanese
4 encephalitis virus. It's original approval was in
5 2009 for individuals that were 17 years and older.
6 Then in May of 2013 it was approved all the way
7 down to 2 months of age. That's what's prompting
8 this pediatric safety review.

9 As I mentioned before, this is a single
10 slide. As you see, you've got your full safety
11 and drug utilization review provided in your
12 background materials. It was a comprehensive
13 review with all those that I had talked about
14 before that were looked at in the review. FDA
15 plans to continue its standard ongoing safety
16 monitoring. We ask whether the committee concurs.

17 DR. HUDAK: So this is open for
18 discussion. Okay. Hearing no questions. Dr.
19 Dracker, do you have any comments? Okay. We'll
20 start from this side of the room over here. Dr.
21 Anne?

22 DR. ANNE: Premchand Anne. I concur.

1 DR. WADE: Kelly Wade. I concur.

2 DR. WHITE: Michael White. I agree.

3 DR. DRACKER: Bob Dracker. I concur.

4 DR. HOEHN: Sarah Hoehn. I concur.

5 DR. CUNNINGHAM: Melody Cunningham. I
6 concur.

7 DR. CAMPBELL: Jeff Campbell. I concur.

8 DR. CATALETTO: Mary Cataletto. I
9 concur.

10 DR. CNAAN: Avital Cnaan. I concur.

11 DR. SHWAYDER: Tor Shwayder. I concur.

12 DR. TURRER: Christy Turrer. I concur.

13 DR. HAVENS: Peter Havens. Concur.

14 DR. SAVEL: Wael Savel. I concur.

15 DR. MOON: Mark Moon. I concur.

16 DR. FISCHER: Gwen Fischer. I concur.

17 DR. HUDAK: Okay. To summarize this for
18 the record then, recommendations from the PAC for
19 both of these vaccines is that the FDA continue
20 its standard monitoring based on the initial
21 safety review.

22 So we have come to a spot in the agenda.

1 It is 8:37. We are 23 minutes ahead of schedule.
2 The next item on the agenda has a fixed start time
3 of 9:00 a.m. because we're scheduled a call in
4 from Dr. Towbin to assist us with that review.
5 So, Dr. Nelson, Dr. Cope, do you have any thoughts
6 other than breaking or? And any other information
7 you'd like to present?

8 DR. HAUSMAN: So the presenters for some
9 of the later products are not present, so that's
10 part of the difficulty.

11 DR. HUDAK: So I guess we'll just sort
12 of --

13 DR. HAUSMAN: We could -- I mean, part
14 of it is we could move one product that Ethan is
15 presenting if the medical officer who is supposed
16 to be there. That's not until 2:00 though, so.

17 DR. COPE: You know, and we don't have
18 the division people.

19 DR> HAUSMAN: That's correct.

20 DR. HUDAK: So I guess we'll just break
21 until 9:00?

22 DR. NELSON: I think that'd be fine.

1 DR. HUDAK: Okay.

2 DR. COPE: People can rest.

3 DR. HUDAK: People can rest. So 9:00 we
4 will get Dr. Towbin on the phone and resume.

5 Dr. Towbin, good morning.

6 DR. TOWBIN: Hello.

7 DR. HUDAK: Okay. We will get started.
8 Our next review is on Sustiva. And just as a
9 point of information for the remaining reviews we
10 have on your speakers a voting system that says
11 yes, no, abstain. So for the remainder of the
12 product reviews we will initially use this, so
13 it's recorded, and then we'll go around the table
14 to solicit any additional comments that members
15 might have.

16 DR. TOWBIN: And I'll be voting by
17 voice.

18 DR. HUDAK: And you'll be voting by
19 voice, right. At this point, since FDA has
20 imputed a conflict of

21 interest to me I'm turning it over to
22 Dr. White, and I will push my chair back from the

1 table rather than walk away.

2 DR. WHITE: Dr. Cope, you're not
3 presenting this? Dr. Yancey, you're presenting
4 this --

5 DR. YANCEY: Yes.

6 DR. WHITE: -- product for us. Thank
7 you.

8 DR. YANCEY: You're welcome. Well, good
9 morning everyone. Good morning to the committee
10 and the audience. I'm Carolyn Yancey, medical
11 officer in the Division of Pediatrics and Maternal
12 Health. This morning I'll be talking with you
13 about Sustiva (efavirenz). This will be the safety
14 review.

15 This is just an outline of the topics
16 we'll cover in this morning's presentation:
17 background, relevant safety labeling, the
18 pediatric studies that support the discussion this
19 morning, pediatric labeling changes, drug use
20 trends, the adverse events that are reported, and
21 then our summary comments for the committee.

22 Sustiva is an antiretroviral agent that

1 is a nonnucleoside reverse transcriptase
2 inhibitor. It's indicated in combination with
3 other antiretroviral agents for the treatment of
4 HIV Type 1 infection in adults and in pediatric
5 patients at least 3 months old weighing at least
6 3.5 kilograms. The dose is 600 milligrams once
7 daily, so maximum dose of 800 milligrams.

8 The formulation is manufactured as 200
9 milligrams as well as a 50 milligram capsule, and
10 a 600 milligram tablet. I just share with the
11 committee that the capsule can be opened and
12 sprinkled on a small amount of food for younger
13 children who cannot swallow a table, or in that
14 case, an elderly person who can't swallow a
15 tablet. The sponsor for this product is Bristo-
16 Myers Squibb Pharmaceuticals.

17 The original approval was September 17,
18 1998 and that was for children 3 years and older.
19 Then in May 2013 it was approved for pediatric
20 patients 3 months of age to 3 years of age. It
21 was those studies that prompted the current safety
22 review that's being presented this morning. Those

1 submissions fulfill the PREA requirement for
2 pediatric patients in the younger age group, 3
3 months and older.

4 A pediatric study was waived in children
5 0 to less than 3 months because this product would
6 be ineffective and/or unsafe in this age group.
7 I'll talk about that briefly a little bit later.

8 The next two slides I address the
9 relevant safety labeling in this slide, Section 4,
10 contraindications. Sustiva is contraindicated in
11 patients with previously demonstrated
12 hypersensitivity to any of the components of this
13 product. By hypersensitivity in parentheses,
14 specifically Stevens-Johnson Syndrome, erythema
15 multiforme, or toxic skin eruptions have been
16 reported.

17 This is a listing of what appears in
18 Warnings and Precautions, Section 5. The list
19 continues to be long: drug interactions,
20 resistance, co-administration with related
21 products, psychiatric symptoms, nervous symptoms,
22 embryo fetal toxicity, rash, which I'll speak to

1 more specifically, hepatotoxicity, convulsions,
2 lipid elevations, immune reconstitution syndrome,
3 and fat redistribution.

4 So the basis of approval for the younger
5 patient is 3 months to 3 years old. It's
6 supported by what you see on this slide. It was
7 matching pharmacokinetics in the younger patients
8 compared to adults, and that demonstrated
9 antiviral activity as well as acceptable safety.

10 There were three open label studies
11 evaluated and they included the PK safety and
12 tolerability, as well as evaluation of antiviral
13 activity of efavirenz in combination with other
14 antivirals. So there were three studies, and the
15 three sub-bullets speak to those open label
16 studies. The first combination was efavirenz with
17 didanosine and emtricitabine. That was in an
18 anti-retro viral naïve and experience pediatric
19 patients, and their ages for that particular study
20 were 3 months up to 6 years of age.

21 The second open label study was
22 efavirenz with didanosine and emtricitabine, a

1 slightly different population. That was in
2 antiretroviral naïve pediatric patients,
3 slightly different age group, 3 months up to 21
4 years of age. And then the third open label study
5 was efavirenz in combination with nelfinavir and a
6 nucleoside reverse transcriptase inhibitor in
7 anti-retro viral naïve, and NRTI experience
8 pediatric patients. Different age group, 3 months
9 up to 16 years of age. And those were the
10 supported studies for that labeling.

11 If you look at safety across these three
12 open label studies, the adverse reactions were
13 very similar to the adverse reactions observed in
14 the adult trials. Except that incidents of rash
15 was higher in pediatric patients. More
16 specifically, 32 percent for all grades,
17 regardless of causality, and more often a higher
18 grade than in adults. I just listed below what
19 that looked like. There were two pediatric
20 patients with grade 3 rash, four pediatric
21 patients with a grade 4 rash, and there were 5
22 pediatric patients who discontinued the study

1 based on rash.

2 The current pediatric labeling in
3 Subsection 8.4, Pediatric use, reads as follow:
4 The safety PK profile and biologic and immunologic
5 responses to Sustiva were evaluated and antiretro
6 viral naïve and experienced HIV 1 infected
7 pediatric patients 3 months of age to 21 years of
8 age in three open label studies. The use of
9 Sustiva in patients younger than 3 months of age
10 or less than 3.5 kilogram body weight is not
11 recommended because safety PK and antiviral
12 activity of Sustiva has not been evaluated in this
13 age group. There is a risk of developing HIV
14 resistance if Sustiva is under dosed.

15 This next slide speaks to the drug use.
16 I just clarify, if you look at the top row, that's
17 for Atripla, a combination antiviral product. If
18 you look specifically at the pediatric drug use, 0
19 to 16, we (have 405 patients. There were 17
20 patients were our data shows that they were less
21 than 11 months of age which is, of course, is not
22 approved indication. If you compare that to the

1 bottom row, Sustiva specifically, the numbers are
2 very similar, 0 to 16 years we have 326 patients.

3 This data is taken from the IMS data and
4 looks at U.S. outpatient and retail pharmacies.
5 It was collected between March 2013 and February
6 2016.

7 The adverse events, this data reported
8 reports the number of adult and pediatric FDA
9 adverse event reporting system that is our FAERS
10 system. This was received since the pediatric
11 labeling was included. If you look at that second
12 line, pediatrics 0 to less than 17 years of age,
13 there were 143 serious adverse events that were
14 reported. We'll go into more detail on that in
15 the next two slides.

16 So the serious adverse events, we have a
17 total pediatric reports reviewed with serious,
18 adverse events' outcomes was 143. The pediatric
19 reports with the outcome of death is 26. Let me
20 first direct your attention to the box on your
21 left, in the lower left side, 0 reports that were
22 excluded which totaled 116. We had duplicates of

1 31. We had transplacental exposure. There were
2 83 cases and that also included 10 deaths, and
3 then there were two no individual patient was
4 identified.

5 So let me direct your attention now to
6 the bold box on your right, pediatric case series.
7 We have a total of 27 and nine of those were
8 pediatric deaths, so nine fatal cases and 18
9 non-fatal cases.

10 The summary of the pediatric fatal cases
11 is as followed. We had immune reconstitution
12 inflammatory syndrome in three pediatric patients,
13 a 14 year old male, HIV infected with pulmonary
14 mycobacterium avium-intracellular complex. A 12
15 year old male, HIV infection Kaposi sarcoma, who
16 had been started on therapy for tuberculous, and
17 an 8 year old girl, HIV infected with pulmonary
18 tuberculosis. Antiretroviral drug resistance was
19 documented in one patient, a 10 year old boy who'd
20 been infected with HIV since about the age of 5.

21 Third category, HIV related
22 opportunistic infection. There were three

1 patients. Two 16 year old girls and one 14 year
2 old boy. And then unspecified infection in two
3 patients, and they happen to be very young,
4 2 year old girl and a 3 month old girl. I
5 just put the footer there in the subsequent
6 slide. Just be aware that unlabeled
7 events will be reported different, and they will
8 be underlined to help you clarify.

9 So the summary of all nonfatal adverse
10 events reported for the pediatric patients, if you
11 look to your left side, the labeled events there
12 were a total of 11. Under Section 5, Warnings and
13 Precautions, you see the details of the categories
14 of the specific events. Under Section 6, Adverse
15 reactions, there were a total of four events, and
16 those are the conditions: peripheral neuropathy,
17 ataxia, there were actually two patients, and
18 pancreatitis, one patient.

19 In the next column to your right, the
20 unlabeled events totaled three. Catatonia was
21 reported in one pediatric patient, 16 year old,
22 and there also were three adult patients who had

1 the same experience. Hypersensitivity and
2 Fanconi syndrome were also reported. These are
3 unlabeled, but they were potentially confounded,
4 so keep in mind that clarification.

5 The disease-related events n=4.
6 Actually, consider that to the left-hand column.
7 That gives you a total of 18 patients.

8 So if we look across the summary of
9 what's been presented with the new, three open
10 label studies that supported the younger labeling,
11 3 months to 3 years of age this concludes the
12 focused safety review for Sustiva. FDA is
13 considering adding the term catatonia to labeling.
14 There has been communication with the sponsor, and
15 there appears to be agreement to revise the label.

16 FDA recommends ongoing routine
17 pharmacovigilance, and at this point I would ask
18 if the committee agrees?

19 DR. WHITE: Thank you for your
20 presentation. We'd ask Dr. Towbin to join us
21 because we have no representative on the committee
22 in child and adolescent psychiatry. He's our past

1 chair here of the Pediatric Advisory Committee and
2 is on the faculty at NIH in child and adolescent
3 psychiatry.

4 Dr. Towbin, did you have any comments
5 about the catatonia? I think that's what we were
6 asking --

7 DR. TOWBIN: Yes. Absolutely.

8 DR. WHITE: -- your assistance with.

9 DR. TOWBIN: Yes. Thank you. Thank you
10 for allowing me to join you this morning. I wish
11 I could be there to see all your bright, smiling
12 faces.

13 It's so hard to know what to make of a
14 single case in the pediatric side of this. But in
15 combination with those adult cases it did, for me,
16 raise a concern, and so I guess the first thing to
17 say is that I was quite pleased that FDA took this
18 up with the sponsor and had talked about it. It's
19 quite obvious that a number of factors may come
20 into play since the appearance of neuropsychiatric
21 symptoms with this drug. The mechanism for that
22 is not at all clear.

1 So I guess the comments that I would
2 make are that it certainly did, to me, seem
3 reasonable to raise this as a treatable side
4 effect that should have attention brought to it.
5 And despite the, kind of, fragility of the data
6 that we get from the FAERS system that it's still
7 very reasonable to think about introducing this in
8 label, in my own opinion.

9 DR. WHITE: Thank you for your comments.
10 We're going to ask you to stay on line, if you
11 don't mind, in case other members of the committee
12 had questions or concerns. Any other comments?
13 Concerns? Regarding --

14 DR. HOEHN: I had a question.

15 DR. WHITE: -- catatonia?

16 DR. HOEHN: Sorry. I had a question
17 unrelated.

18 DR. WHITE: Identify yourself.

19 DR. HOEHN: Oh, sorry. Sarah Hoehn. I
20 had a question unrelated to catatonia, but related
21 to this presentation. Can I ask it?

22 So I just didn't know, I didn't see

1 anything that was per kilo dosaing, and the
2 labeling says it goes down to 3.5 kilos in a baby
3 3 months of age. So I just didn't know if there
4 was anything in the labeling that should address
5 per kilo dosings if you're talking about giving a
6 200 milligram capsule to a 4 kilo baby. So my
7 question was dosing related in labeling.

8 DR. WHITE: Would any of you like to
9 address that for us?

10 DR. YANCEY: I'm going to defer to the
11 colleagues from the Division of Antiviral
12 Products. Can you introduce yourselves please?

13 DR. FARROW: James Farrow, Division of
14 Antiviral Products, FDA. If you go into the
15 labeling section of the Indications and Usage Dsoage
Administration there should be the
16 recommended dosage based on the weight. So even
17 though that presentation just highlighted what the
18 dose is, the actual dosing recommendation there's
19 a -- if you look in Section 2 it goes by weight
20 band 3.5 to 5 kilos, 5 to 7.5, et cetera. So it is
21 specified how much to give based on their weight
22 band.

1 DR. WHITE: Doctor, I can't see your
2 name, sorry.

3 DR. HAVENS: Peter Havens.

4 DR. WHITE: Thank you.

5 DR. HAVENS: It might also be pointed
6 out that the HAB U.S. HRSA guidelines for
7 antiretroviral therapy don't actually recommend
8 its use in children under age 3 without genetic
9 testing because there's rapid metabolizers and
10 slow metabolizers for whom there's a four-fold
11 difference in dosing recommendations made by that
12 guidelines committee.

13 The FDA recommended weight band dose is
14 about halfway in between that. But some of the
15 central nervous system side effects are actually
16 related to blood concentrations of the drug.
17 Given the genetic determinants of drug clearance,
18 and therefore, drug concentration the guidelines
19 committee has recommended a genetically determined
20 dosing algorithm and does not routinely recommend
21 it for children under age 3 years.

22 DR. WHITE: Any other thoughts or

1 comments? Dr. Shwayder?

2 DR. SHWAYDER: Well, since I'm the only
3 dermatologist on the committee I just want to
4 point out on page 44 where they list the various
5 side effects that everything that's listed there
6 could be considered eczema, with the exception of
7 precancerous lesions. Because eczema is a red
8 itchy, sometimes bumpy, sometimes flat, and
9 everything that list that list is red, itchy,
10 sometimes bumpy, sometimes flat.

11 If it's important, we can develop a
12 clear clinical guideline for side effects of drug,
13 so you're not wrapping into this -- all the kids
14 that come into my clinic for the last three years
15 who have eczema or subdermal or all the other
16 things that happen to little kids. That'd
17 probably be a good idea and then you can elude out
18 this data. That's all.

19 DR. WHITE: Thank you for your comment.
20 Any other comments or concerns? Did the FDA want
21 a recommendation regarding labeling?

22 DR. COPE: Yes.

1 DR. WHITE: So we should take a vote on

2 --

3 DR. COPE: With discussions.

4 DR. WHITE: -- whether we should proceed
5 with changing the label to add catatonia, is
6 that...

7 DR. TOWBIN: Dr. White, I have a
8 question about this.

9 DR. WHITE: Yes. Go ahead.

10 DR. TOWBIN: This is Dr. Towbin. I was
11 wondering, in light of Dr. Havens' comments
12 whether there would be anything in the labeling to
13 suggest that the genetic assessment for rapid
14 metabolizing would be indicated in children under
15 3 as part of the label?

16 DR. BELEW: So I can address the first
17 question that was raised with regards --

18 DR. WHITE: Would you --

19 DR. BELEW: -- to labeling.

20 DR. WHITE: -- identify yourself,
21 please.

22 DR. BELEW: Yodit Belew, Division of

1 Antiviral Products.

2 So we're currently in discussion with
3 the sponsor with regards to labeling and the
4 wording. So at this point we don't have specific
5 wordings other than that we will be adding it on.
6 But exactly how and where is under discussion with
7 the sponsor.

8 DR. TOWBIN: So that was in regard to
9 catatonia, I assume, but it leaves open the
10 question about Dr. Havens' --

11 DR. BELEW: Right.

12 DR. TOWBIN: -- information, and I was
13 wondering where that stands?

14 DR. BELEW: So for consideration to
15 adding information into the label we would have to
16 work with the sponsor, and we would have to have
17 the actual data submitted by the sponsor to
18 include such information into the label.

19 DR. TOWBIN: This is Dr. Towbin once
20 again. Given the correlation between the data
21 that Dr. Havens' suggested, and it sounds as if
22 that was a consensus guideline, so it wasn't just

1 one person's one-off idea, but actually it does
2 seem that there may be some data there. Although,
3 this is not data that I know. And given the
4 correlation between that data and these
5 neuropsychiatric symptoms it would seem that just
6 adding catatonia would be insufficient as a
7 guideline for practitioners, and that a
8 recommendation for obtaining that genetic
9 assessment would be appropriate for this drug
10 given the risks.

11 DR. HAVENS: This is Dr. Havens again.
12 I think getting that into the label becomes really
13 complicated because you then have to have a
14 standard way to measure the specific genotypes
15 which is not readily available. Which is why the
16 committee, the guidelines committee, went to the
17 general recommendation to not use it, and if
18 you're going to then use it in the context of
19 using blood concentrations to monitor where you
20 are to avoid both resistance from low blood
21 concentration or toxicity from a high
22 concentration, which is a more practical way to

1 approach it.

2 I think the guidelines committee has
3 members on it from the FDA and we work closely to
4 bring together what's possible from the labeled
5 indications and make that work in practice with
6 guidelines that flow from the labeled indications.
7 But may never get changed further because of
8 impediments to changing the label which are it's a
9 pretty high bar. In this case, especially if you
10 need a blood test prior to choosing a dose.

11 DR. TOWBIN: This is Dr. Towbin, again.
12 Dr. Havens, thank you so much. I actually --
13 there's so much wisdom in your comments there, and
14 so I appreciate them very much.

15 Would there be a way in which the
16 recommendation for following blood levels and the
17 concern about rapid metabolizers being at higher
18 risk be something that could be considered as part
19 of the labeling then?

20 DR. HAVENS: That's an FDA question.

21 DR. TOWBIN: Yes, it is.

22 DR. WHITE: Dr. Nelson?

1 DR. NELSON: Skip Nelson, OPT. I won't
2 address that directly, but this general issue of
3 the need for genetic testing around issues of
4 rapid metabolizers, slow metabolizers and so on
5 and so forth is an important topic. It relates to
6 a number of other different drugs, but I just call
7 the attention to the committee that the extent
8 that you put that in the label you end up, A, you
9 need an in vitro diagnostic device which goes to
10 the question of whether or not a genetic test is,
11 in fact, available in the commercial setting as
12 opposed to the research setting.

13 DR. TOWBIN: Mm-hmm.

14 DR. NELSON: Or whether there are other
15 approaches to being able to determine whether
16 someone is or is not a rapid or slow metabolizer
17 and so on and so forth. So that becomes an issue,
18 and you then link that device to the use of the
19 drug. So there are some interesting, albeit it
20 important, complex questions around how drugs and
21 devices would then interact around the labeling.

22 It's not unusual for FDA to try to take

1 a middle position where you wouldn't require the
2 use of a particular device, particularly if it's
3 not available commercially. But might try to work
4 out some process by which, you know, the
5 recommendations of the committee to dose
6 appropriately if you're a rapid or slow
7 metabolizer could be sorted out clinically.

8 So it's a more general issue, and
9 particularly, as we go towards precision medicine
10 where dosing of different drugs are related to
11 slow and rapid metabolizers it's not unique to
12 this particular product.

13 DR. TOWBIN: Thank you for that, Dr.
14 Nelson. I do have a follow up question which is
15 since this is not a drug that I use in any routine
16 way, is monitoring blood levels standard practice?

17 DR. HAVENS: No, it's not.

18 DR. TOWBIN: So would there be room to
19 suggest that and at least raise practitioners'
20 awareness that the experience for rapid
21 metabolizers could put them at higher risk?

22 DR. HAVENS: Yes. Therapeutic drug

1 monitoring is recommended by the pediatric
2 guidelines for the United States which form the
3 basis of many other guidelines, and is used by
4 many of the drug compendia people to inform what
5 they put into readily available online resources
6 in combination with the labeled information put
7 out by the FDA.

8 DR. TOWBIN: So we've got --

9 DR. HAVENS: That was Havens again.

10 DR. WHITE: Dr. Shwayder?

11 DR. SHWAYDER: Tor Shwayder. So I'm
12 looking at slide 14. There's almost 400 kids and
13 they had the one case of the catatonia. I need to
14 ask, since I don't do this, can you get catatonia
15 from having HIV? Can you get catatonia from
16 having a high fever? Can you get catatonia from
17 any of the other drugs that they might be on to
18 treat their HIV?

19 If we link this to catatonia then it
20 stinks. It stinks. And are we -- it behooves us
21 to know whether it was cause and effect.

22 DR. WHITE: Anyone from the FDA like to

1 comment?

2 DR. BELEW: Yodit Belew, DADP. Thank you
3 for that comment. So we did struggle with that
4 specific case, and I believe you guys got the
5 narrative for the case. Paula can get into the
6 details, but there are some limitations into the
7 -- that single report with regards to weight loss.
8 Maybe that patient was overdosed for a little bit
9 when he got that symptom, and then when they
10 reverted back to his original dose it seems like
11 the symptoms went away.

12 But given that there were three other
13 cases in the adult population that were identified
14 that was one of the reasons to put it in the
15 labeling. But stepping back, efavirenz is known
16 to have neuropsychiatric adverse events. If you
17 look in the warning and precaution section the
18 psychiatric events, it's a laundry list of a
19 number of events.

20 So looking at it from that end it's not
21 unreasonable to think other psychiatric events
22 could occur. So that was sort of the thinking

1 behind why to include it in the label.

2 DR. TOWBIN: This is Dr. Towbin. Just
3 to add a comment here. So the thing that would be
4 a bit special about catatonia, as FDA has pointed
5 out, is that one might not be looking for that
6 being linked to the drug. Even though these other
7 neuropsychiatric symptoms are listed. I think FDA
8 has it right on the second issue with is the
9 intervention for catatonia might be very different
10 than the intervention for some of these other
11 neuropsychiatric symptoms, and so adding it to
12 this section of the labeling actually made good
13 sense.

14 But I fully agree that based on one case
15 one might not to want to take these steps. But
16 when you see the experience with rechallenging
17 the patient, causing the symptoms once again, and
18 you add it to what the adult experience has been
19 it would seem a safe step to add this. I also
20 think Dr. Haven's comments, once again, are
21 relevant here. That the genetic predisposition of
22 some individuals to rapidly metabolize this drug

1 could be linked to these neuropsychiatric
2 symptoms. Therefore, one wouldn't expect to
3 necessarily see a great number of individuals with
4 this problem, but that could explain why some do.

5 MS. GISH: As far as causality, there
6 were three adult patients --

7 DR. WHITE: Could you identify yourself
8 please?

9 MS. GISH: I'm sorry. I'm Paula Gish.
10 I'm an OSE safety evaluator. There were three
11 adult cases with a temporal relationship and all
12 of them had a positive de- challenge, and two of
13 those people had high drug levels of efavirenz, 6
14 to 25 times the normal level. One had a positive
15 re-challenge, so that's where the causality came
16 in.

17 DR. WHITE: If I might summarize. Dr.
18 Cnaan?

19 DR. CNAAN: One more small comment.
20 That is that the prevalence of catatonia in the
21 U.S. is 90,000 cases a year from everything. And
22 so if in the context of these short, relatively

1 short clinical trials and these small number of
2 people, relatively, we ended up with four cases,
3 three adults and one pediatric that further
4 supports that there is something happening here.

5 DR. WHITE: So if I might summarize.
6 We're going to vote yes if we feel that we should
7 support consideration of addition of catatonia to
8 the labeling for this drug. Can we start -- I
9 guess we're going to use the voting thing here.
10 Yes would be to support. No would be that we
11 don't feel it's necessary. If you want to press
12 yes or no please?

13 DR. NELSON: Michael, let me just
14 clarify.

15 DR. WHITE: I'm sorry.

16 DR. NELSON: So we're going to have two
17 votes.

18 DR. WHITE: We're going to have two
19 votes, yes.

20 DR. NELSON: I just want to be clear.
21 But the question -- I've heard some discussion
22 around levels and that sort of thing. So the

1 catatonia is one issue, but the discussion of
2 therapeutic drug monitoring, is that something
3 that the committee wants to opine on as well?

4 DR. TOWBIN: Dr. Towbin would like that
5 to be opined on. Thank you, Dr. Nelson.

6 DR. WHITE: I was thinking about
7 conserving that for comments going around the
8 table, but if you think we should --

9 DR. NELSON: Well, I think --

10 DR. WHITE: -- consider that as a second
11 round.

12 DR. NELSON: -- comments around the
13 table don't have the same cache as the committee's
14 opinion on whether therapeutic drug monitoring or
15 attention to levels or whatever. So, you know, I
16 would, you know, if you want to go around about
17 catatonia that's fine, and before you do the other
18 have some discussion about whether you think that
19 ought to --

20 DR. WHITE: Okay.

21 DR. NELSON: -- be a recommendation to
22 committee or not. Because a discussion doesn't

1 carry much cache as opposed to a vote.

2 DR. WHITE: Alright. Let -- go ahead.

3 DR. HAVENS: What do you mean a
4 recommendation about therapeutic drug monitoring?
5 Peter Havens.

6 DR. NELSON: Well, to back up. Whether
7 or not the label ought to include something along
8 the lines of what you've articulated is the
9 recommendation around practice guidelines about
10 the importance of monitoring, vis-à-vis, rapid
11 metabolizers, and the potential link to the
12 catatonia which we're adding to the label.

13 Whether that's something you as a
14 practitioner think would be helpful in the label
15 itself as opposed to in the guidelines? I'm just
16 following up on your comments about what the
17 guidelines currently say.

18 DR. HAVENS: Peter Havens. So then the
19 recommendation or so we might make a statement
20 that FDA would discuss with the sponsor the
21 potential for putting in a recommendation for
22 therapeutic drug monitoring for smaller children.

1 DR. NELSON: That's the question.
2 Whether you think you could articulate that in a
3 way that is votable.

4 DR. WHITE: Okay. I think most of us
5 have pressed the -- can we defer for a moment and
6 vote on the first issue which was to support the
7 labeling? Since I think most of us have pushed a
8 button. Some of us have not, and then we'll open
9 discussion for Dr. Nelson's consideration.

10 Have we completed the voting on the
11 first suggestion? Okay. And do we have that
12 vote? It looks as if all have voted in favor of
13 suggesting a considering of adding catatonia to
14 the label. We still have to go around the table.
15 Can we start with -- can't read your name, sorry.

16 DR. FISCHER: It's Gwen Fischer. I
17 concur with the addition to the labeling.

18 DR. MOON: Mark Moon, I concur.

19 DR. SAVEL: Wael Savel. I concur.

20 DR. HAVENS: Peter Havens. I concur.

21 DR. TURRER: Christy Turer. I concur.

22 DR. SHWAYDER: Tor Shwayder. I concur.

1 DR. CNAAN: Avital Cnaan. I concur.

2 DR. CATALETTO: Mary Cataletto. I

3 concur.

4 DR. CAMPBELL: Jeff Campbell. I concur.

5 DR. CUNNINGHAM: Melody Cunningham. I

6 concur.

7 DR. HOEHN: Sarah Hoehn. I concur.

8 DR. DRACKER: Bob Dracker. I concur.

9 DR. WADE: Kelly Wade. I concur.

10 DR. ANNE: Premchand Anne. I concur.

11 DR. WHITE: Thank you all. Now, the

12 question --

13 DR. TOWBIN: Dr. White?

14 DR. WHITE: Yes?

15 DR. TOWBIN: This is Dr. Towbin --

16 DR. WHITE: Yes, doctor?

17 DR. TOWBIN: -- and I vote yes.

18 DR. WHITE: Thank you. I'd almost

19 forgotten. Thank you for your vote and your --

20 DR. TOWBIN: You know, out of sight is

21 out of mind.

22 DR. WHITE: Well, not out of mind, but

1 so the question has been raised about whether we
2 should make a recommendation or not regarding drug
3 level acquisition to guide treatment. I guess we
4 would do this for the pediatric population only
5 since we don't really have any sway in the adult
6 world.

7 Is there an opinion from any of the
8 committee members regarding whether we should put
9 that proposal forth or not? We have two people on
10 the end. I'm sorry, help me with names.

11 DR. HOEHN: Sarah Hoehn. I had a
12 question related to that. DR. Havens mentioned
13 that HRSA doesn't recommend using it in the first
14 three years of life, so I didn't know if that
15 should be linked to the question about consider
16 therapeutic monitoring -- if you should especially
17 consider therapeutic blood levels under 3 years of
18 age.

19 I just didn't know if we should have any
20 connection to that based on the follow up. To
21 connect the labeling to what Dr. Havens said the
22 consensus guidelines are.

1 DR. HAVENS: This is Dr. Havens. The
2 pediatric guidelines state that therapeutic drug
3 monitoring is recommended with an efavirenz
4 concentration measured two weeks after initiation.
5 Some experts would also measure at three years
6 when making the dose adjustment. So that's what
7 the HRS guidelines recommend.

8 DR. CUNNINGHAM: Thank you. Melody
9 Cunningham. So if in the adults the levels were 6
10 to 25 times higher than anticipated then it seems
11 to me, it's almost a no-brainer about whether we
12 should make that recommendation for monitoring,
13 and perhaps some of those other side effects that
14 are already labeled may be related to drug levels
15 and the, you know, rapid metabolizers.

16 DR. WHITE: Dr. Havens, again.

17 DR. HAVENS: Well, no. Remember what
18 Dr. Nelson said, that as soon as you make a
19 recommendation to link a test with drug usage it
20 gets way more complicated because you have to
21 approve the test. Not everybody has availability
22 of the test. People won't pay for the test. And

1 so usage becomes dramatically more complex.

2 DR. WHITE: If I might summarize in
3 response to Dr. Nelson. It seems as if this
4 particular question we weren't provided the
5 information we probably need to make a
6 recommendation for drug level monitoring. But it
7 might be a question that we could ask the FDA to
8 investigate and bring back to committee at the
9 next meeting for consideration. With more
10 information regarding whether levels are indicated
11 or helpful.

12 Are there other opinions, maybe,
13 regarding that? Dr. Wade?

14 DR. WADE: Kelly Wade. Before, I think,
15 we're going to turn it to the expert
16 representative from the FDA, I would just ask if
17 you can help clarify or remind us the information
18 that's already in the label under clinical
19 pharmacology or clinical pharmacokinetics, and how
20 much this discussion of variation and metabolism
21 and genetic influence of drug metabolism may
22 already be in the label, just in another section?

1 Can you just remind us what information about this
2 topic is already in the label in a different
3 section?

4 DR. VISWANATHAN: Just give us a moment.
5 This label is very extensive, and we are just
6 reviewing it before we comment.

7 DR. BELEW: While Prabha is looking at
8 the label I also just want to make a comment about
9 the discussion at hand with regard to therapeutic
10 drug monitoring. So if we assume that efavirenz,
11 and it has been demonstrated that it does have
12 neuropsychiatric adverse events, demonstrated both
13 in adults and pediatrics. We can't divorce the
14 two populations and recommend drug therapeutic for
15 pediatrics only. If that's the path that we're
16 taking then would have to be all population and
17 not just pediatric patients.

18 The other comment that I want to make is
19 that efavirenz has been on market since the 90s,
20 so it's a pretty mature drug, and it's been used
21 as first-line regime in adults for years. So the
22 other question is for those who are already taking

1 the drug, even if they may or may not have
2 psychiatric adverse events, would they then have
3 to have therapeutic drug monitoring even if they
4 have been on the drug for years?

5 So there are a lot of questions and I
6 definitely agree that the data should be reviewed
7 and presented before it's voted on.

8 DR. WHITE: Dr. Cunningham?

9 DR. CUNNINGHAM: Melody Cunningham. I
10 just wanted to clarify. I wasn't suggesting
11 genetic testing which is clear is not readily
12 available, but therapeutic drug level monitoring.

13 DR. WHITE: Can I attempt to summarize
14 and maybe bring a question that we can vote? Yes,
15 go ahead.

16 DR. BELEW: If I could just --

17 DR. WHITE: FDA.

18 DR. BELEW: FDA. Make an additional
19 comment related to what was just said. So if
20 we're not doing genetic testing we're basically
21 monitoring blood levels. Then patients are
22 already on the drug if you're doing, so how does

1 the testing or adding that additional information
2 change practice management?

3 Because if you're already on the drug
4 you can also wait to see if they have adverse
5 events. Then decide to switch regime instead of
6 just doing blood levels.

7 DR. WHITE: Dr. Havens, would you like
8 to comment on that part of it?

9 DR. HAVENS: The biggest effect of the
10 genetic differences seems to be in the youngest
11 children under age 3. I think that making a
12 general recommendation for monitoring plasma
13 concentrations, as FDA points out, would
14 dramatically change what many people do already.

15 It should be noted that in many studies
16 up to 20 percent of people stop efavirenz because
17 of drug side effects. They're not usually severe.
18 They just can't concentrate or they have bad
19 dreams. So the clinical monitoring is usually
20 taken as a reasonable approach to this problem.

21 DR. WHITE: Dr. Cunningham?

22 DR. CUNNINGHAM: Sure. Melody

1 Cunningham. So the way that I see that it might
2 change things therapeutically is if the patient
3 has a side effect you check the levels, and if
4 they're high they may stay on this drug that's
5 effective for them. But the dose might be
6 diminished and mitigate their side effects. So
7 that's how I see it might be clinically relevant.

8 DR. BELEW: Then you run the risk of
9 development of resistance, so you wouldn't
10 actually decrease the dose if they're not
11 tolerating the drug because of adverse events.
12 You would just discontinue it.

13 DR. WHITE: Dr. Havens?

14 DR. HAVENS: So, first of all, yes, to
15 the first question of what you would do if you had
16 somebody who had a side effect with a documented
17 high plasma concentration. You could decrease the
18 dose. I would argue that this is the place where
19 guidelines are better than changing the label.

20 That there is a place for the
21 collaboration of FDA and guidelines writing
22 committees. We've already referred to this when

1 we talked about the vaccines where FDA had
2 recommended or had approved it down to age 2
3 months, and then the question came up, what did
4 CDC and ACIP recommend. And in a same kind of
5 way, I think that FDA makes labeled
6 recommendations that are appropriate and
7 reasonable, and then guidelines committees can
8 take them on and apply them. In your case, to a
9 practice activity.

10 Then in response to the FDA perspective.
11 Right, if you were going to change based just on a
12 clinical adverse event you wouldn't decrease the
13 dose because you wouldn't know what the right dose
14 was to use. But, in fact, we use efavirenz plasma
15 concentrations like verapamil plasma
16 concentrations, very closely in our pediatric
17 practice so that we make sure we have the right
18 dose and find a wide variability in dose that is
19 needed to give appropriate therapeutic drug
20 concentrations.

21 But I think that that really is the
22 purview of a guidelines for clinical practice

1 rather than a change in the FDA label which has a
2 completely different level of difficulty and
3 meaning in the public forum.

4 DR. BELEW: Thank you, Dr. Havens. To
5 add to that, while you may adjust the dose based
6 on guidance recommendation, for us to recommend
7 changing a dose we have to have a clinical trial
8 that has shown a lower dose has been shown to be
9 effective. We cannot just recommend a lower dose
10 without having a clinical trial.

11 And particular, for adults or
12 pediatrics, for that matter. So if we don't have
13 an alternative dose already recommended in the
14 label that would have to be a new study
15 demonstrating an effective therapy from a lower
16 dose.

17 DR. TOWBIN: This is Dr. Towbin, I just
18 wanted to make one comment. I'm very grateful to
19 Dr. Havens for the comments that he's making. I
20 would concur with his perspective that using the
21 label to establish practice really can be very
22 cumbersome.

1 But I think the other side is we still
2 have this question outstanding about whether the
3 label includes some of the concerns about rapid
4 metabolizers, as Dr. Cunningham has so nicely laid
5 out. And so I think, for me, the question would
6 be whether there could be a value for
7 practitioners and patients of making clear that
8 there is a risk for rapid metabolizers of
9 increased ill effects, neuropsychiatric effects in
10 particular.

11 That might actually guide things like
12 family history or other kinds of experiences with
13 other agents in the decisions about using these
14 agents. Since we know rapid metabolizers may be
15 individuals who've had adverse events to other
16 drugs.

17 DR. WHITE: Dr. Hausman?

18 DR. HAUSMAN: Hi. This is Ethan Hausman
19 from Pediatric and Maternal Health. With respect
20 to the comments that just came up, one of the
21 difficulties and shortcomings with making those
22 recommendations without actually having the

1 hard-core data in the beginning is one can infer
2 from the FAERS database, and even from practice
3 guidelines which may be supported by class A, B,
4 or C evidence that there might be a link. But it
5 makes it very difficult to actually inform the
6 label constructively about therapeutic drug
7 monitoring, particularly for adverse events, when
8 we don't have the support of good, quality data.

9 DR. WHITE: Dr. Nelson?

10 DR. NELSON: If I may, just a couple of
11 comments. You know, part of my interest in this
12 conversation is I gave a talk just yesterday to
13 the T-32 NICHD/NIGMS clinical pharmacology training
14 program. And heard a very interesting
15 presentation, I won't mention the drug, by Steve
16 Leeder where he presented some data, and, Ken,
17 you'd be interested about ADHD and a particular
18 drug that may or may not be working well because
19 of differences in slow, rapid, fast metabolizers
20 and so on and so forth.

21 So this is a general issue that impacts
22 in pediatrics. I guess I might be so bold as to

1 suggest I don't hear a sort of clear consensus
2 emerging from this conversation, and I just wonder
3 if there would be a way at some point in the
4 future if we can, as we are trying to get
5 important things on the agenda for the PAC, maybe
6 have a broader discussion of the role of
7 therapeutic drug monitoring, genetic testing for
8 rapid and slow metabolizers to six or whatever.

9 DR. TOWBIN: Mm-hmm.

10 DR. HAVENS: As a more general
11 conversation. Because this is not unique to this
12 product and it's a very, you know, complex issue
13 involving both clinical trials and future
14 diagnostic devices and so on and so forth. Impact
15 on access, etcetera. So an important topic.

16 I would hesitate to have a premature
17 vote on something that is, as Peter points out,
18 fairly complex in a relationship between the label
19 of practice guidelines, understand of genomics,
20 et cetera. So, you know, and maybe we could try to
21 think down the line of a broader conversation
22 about that. I mean, this is one example, but

1 there are other examples that one could bring to
2 bear on that topic.

3 DR. WHITE: I'm going to try to
4 summarize this. Yes, Dr. Moon or not Dr. Moon.
5 Go ahead, Dr. Jones.

6 DR. JONES: I just had a comment,
7 Bridgette Jones. On those same lines, I think
8 this is a really complicated issue and I think,
9 you know, maybe there are some assumptions being
10 made that genetic variation is playing a role in
11 alternative exposures in its relationship to the
12 catatonia or other side effects. But other things
13 also should be considered like drug interactions.
14 Maybe these patients were on several other drugs
15 that could interact with the metabolism of the
16 drug and effect exposures and also, the impact of
17 ontogeny and age.

18 The fact that some children, when
19 they're younger, some of the enzymes may work
20 differently related to age. So I think there's a
21 lot of other factors that should be considered
22 besides just genetics.

1 DR. WHITE: I'm going to try to
2 summarize this and help me, Dr. Nelson, you might
3 help me clarify this. It appears that there are
4 some concerns about the potential for drug levels
5 to be interacting with the side effects that we've
6 seen.

7 So I think what I'd like to do is ask
8 the FDA to review the data on drug levels and
9 genetic variance in this particular drug and come
10 back to us with a recommendation for whether to
11 proceed with consideration of changes in the label
12 related to any potential observations that you
13 make.

14 Dr. Nelson, does that clarify it well
15 enough?

16 DR. NELSON: Well, that's fine. But I
17 guess, in my mind, Judy and I can think downstream
18 about topics. I mean, for example, you may
19 remember at the last meeting we said let's talk
20 about neuroapoptosis in a few years when we have
21 clinical trial data. I mean, this may be
22 something that merits a broader discussions. Not

1 focused on this particular drug but, you know, the
2 drug, Ken, that was presented yesterday afternoon
3 was for ADHD. So, I mean, it's a broader topic.

4 So we could bring in a number of
5 different examples and have a broader discussion
6 of this issue as the emphasis on precision
7 medicine evolves. That's what I'm thinking. I
8 mean, that's a more specific drug related question
9 which we can certainly fold into it. When we
10 could carve out time for that, we'd have to look
11 at our schedule. But that's sort of what I was
12 thinking. You know, work with the people within
13 the FDA about how useful that is, but really take
14 attention off of this product, per say, and
15 broaden it to say how do we approach that?

16 Particularly in pediatrics where those
17 genomic interactions may have more of an impact as
18 you get to lower weights, and so on and so forth.
19 So that was the idea. I don't think we
20 necessarily need a vote on that. Maybe a sense of
21 the committee about whether that's a worthwhile
22 direction to go.

1 DR. WHITE: Well, I think we've raised
2 the question in this specific drugs in a number of
3 peoples' minds, so I think we have to -- maybe we
4 don't have to, but I would feel like we should
5 probably make a recommendation or not that this
6 specific drug be considered and the data brought
7 back to us.

8 And then your recommendation is for a
9 broader educational perspective and I think --

10 DR. NELSON: Well, I guess I'm not sure
11 what data we have and that's --

12 DR. WHITE: And we may have none.

13 DR. NELSON: Yeah.

14 DR. WHITE: We may have none.

15 DR. NELSON: Look at the data.

16 DR. WHITE: But that's okay. If that's
17 the information that comes back is that there is
18 no data then it's a quick discussion.

19 DR. BELEW: Yodit Belew.

20 DR. WHITE: Go ahead.

21 DR. BELEW: I just want to mention a
22 question was brought up about the label and what's

1 included in the clinical pharmacology section. It
2 does talk about its metabolism and how it's CYP
3 inducer. So you can imagine if it's a CYP
4 involvement how different people would metabolize
5 it and who would have a higher level versus not.

6 DR. WHITE: I'm looking for guidance.
7 This is new to me. I think we have to wrap this
8 up, so a vote.

9 DR. NELSON: To me a vote carries weight
10 when you have a labeling recommendation, and the
11 reason for that is because this committee is the
12 place where differences of opinion between
13 divisions and the sponsor are adjudicated although
14 we've never had that happen.

15 So in the absence of a clear -- I mean,
16 you know, in the --

17 UNIDENTIFIED MALE: There's no
18 consensus.

19 DR. NELSON: In the absence of a clear
20 labeling recommendation I'm not sure, necessarily,
21 we need a vote to say this is an important topic
22 to bring back to committee. I think it's an

1 important topic to bring back to the committee. I
2 don't know if that would be in 6 months. I don't
3 know if that would be in 12 months.

4 We would have to line up some drugs.
5 Line up the clinical pharmacologists, get the
6 pharmacogenomics people involved, et cetera, and
7 plan that which would probably put it out to, at
8 best, a year from now. So I, you know, I think
9 our office can work on trying to put that together
10 independent of a vote of the committee, frankly.

11 DR. WHITE: Dr. Havens?

12 DR. HAVENS: I'm very supportive of
13 that. I'm feeling a little guilty that I've
14 opened up a can of worms here. But I do think
15 that this is part of a much broader discussion and
16 how to bring labeled indications to bear on
17 clinical practice, and what's the most effective
18 way to do that in a rapidly changing environment,
19 and whether or not it's genetics or drug
20 concentrations that are really the issue.

21 As we heard earlier, this is a very
22 important issue that changes with patient age

1 because of the maturation of different enzymes and
2 the relative contribution of liver and body
3 surface area, blah, blah. So it's a very
4 complicated issue that, I think, bringing it
5 together with a variety of different drugs really
6 would be very useful.

7 I only hope that you get to it before I
8 retire from the committee.

9 DR. TOWBIN: This is Dr. Towbin just
10 coming in. So. Dr. Havens, I won't allow you to
11 take responsibility for opening the Pandora's Box
12 single handedly. I assisted you in that or I may
13 have been the one with the crow bar and you were
14 just there with the information.

15 But I do think that Dr. Nelson's
16 suggestion is an excellent suggestion. I think
17 this is a really good role. My view of the PAC is
18 that this is a really good role for the PAC to
19 play with FDA, to think about these broader
20 issues.

21 I guess, my issue about the label is
22 that I think the label can be a way of informing

1 practitioners about risks and concerns. And so,
2 unfortunately, I don't have the label in front of
3 me, but the question that I would raise, not for a
4 vote, but just to kind of put out there is whether
5 the language about metabolism is strong enough or
6 clear enough so that people would be aware that
7 that's a thing that they should be thinking about.
8 And that blood level monitoring would be a
9 consideration in someone who is presenting,
10 particularly, with neuropsychiatric side effects
11 and as the kind of first line.

12 I think the comment about, I think it
13 was Dr. Jones, that said that, you know, there
14 are other drugs on board. There are drug
15 interactions. And yet, a blood level would be
16 really the best way to determine that someone
17 really has much too much on board and that
18 something needs to be done about that.

19 DR. WHITE: We have comments from the
20 FDA.

21 DR. BELEW: Yes, Yodit Belew. If you
22 look in the Warning and Precaution section the

1 first warning, 5.1, is drug interactions, and it
2 clearly states efavirenz plasma concentration may
3 be altered by substrates, inhibitors, or inductors
4 of CYP3A. Likewise, efavirenz may alter plasma
5 concentration of other drugs metabolized by CYP3A.
6 So that is the first warning with regards to the
7 potential changes and the concentration of
8 efavirenz.

9 DR. TOWBIN: Thank you for that.

10 DR. WHITE: So I'm going to try one more
11 time. I am going to bring this to vote because I
12 think that's the only way with all the comments we
13 can resolve it. I would like to suggest that the
14 FDA, we're going to vote to request that the FDA
15 come back to us with information regarding use of
16 label of -- pardon me, drug levels and possible
17 genetic variation.

18 Did I make that clear enough for a vote?
19 So a yes vote will be --

20 DR. HOEHN: Can I just
21 clarify?

22 DR. WHITE: Sure.

1 DR. HOEHN: Is that for this
2 drug in particular or for --

3 DR. WHITE: For this drug in --

4 DR. HOEHN: -- or for Dr.
5 Nelson's comment of a --

6 DR. WHITE: No.

7 DR. HOEHN: -- broader
8 discussion?

9 DR. WHITE: No. For this drug in
10 particular I think the broader educational
11 objectives can be met without a recommendation.
12 Is that correct, Dr. Nelson?

13 DR. NELSON: Whether I would
14 characterize it as educational, I think, would be
15 the open question. But, I mean, if you think you
16 want to see specifically about this drug that's
17 fine, but it's, you know, but.

18 DR. WHITE: I think we need to vote on
19 it. I'm not sure everyone will agree.

20 DR. NELSON: I don't think we do. I
21 mean, I haven't heard a clear recommendation
22 that's come out from that. So, I mean, if you

1 want to -- so to just say you'd like the data
2 back, if you want to see the data at some point
3 then that's fine. But, you know, it's unclear
4 what you would do with that data at this point in
5 time, so I don't think you need a vote,
6 necessarily, to resolve that because there's no
7 question that I think it --

8 DR. WHITE: Okay. Dr. Cnaan?

9 DR. CNAAN: I think what we're hearing
10 is that there's enough around the committee that
11 we would like to see what the data are, and also
12 any association with side effects. Maybe there is
13 none between the levels in side effects. Maybe
14 there is. But I think we're in a position where
15 none of us feel comfortable making any
16 recommendation about labeling, but we just want to
17 know a little more. That's what I'm hearing.

18 DR. WHITE: I'm sorry, I --

19 DR. HOEHN: Sarah Hoehn. I have another
20 question. I didn't know based on the language of
21 the labeling if there could be recommendation to
22 say, consider therapeutic drug monitoring when

1 toxicity. Because they talk about seeking
2 immediate medical evaluation. If you could just
3 add four words to say consider checking a level if
4 they develop toxicity.

5 DR. BELEW: Yodit Belew. I think from
6 clinical practice if someone is having side
7 effects, regardless of what the drug level is, you
8 would manage that patient according to symptoms.
9 So you'll either discontinue regardless of the
10 drug level or continue if the side effect is not
11 severe.

12 DR. WHITE: Okay. I'm sort of caught
13 between what Dr. Nelson is asking and my feeling
14 from the committee that the committee's
15 uncomfortable with the information that we have.
16 The only way I can think to get through this is to
17 call a vote which would be we would like the FDA
18 to come back to us with a review of the role of
19 drug levels in genetic testing for this specific
20 drug, and that would be the vote. Yes, we would
21 like them to come back. No, we will like we have
22 the information we need and we are comfortable

1 with the FDA continuing routine monitoring.

2 That question will come up later because
3 we have to vote on that specifically. Can we vote
4 now? Is the vote complete, and Dr. Towbin?

5 DR. TOWBIN: Dr. Towbin votes no.

6 DR. WHITE: No, okay. Is the vote
7 complete? Okay. It looks like yes, the committee
8 would like you to come back with some information
9 regarding the potential use of drug levels and
10 genetic testing for this specific drug.

11 Now, the question that was raised by the
12 FDA initially was return to routine monitoring, I
13 believe?

14 DR. NELSON: You need to go
15 around the room.

16 DR. WHITE: Oh, I'm sorry. Yes, thank
17 you for reminding me. Do we start down there?
18 We'll start down there.

19 DR. FISCHER: It's Gwen Fischer. I
20 voted no based on the reasons that Dr. Havens
21 brought up, but I would be interested in hearing a
22 more general conversation about this in the

1 future.

2 DR. MOON: Yeah, Mark Moon. I voted no.
3 I mean, we could do this for any drug.

4 DR. SAVEL: Wael Savel. I voted no. I
5 agree with Dr. Nelson and with Dr. Moon that we
6 can do this for many other drugs, and I can think
7 of at least ten drugs I use on a daily basis on my
8 patients that could benefit from drug monitoring
9 and/or genetic testing before prescribing those
10 medications.

11 I think the issue here is age dependence
12 and whether that should be included or not. So if
13 patients under 3, if they are more susceptible to
14 toxicity because they're rapid or slow
15 metabolizers. I think that's a separate issue
16 from the general consensus here.

17 I do think that this is an important
18 topic that we should discuss, in general, but not
19 necessarily pertaining to this specific drug. But
20 in general, I think we could definitely use more
21 information about it.

22 DR. HAVENS: Havens, no.

1 DR. TURER: Turer. I had voted yes,
2 although I do concur with your statement. It's
3 more about the broader conversation and not so
4 much about the specific drug, so if that is the
5 question then I would change my vote to a no.

6 DR. SHWAYDER: Shwayder. I voted yes.

7 DR. CNAAN: Avital Cnaan. I voted yes.
8 I feel that regardless of the broader discussion,
9 which is definitely great, whatever slim
10 information exists on this one it would be a good
11 idea to see it in about a year and see if we have
12 anything or it is so slim and thin that we cannot
13 for this one. Regardless of the general
14 conversation.

15 DR. CATALETTO: Mary Cataletto. I voted
16 yes.

17 DR. CAMPBELL: This is Jeff Campbell. I
18 actually obtained.

19 DR. CUNNINGHAM: Melody Cunningham. I
20 voted yes. Although as I think of the comments at
21 the other end of the table, I think if I thought
22 about whether to do this or to look at the broader

1 view I think that the broader view is more
2 important, and it probably does relate to many
3 drugs. So I would actually change my vote to no.

4 DR. HOEHN: Sarah Hoehn. I voted yes,
5 but I would agree with the other half of the table
6 and change my vote to no.

7 DR. DRACKER: Bob Dracker. I would vote
8 no. I think it will interfere with use of the
9 drug.

10 DR. WADE: Kelly Wade. I voted yes in
11 case this is a unique scenario in the lower age
12 dependence children. But I support the more
13 general conversation of the rule of the label
14 information in this domain.

15 DR. ANNE: Premchand Anne. Yes.

16 DR. WHITE: After all the vote changes,
17 and the fact that I actually pressed the button
18 and wasn't supposed to I think the vote is no.
19 There's a strong consensus that future programs
20 considering this, whether educational or
21 informative, I'm not sure how to characterize it
22 would be.

1 DR. TOWBIN: Dr. White, I just had --

2 DR. WHITE: Yes. I'm sorry, Dr. Towbin.
3 I keep forgetting. I apologize.

4 DR. TOWBIN: Oh, no, no. It's fine. No
5 offense taken. So my vote was no. I do think
6 that it could be productive, really on both sides,
7 that is for FDA to have the PAC's advice on how to
8 think about these issues in the broader context,
9 and also for the PAC to hear from FDA. How they
10 think about it and would understand an approach to
11 this issue. I think that actually could be a
12 constructive conversation and useful. But I don't
13 think it should be about this specific drug and
14 that was my rationale for voting now.

15 DR. WHITE: Thank you, all, for your
16 comments. The final vote that we have is FDA
17 recommends ongoing routine pharmacovigilance for
18 this drug, and the question is does the committee
19 concur. Can we call that vote? We need the
20 lights please.

21 And the vote is unanimous in favor of
22 routine pharmacovigilance.

1 DR. TOWBIN: And that includes Dr.
2 Towbin who concurs.

3 DR. WHITE: Thank you, Dr. Towbin. How
4 many times can I forget you're there today?

5 DR. TOWBIN: It's fine. You know what?
6 When we see each other it's always a warm
7 occasion.

8 DR. WHITE: Yes. We need a picture of
9 you on the screen here, just so I know that you're
10 there.

11 DR. TOWBIN: No. Please don't scare the
12 participants like that.

13 DR. WHITE: We'd like to thank you for
14 your participation today and your insightful
15 comments.

16 DR. NELSON: We still need to go around
17 the room.

18 DR. WHITE: Thank you, Dr. Nelson. I
19 was not prepared for this at all.

20 DR. ANNE: Premchand Anne. Yes.

21 DR. WADE: Kelly Wade. Yes.

22 DR. DRACKER: Bob Dracker. Yes.

1 DR. HOEHN: Sarah Hoehn. Yes.

2 DR. CUNNINGHAM: Melody Cunningham. I
3 concur.

4 DR. CAMPBELL: Jeff Campbell. I concur.

5 DR. CATALETTO: Mary Cataletto. I
6 concur.

7 DR. CNAAN: Avital Cnaan. Yes.

8 DR. SHWAYDER: Shwayder. Yes.

9 DR. TURER: Turer. Yes

10 DR. HAVENS: Peter Havens. I concur.

11 DR. SAVEL: Wael Savel. I concur.

12 DR. MOON: Mark Moon. I concur.

13 DR. FISCHER: Gwen Fischer. I concur.

14 DR. WHITE: Dr. Towbin, I think you've
15 already expressed your comments. Thank you very
16 much for your participation today.

17 DR. TOWBIN: Thank you very much. I
18 concur as well.

19 DR. WHITE: And thank the committee for
20 your patience in my taking charge of the meeting.

21 DR. TOWBIN: It's all good. Thank you
22 very much for letting me join you for this

1 discussion, and to participate in this important
2 work. Bye, for now.

3 DR. WHITE: Dr. Hudak has pulled his
4 chair back to the table. You all will be happy
5 for that.

6 DR. HUDAK: Thank you, Dr. White. Well
7 done. I just might take the chair's prerogative
8 here not to speak about Sustiva, but to point out
9 that the FDA website actually has a section
10 dealing with the drugs that have label information
11 on pharmacogenomics. At my last check back in
12 April I think there were 100 drugs that have
13 information on different metabolism and different
14 pharmacogenomics, so I think this is a relevant
15 subject to entertain on a more broad basis.

16 So we will get back with the program.
17 We were a little off schedule. So I'll have to
18 cogitate on what we do about a break, but we will
19 proceed with the next presentation which is on
20 Topamax. Here to do that is Dr. Khurana.

21 UNIDENTIFIED FEMALE: We have someone
22 new to the table.

1 DR. HUDAK: Someone new to the table.
2 We have someone new to the table.

3 DR. LEVIN: Hi. Bob Levin, FDA,
4 Pharmacovigilance, OSE.

5 DR. HUDAK: Very good. All right. And,
6 Dr. Khurana. Thank you.

7 DR. KHURANA: Thank you. Good morning.
8 I'll be presenting the pediatric focus safety
9 review today for Topamax. This is the outline
10 which I'll be following.

11 So first, by way of background, Topamax
12 is an antiepileptic drug containing topiramate as
13 the sole active ingredient. It's approved as oral
14 tablets and oral sprinkle capsules. Topamax was
15 first approved in the U.S. in 1996 as an adjunct
16 to treat partial onset seizures, initially only in
17 adults, but is now currently approved at both mono
18 therapy and adjunctive therapy for several
19 different seizure types in both adults and
20 pediatric patients down to 2 years of age.

21 Topamax's March 2014 approval for
22 extension of the migraine headache prophylaxis

1 indication to adolescence prompted this pediatric
2 focus safety review.

3 The next few slides highlight relevant
4 safety information in Topamax labeling. Current
5 labeling does not include a boxed warning or
6 contraindications for use in adults or pediatric
7 patients. The warnings and precautions section
8 contain 16 subsections which are listed over the
9 next two slides, with prominence given to the
10 possibility of visual complications and adverse
11 neuropsychiatric events including suicidal
12 behavior and ideation.

13 The efficacy of Topamax as a migraine
14 prophylaxis in adolescents was established in a
15 multicenter, randomized, double blind, parallel
16 group trial in 103 patients 12 to 17 years of age
17 with episodic migraine headaches with or without
18 aura. The patients were randomized to receive
19 Topamax 50 milligrams daily, 100 milligrams daily
20 or placebo.

21 Trial results showed the superiority of
22 the 100 milligram Topamax dose over placebo for

1 the primary efficacy endpoint. The long term
2 safety of Topamax as migraine prophylaxis in
3 adolescence was based on the pivotal efficacy
4 trial. As well as from a flexible dose placebo
5 control study in a broader pediatric age range,
6 and from the open label extension phases of three
7 studies of migraine prophylaxis, primarily in
8 adults, that collectively included
9 adolescents. Most of the adverse
10 reactions in the adolescent
11 migraine patients was similar to the
12 known safety profile of Topamax in adults and
13 pediatric patients treated for other indications.
14 Newly recognize adverse reactions are highlighted
15 in bold on this slide, and were incorporated into
16 labeling with approval of the migraine prophylaxis
17 indication in adolescents.

18 Both pediatric trials were summarized in
19 the pediatric use subsection with cross references
20 to the relevant sections in Topamax labeling.
21 This information is detailed over the next few
22 slides. Trial information was included throughout

1 labeling since the product is approved in
2 pediatric patients.

3 Now let's look at the use of topiramate.
4 This table displays the total number of pediatric
5 patients 0 to 18

6 years of age who received a dispensed
7 prescription for topiramate from U.S. outpatient
8 retail pharmacies from March 1, 2014 to February
9 29, 2016. Pediatric patients 0 through 17 years of age
10 accounted for approximately 7 percent of
11 topiramate use during this time period.

12 Now we'll look at the pediatric-focused
13 adverse events. We identified 121 U.S. pediatric
14 reports with topiramate reporting a serious
15 outcome from March 1, 2014 which was the date of
16 the last pediatric labeling change for Topamax to
17 February 29, 2016. After adjudication, 45 reports
18 were excluded for the reasons listed on the bottom
19 left of this slide, resulting in the selection of
20 77 domestic cases of topiramate use reporting a
21 serious outcome which were the basis for this
22 pediatric-focused safety review.

1 These included three fatal cases and 73
2 non-fatal cases which described a total of 190
3 drug event combinations. A drug event combination
4 is a drug and adverse event combination reported
5 in at least one case in the database. Cases may
6 have more than one drug event combination. For
7 purposes of this review, we focused on deaths, and
8 serious unlabeled drug event combinations.

9 Three patients died. The reported death
10 was associated with a respiratory infection in one
11 case, and with a seizure in another case. The
12 cause of death in both cases was likely disease
13 related. Concomitant use of other anti-epileptic
14 drugs in these two cases could have confounded the
15 assessment.

16 The third case reported cardiac and
17 respiratory arrest due to a completed suicide with
18 ingestion of an unknown amount of topiramate.
19 This case did not contain enough details for
20 assessment.

21 The majority of the serious reported
22 drug event combinations were consistent with the

1 known risks described in Topamax labeling, and no
2 apparent increased severity was observed in these
3 cases. We identified six cases reporting seven
4 serious, unlabeled drug event combinations of
5 interest with topiramate use in the pediatric
6 population. Including the fatal case of cardiac
7 and respiratory arrest from a completed suicide
8 that was previously discussed.

9 The adverse reaction section of Topamax
10 labeling currently includes anorexia and weight
11 decrease. But we identified three cases which
12 reported the eating disorders of anorexia nervosa
13 and bulimia nervosa in adolescent females who were
14 taking Topamax to treat migraine. All three
15 adolescents reported either a family history of
16 eating disorders, a personal medical history of
17 anorexia nervosa or major depressive disorder.
18 All of which are risk factors for anorexia nervosa or
19 bulimia.

20 One case reported acute kidney injury
21 and hypovolemic shock secondary to acute hepatic
22 failure in an 11

1 year old boy who had been receiving
2 topiramate for epilepsy for 10 years prior to his
3 presentation. His liver function and associated
4 laboratory abnormalities improved with
5 discontinuation of topiramate. A liver biopsy was
6 reportedly consistent with drug-induced liver
7 injury.

8 Hepatic failure is listed in the
9 post-marketing adverse reactions section of
10 labeling. However, to date, FDA has had
11 inadequate information to justify a more prominent
12 location for hepatic failure and labeling. One
13 case reported the unlabeled event of respiratory
14 failure in a two week old male who experience
15 seizures, but this case lacked sufficient details
16 for assessment.

17 Pediatric focused safety reviews for
18 Topamax were previously presented to the PAC in
19 2011 and again in 2013. Discussions at these
20 meetings largely centered on exploring how to
21 assess the effect of topiramate related metabolic
22 acidosis on the development of potentially serious

1 adverse outcomes such as decreased bone density,
2 growth retardation and kidney stones.

3 In order to address some of these safety
4 concerns, FDA issued a post-marketing requirement
5 under PREA in 2011 for a controlled long-term
6 study assessing the effect of topiramate on these
7 potentially serious adverse outcomes in pediatric
8 patients. The final study report is due in
9 September 2018.

10 This concludes the pediatric focused-
11 safety review for Topamax. We identified no new
12 pediatric safety signals. FDA plans to monitor
13 for anorexia nervosa, bulimia nervosa, and acute
14 hepatic failure in all patient populations. FDA
15 recommends continuing ongoing surveillance. FDA
16 will review the PREA PMR study report once the
17 study is completed.

18 Does the committee concur?

19 DR. HUDAK: Thank you, Dr. Khurana. So
20 we are now open for discussion and comment on
21 this. Dr. Dracker?

22 DR. DRACKER: I think I had something to

1 do with this original FDA approval going back a
2 couple years for migraines in adolescents. I just
3 wanted to comment. I have never had an adverse
4 reaction in children because I always, for any of
5 the drugs I use, whether it's this drug or any
6 other psychotropic-like drug I always do minimal
7 effective dosing.

8 So I've seen other colleagues, whether
9 psychiatrists or family practitioners use very
10 high dosing very quickly, and I always found when
11 I use this drug with caution because the side name
12 for it is Topamax not -- which is the biggest
13 complaint patients have when they take this drug.
14 I've never seen that. It's been very safe and
15 it's been very invaluable for children.

16 DR. HUDAK: Other comments?

17 DR. TURER: Christy Turer. I had a
18 concerns regarding the anorexia and bulimia, and
19 in reading the cases I do wonder, particularly
20 with the bulimia, if that was a pre-existing
21 condition not brought out by the Topamax which
22 cannot be sorted out.

1 But in terms of labeling, I do think,
2 you know, there are two approaches. One would be to
3 monitor for anorexia and bulimia over the upcoming
4 year and reconsider this in a year. Another way
5 to go about it would be to say that, in
6 particularly girls with -- any patient, truly,
7 with eating disorders, that clinicians may
8 consider an alternative drug to treat, in
9 particular, migraines.

10 Just because we use these drugs for
11 weight loss. Topiramate in combination with phentermine
(Qsymia). We know in the kids, when

13 I'm treating children with overweight and obesity
14 who have migraines this is particularly effective
15 for them to lose weight. So I think that there's
16 a real risk in prescribing a drug that's known to
17 cause weight loss to patients that have eating
18 disorders.

19 I think that's important for clinicians
20 to know and to screen for. So I'd be interested
21 in others' thoughts about that. In particular,
22 because, you know, the risk of suicidality or the

1 risk of death in anorexia is pretty high. And
2 though unrelated in that 16 year old who
3 overdosed, he died. So that's concerning to me.
4 It raised my concern.

5 DR. HUDAK: Dr. Dracker?

6 DR. DRACKER: I just want to comment.
7 Some of the information that has come from the
8 adult literature is that the weight loss you see
9 with Topamax can be persistent, even after you
10 stop the drug, and it's not necessarily related to
11 behaviors, whether it's anorexia or bulimia. It's
12 something intrinsic in the drug that really
13 engenders weight loss, and they have continued
14 weight loss after they stop the drug.

15 My own personal experience, although
16 small, is that I have not seen anorexia or
17 bulimia. I have not even seen weight loss. Only
18 because, I personally, try to go very low dosage
19 to get the effect needed.

20 DR. HUDAK: Yes. Dr. Anne.

21 DR. ANNE: It seems like the incidences
22 of anorexia and bulimia is so minimal. It's much

1 less than the presence in the general population.
2 So, I mean, is there any particular reason to pay
3 attention to these particular disorders? You
4 know, for anorexia it's about slightly less than 1
5 percent and 1.5 percent in bulimia.

6 The incidence of this in these
7 particular studies in 0 to 17 group is very small,
8 one to two out of 200 some thousand kids.

9 DR. TURER: I think my concern is more
10 a risk for abuse. Much like for, you know, a
11 narcotic drug. We'd say in a patient who has
12 known predisposition to drug seeking or, you know,
13 opioid pain drug abuse. You want to really
14 exercise caution in using that drug. I think that
15 the same applies here.

16 DR. HUDAK: Is someone from FDA able to
17 clarify what there might be in the label about
18 this issue?

19 DR. HERSHKOWITZ: Hi. Norm Hershkowitz.
20 I'm the epilepsy team leader, but I handle
21 Topamax. Before we put something in the label,
22 first of all, we need good confirmation that this

1 is an in fact causally related. As kind of
2 suggested by others, as well as our reviewers,
3 there's really insufficient information to
4 determine any causality.

5 You're suggesting that because there's a
6 potential for abuse based upon its known appetite
7 suppressant effect that we should provide it in
8 the label. I can't think of any precedent where
9 we've done that. This might be listed under a
10 clinical practice. I mean, I can raise it at one
11 of our meetings whether there is -- but you see,
12 we don't think it right now -- we don't have
13 evidence that this is causally. But this is more
14 of a clinical practice decision.

15 I think some of the others on the panel
16 kind of implied that this might be more of a
17 clinical practice decision. I would like to know,
18 really, what the panel thinks about this. Without
19 a causality, is this a clinical practice decision?

20 I mean, does one have to be careful, for
21 instance, does appetite suppressants like
22 stimulants have that warning in their label? I

1 don't know. I don't treat the -- or I didn't
2 treat. I'm now a regulator, of course, for many,
3 many years. But my suspicion is -- maybe what the
4 plan should be to determine if there's a precedent
5 for it, and to look in some of the other appetite
6 suppressants and determine if there is a warning.

7 Because this is kind of, again, a
8 clinical opinion. I don't know if this satisfied
9 your or if it satisfies the committee. I would be
10 interested to know what you all think.

11 DR. TURER: Well, that's why I said one
12 of the avenues may be to continue to monitor for
13 this, not add it to the label. But then look over
14 the next year, and particularly as they're a
15 direct drug to population marketing of these
16 things. There are well-connected, you know, blogs
17 and social media things where girls with eating
18 disorder reach out to one another and teach each
19 other about mechanism to help them with appetite
20 suppression.

21 So, I agree, these are very limited
22 cases, and maybe it bears watching this. I --

1 DR. HERSHKOWITZ: I believe, isn't that
2 our plan?

3 DR. TURER: And coming back to it. But
4 I want to stress that this is a concern that I
5 have, particularly given the cases that were
6 presented to us.

7 DR. HERSHKOWITZ: Well, maybe what I can
8 say is we'll raise this at one of our safety
9 meetings and we'll determine if there is precedent
10 for warning clinicians that there is a potential
11 abuse for this. Although, again, it's -- and
12 we'll see if there's precedent, and maybe I can
13 say that.

14 But does anybody else from the FDA or --
15 have an opinion on this?

16 DR. ALEXANDER: This is Dr. Alexander
17 from the Division of Pediatric and Maternal
18 Health. So I would say that there is clear
19 labeling. I mean, the issue of anorexia and
20 weight loss were identified within the clinical
21 trials. So there is labeling that sort of
22 indicates that this is a known adverse reaction of

1 the drug. That you have this kind of effect.

2 So with regards to the issue of labeling
3 for anorexia, I do think that the question does
4 become, you know, how much would we need to do
5 that for other similar drugs that also have that
6 kind of weight loss effect. And so I take the
7 point with regards to the potential concerns about
8 the use of this drug in that population. But then
9 this is a drug that's also -- needs to be
10 prescribed for patients.

11 So hopefully that type of control is
12 something that people would recognize, especially
13 if it's known that this drug has this issue. That
14 patients with eating disorders will be patients
15 that you might want to avoid such medications in.

16 DR. HUDAK: Dr. Dracker?

17 DR. DRACKER: I just want to mention,
18 personally, I think this drug has very limited
19 potential for abuse. Because when you try to take
20 more of this drug for an appetite suppressant
21 purpose the suppression is so profound the individuals
22 will not take this for appetite suppression. The

1 girls really don't like, or boys, don't like
2 taking the medication at high doses because of
3 that effect.

4 So I think if there was a cultural
5 approach to taking more of this drug to get
6 appetite suppression I think there's better
7 alternatives that wouldn't give them degree of
8 super they're going to experience.

9 DR. HERSHKOWITZ: Can I say again, my
10 impression listening to the panel and people who
11 have dealt with this drug that this is more of a
12 decision, a personal clinical judgement decision.
13 Although, I think it's worthwhile to continue to
14 examine the issue. But that's my impression that
15 I get from -- you know, I would say a majority,
16 and a small majority because not many people have
17 spoken out on this.

18 But of those who spoke out on this it --
19 but, I mean, certainly, we will take this
20 seriously and we'll continue monitoring. I don't
21 personally think a drug safety communication, this
22 is my opinion and may differ, is all that helpful

1 because I don't think we have enough evidence.
2 Unless we look at other -- you know, maybe this is
3 a global issue if you look at other suppressants.

4 But, you know, the problem with other
5 suppressants, and this goes for what was
6 previously said, other suppressants certainly have
7 psychogenic propensity to be abused. They give
8 you a high. This gives you more of a low than
9 anything else and confounds you.

10 So I think it's probably, in sum, it's
11 probably best to just continue monitoring and
12 determine if we establish a signal that's real.
13 This is my feel.

14 DR. HAUSMAN: Hi. This is Ethan Hausman
15 from Pediatric Maternal Health. Usually the
16 comment I'm about to make comes towards the end of
17 the discussion, but it seems to be relevant now,
18 and I'm speaking a little bit for the
19 pharmacovigilance people.

20 Routine monitoring includes a robust,
21 ongoing monitoring of FAERS which is the adverse
22 event reporting system. So the fact that the

1 signals come up, it already means that the signal
2 or potential signal is in the safety evaluator's
3 radar screen. So routine monitoring would not
4 consign this to the dust heap. It means that they
5 would look at it as they usually do when they look
6 through their assignment portfolios.

7 DR. KAPCALA: Len Kapcala. I'm a medical
8 officer in the neurology division. I just also want
9 to just comment that there's only one approved
10 dose for migraine prophylaxis in adults and
11 adolescents. So, I mean, if you're using lower
12 dosing or higher dosing it's not approved or
13 recommended dosing.

14 DR. HUDAK: It's within the realm of
15 individual subscriber discretion for the lower
16 dose.

17 DR. LEVIN: Hi. This is Bob Levin from
18 FDA pharmacovigilance. Dr. Turer, you raise a
19 lot of excellent points, obviously. We do plan on
20 -- it's high on our list for this drug of
21 continuing to do specific monitoring for these
22 possibilities of abuse, misuse, and just eating

1 disorders in general. Dr. Long here will be doing
2 that, specifically.

3 Also, the other good points you raise
4 are about how, like in many populations, eating
5 disorder populations may be quite sophisticated
6 and clever about what they might do,
7 surreptitiously or otherwise. I think you made a
8 point about possibly monitoring, in addition to
9 regular routine pharmacovigilance of our FDA
10 adverse event database it is something worth
11 looking into other venues on the web to see if --
12 that often does produce a lot of useful
13 information. So I think it's another great
14 suggestion that we'll look into.

15 DR. HUDAK: I think we had a question.
16 Dr. Cunningham?

17 DR. CUNNINGHAM: Melody Cunningham. I
18 had a question. I did look through the FDA label
19 for methylphenidate and there is nothing about
20 eating disorders in that label.

21 DR. HUDAK: Okay. Any other comments.
22 So, in summary, it appears that there is

1 reasonable information in the label for Topamax
2 that practitioners can put two and two together
3 here on a risk assessment, and that the FAERS and
4 other monitoring has identified this as a new
5 issue, and that you're intent on looking at this
6 with increased fervor going forward.

7 So I would call the question to vote
8 then about the recommendation to continue the
9 ongoing surveillance with specific attention to
10 these issues of eating disorders and acute hepatic
11 failure. So a yes vote, no vote, abstain on your
12 speaker.

13 DR. LONG: This is Karen Long, safety
14 evaluator from Division of Pharmacovigilance. I
15 just wanted to mention. This is on the radar for
16 us for monitoring, and because of the reasons that
17 you discussed. I can tell you that from our
18 weekly monitoring of the reports that there are no
19 other reports of this.

20 So this is why it came up on the radar
21 because when we were doing this review, we do
22 realize that these are important adverse events,

1 especially in adolescent aged individuals. But we
2 have not seen any other reports besides the ones
3 that are reported here. That gives you a little.

4 DR. HUDAK: Okay. Is voting concluded?
5 Everybody has voted? So can we see that? Okay.
6 We'll go around the room. Dr. Fischer first.

7 DR. FISCHER: Gwen Fisher. I agree.

8 DR. MOON: Mark Moon. I agree.

9 DR. SAVEL: Wael Savel. I concur.

10 DR. HAVENS: Peter Havens. Yes.

11 DR. TURER: Christy Turer. I concur.

12 And I'd just like to state that the difference
13 between methylphenidate and topiramate is that
14 methylphenidate is not part of an FDA approved
15 drug for weight loss. That's the key point.

16 DR. SHWAYDER: Shwayder. Concur.

17 DR. CNAAN: Avital Cnann. Concur.

18 DR. CATALETTO: Mary Cataletto. Concur.

19 DR. CAMPBELL: Jeff Campbell. Concur.

20 DR. CUNNINGHAM: Melody Cunningham.

21 Concur.

22 DR. HOEHN: Sarah Hoehn. Concur.

1 DR. DRACKER: Bob Dracker. I concur. I
2 would just want to comment that we should monitor
3 unexplained weight loss, not necessarily just
4 anorexia or bulimia.

5 DR. WHITE: Michael White. Agree.

6 DR. WADE: Kelly Wade. Agree.

7 DR. ANNE: Premchand Anne. Concur.

8 DR. HUDAK: Okay. So the summary there
9 is that the committee unanimously agrees with the
10 FDA recommendation to continue monitoring with
11 attention to these several issues.

12 (Recess)

13 DR. HUDAK: We'll get started now. FDA
14 people at the table can introduce yourselves,
15 we'll get started here.

16 DR. HARINSTEIN

: Lisa Harinstein.

17 Division of Pharmacovigilance.

18 DR. DANNIS: Marjorie Dannis, Division
19 of Gastroenterology and Inborn Errors Products.

20 DR. RAJPAL: Anil Rajpal, clinical
21 team leader, Division of Gastroenterology and
22 Inborn Errors Products.

1 DR. GREENE: Patty Greene, Division of
2 Epidemiology.

3 DR. HUDAK: Very good. So we have Dr.
4 Radden, you're here for a doubleheader. Okay. So
5 you will present first on these three products.
6 Asacol and Asacol HD and Delzicol. Maybe in the
7 course of your presentation you can clarify for us
8 whether we should be voting on your
9 recommendations separately or as a unit, perhaps.

10 DR. RADDEN: All right. Good morning.
11 So, as mentioned, I'll be discussing the pediatric
12 focused safety review for these three mesalamine
13 products, Asacol, Asacol HD, and Delzicol. I'll
14 be following the outline shown here.

15 So there are currently eight FDA
16 approved mesalamine products marketed in the U.S.,
17 all of which are noted here with various
18 formulations, routes of administration, approved
19 indications, and approved populations for use.
20 While this review focuses on Asacol, Asacol HD,
21 and Delzicol, data for all mesalamine products
22 were also evaluated. Asacol and Delzicol,

1 however, are the only mesalamine products approved
2 for use in children.

3 So mesalamine is an aminosalicylate
4 indicated for the treatment and maintenance of
5 remission of mildly to moderately active
6 ulcerative colitis or UC. Asacol and Delzicol are
7 approved for both treatment and maintenance.
8 However, only the treatment indication is approved
9 in pediatric patients down to 5 years of age.
10 Asacol HD is only approved for treatment of
11 moderately active UC and only in adults.

12 Asacol and Asacol HD are delayed release
13 tablets in 400 milligram and 800 milligram doses,
14 respectively. Delzicol is a delayed release
15 capsule that contains four smaller 100 milligram
16 tablets. Pediatric dosing for Asacol and Delzicol
17 is weight-based with a maximum of 2.4 grams daily,
18 divided in two doses.

19 Asacol was approved in 1992 followed by
20 Asacol HD in 2008, and most recently Delzicol was
21 approved in 2013. There have been multiple
22 pediatric labeling changes for these three

1 products. Though, initial pediatric labeling for
2 these products occurred in October 2013 for Asacol
3 and Asacol HD. In April 2014 for Delzicol which
4 triggered this safety review.

5 Based on these labeling changes, Asacol
6 and Delzicol are currently approved for the
7 treatment of UC in patients 5 years and older, but
8 none of the products are approved for maintenance
9 of UC in pediatric patients. However, there is a
10 pediatric study requirement pending to evaluate
11 Delzicol for maintenance.

12 I want to pause at this point to
13 highlight a few safety activities that have
14 occurred in order to provide additional context to
15 the background information for these products.
16 FDA became aware of a potential reproductive and
17 fetal developmental effects with dibutyl
18 phthalate, an excipient in Asacol and Asacol HD.
19 In March 2009, asked the sponsor to develop
20 formulations without this excipient.

21 The sponsor complied and Delzicol was
22 developed as a phthalate free formulation to

1 replace Asacol. Following Delzicol's approval in
2 February 2013, Asacol was removed from the U.S.
3 market in March 2013. Additionally, a new
4 phthalate free formulation of Asacol HD was
5 approved a few months ago in May 2016.

6 Furthermore, in April 2014, the Division
7 of Pharmacovigilance evaluated 53 post-marketing
8 reports of Delzicol related to difficulty
9 swallowing and drug administration errors. They
10 provided recommendations to update Delzicol
11 labeling and request further monitoring by the
12 sponsor. However, following a review by the
13 Division of Gastroenterology and Inborn Errors
14 Products, in July 2015, the noted safety concerns
15 were subsequently mitigated by the approval of the
16 currently marketed formulation of Delzicol,
17 containing the four smaller tables within one
18 capsule.

19 Now I'll continue with the pediatric
20 study supporting the labeling changes for this
21 safety review. Efficacy for Asacol and Delzicol
22 in pediatric patients was supported by adequate

1 and well-controlled studies of Asacol in adults in
2 addition to a single study of Asacol in 82
3 pediatric patients 5 to 17 years of age, and a
4 demonstration of bioequivalence between Asacol and
5 Delzicol.

6 However, one Asacol HD tablet was not
7 demonstrated to be bioequivalent to two Asacol
8 tablets. Therefore, dosing could not be
9 established for Asacol HD to support pediatric
10 approval.

11 A pediatric study was conducted for
12 maintenance of remission of UC with Asacol.
13 However safety and effectiveness was not
14 established. Likely related to premature
15 termination of the trial and the dose range
16 studies.

17 Ultimately, the labeling changes
18 associated with Asacol include changes to Section
19 8.4 which describes how safety and effectiveness
20 have been demonstrated in patients

21 years and older for treatment, but not
22 in patients less than 5 years of age nor for the

1 maintenance indication in any pediatric age group.

2 Additionally, pediatric PK, dosing,
3 adverse reactions, and clinical trial data were
4 included throughout labeling. Similar changes
5 were made to Delzicol labeling. Labeling for
6 Asacol HD directs prescribers to other approved
7 mesalamine products for information on pediatric
8 use.

9 Now, before we look at the use of
10 Asacol, Asacol HD, and Delzicol I want to note
11 some of the safety labeling for these products
12 which will be discussed again later in the review.
13 Note that both the warnings and precaution
14 section, and the post-marketing experience
15 subsection include information on interstitial
16 nephritis.

17 Now let's look at use. This table
18 displays the nationally estimated number of
19 patients with a dispensed prescription for Asacol
20 HD and Asacol from U.S. outpatient retail
21 pharmacies during the review period of October
22 2014 through February 2016. You'll notice that

1 pediatric patients 0 to 17 years accounted for
2 approximately 3 percent of total patients with a
3 dispensed prescription for both Asacol HD and
4 Delzicol. Patients 5 to 17 years of age accounted
5 for the vast majority of pediatric use. A similar
6 trend is noted with Delzicol.

7 Now, let's turn our attention to the
8 safety and pediatric focused adverse events. The
9 review included a search for all mesalamine
10 products from the approval day of the first
11 marketed mesalamine product in December 1987 to
12 February 2016. You'll notice that of the 535
13 events reported for pediatric patients, 385 were
14 deemed serious with 19 deaths.

15 Now I'll walk you through the selection
16 of the final case series. Of the 385 serious
17 pediatric reports, 381 were reviewed and excluded
18 from the pediatric case series for the various
19 reasons listed here. Note that of the 19 reports
20 with an outcome of death, seven reports were
21 duplicates, six reports describe transplacental
22 exposures, and one report had insufficient

1 information to assess causality. The remaining
2 five reports involved patients receiving multiple
3 immunosuppressant medications who died as a result
4 of strong alternative causes, including
5 hepatosplenic T-cell lymphoma, hemophagocytic
6 syndrome, disseminate intravascular coagulation
7 secondary to bacteremia, and Epstein-Barr virus
8 associated lymphoproliferative disorder.

9 That left us with four cases and no
10 deaths. Of the four unlabeled, non-fatal, serious
11 adverse events, two involved benign intracranial
12 hypertension, and two involved nephrogenic
13 diabetes insipidus.

14 The first case of benign intracranial
15 hypertension or BIH involved a 15 year old female
16 who developed neck pain, headache, and scotoma one
17 month after starting Pentasa, another mesalamine
18 product. She was diagnosed with BIH and
19 papilledema, and most of her symptoms resolved
20 with reduction of the mesalamine dose, and
21 addition of acetazolamide.

22 Following a UC relapse three months

1 later, mesalamine was discontinued and corticosteroids
2 were initiated, but her scotoma
3 persisted.

4 The second case involved an 11 year old
5 female who developed worsening headaches after
6 starting an unspecified mesalamine product. She
7 was found to have optic disc edema and elevated
8 erythrocyte sedimentation rate, and a normal head
9 CT. Following discontinuation of mesalamine and
10 initiation of corticoid steroids her symptoms
11 partially resolved.

12 Based on these findings, the Division of
13 Neurology Products reviewed these two cases, in
14 addition to another case report of BIH in a 23
15 year old female. However, the division was unable
16 to distinguish whether the cases were the result
17 of BIH or cerebral venous thrombosis. Due to
18 insufficient imaging, responses to acetazolamide
19 or corticosteroids, and the association of both
20 of these conditions in patients with inflammatory
21 bowel disease.

22 Two cases associated with nephrogenic

1 diabetes insipidus or NDI and interstitial
2 nephritis were also identified. Recall that
3 mesalamine products are currently labeled for
4 interstitial nephritis.

5 The first involved a 14 year old female
6 who developed NDI and interstitial nephritis
7 approximately five months after starting another
8 oral mesalamine product for the treatment of UC
9 which was confirmed with water deprivation and
10 vasopressin testing and renal biopsy. Following
11 discontinuation of mesalamine and initiation of a
12 corticosteroid, the NDI resolved and the
13 interstitial nephritis partially improved.
14 However, drug induced lymphocyte stimulation
15 testing was positive for mesalamine.

16 In the second case, a 9 year old male
17 being treated for UC developed interstitial
18 nephritis without confirmed histopathology, and
19 NDI after the increase of another oral mesalamine
20 product, and the addition of mesalamine rectal
21 enema. His symptoms resolved after mesalamine was
22 discontinued.

1 The Division of Cardiovascular Renal
2 Products conducted a review of this safety
3 concern, and it concluded that the events of NDI
4 were likely drug related and recommended that NDI
5 be added to the list of adverse reactions in the
6 post-marketing section of product labeling for
7 those drugs labeled as causing tubule interstitial
8 nephritis.

9 This concluded the pediatric focused
10 safety review. The review identified benign
11 intracranial hypertension as a safety signal.
12 However, imaging was insufficient to distinguish
13 the event from cerebral venous thrombosis.
14 Nephrogenic diabetes insipidus was also identified
15 as a safety signal. Based on the available data,
16 the FDA recommends no changes to mesalamine
17 product labeling for benign intracranial
18 hypertension at this time.

19 However, FDA recommends adding
20 nephrogenic diabetes insipidus to the list of
21 adverse reactions listed in the post-marketing
22 section of mesalamine product labeling. FDA also

1 recommends continuing ongoing routine
2 pharmacovigilance monitoring.

3 I'd like to acknowledge my colleagues on
4 this slide for their assistance.

5 DR. HUDAK: Thank you.

6 DR. RADDEN: So, in response to your
7 question, we looked at the review of mesalamine
8 products as a whole, so I believe that you can
9 consider the questions that we are posing in our
10 recommendations as a whole for all mesalamine
11 products.

12 DR. HUDAK: Thank you very much. Dr.
13 White?

14 DR. WHITE: I've been accused of looking
15 at the data too closely, but I have something
16 that's confusing me. Asacol was taken off the
17 market in March of 2013 and the table that we have
18 in our data that we were given for review, October
19 2013 to February 2016 there 3,700 prescriptions,
20 apparently, that were given out after the drug was
21 removed from the market.

22 In that same diagram or that same chart

1 is labeled as 2014 to 2016 in your presentation.
2 Is that just a problem with the way we're
3 compiling the data, and where it's coming from,
4 and the way it's presented to us in the different
5 databases? That you could have 3,700
6 prescriptions dispensed after it was taken from
7 the market?

8 DR. RADDEN: I'll have to defer that to
9 the use.

10 DR. GREENE: This is Patty Greene. Yes,
11 we actually have residual prescriptions that
12 actually trickle down in our data for longer than
13 after the product is taken off the market. So
14 it's very common to see that. We have trickling
15 of prescriptions that are still in the system.

16 DR. WHITE: How do I know which dates to
17 believe because the numbers are identical? Is it
18 from October 2014 or October 2013?

19 DR. GREEN: Oh, I'm sorry.

20 DR. WHITE: It's the same numbers in two
21 different places. One is in the data we were
22 given for review and then the other is in the

1 chart and the slide.

2 DR. GREENE: I'm sorry. That's an error.
3 It should be October 2013.

4 DR. WHITE: Okay.

5 DR. GREENE: Yes.

6 DR. WHITE: Thank you.

7 DR. HUDAK: Okay. So this is open for
8 discussion. Interesting, two different
9 conclusions about safety signals. Any comments?
10 Dr. White, you were saying something?

11 DR. WHITE: Not intentionally.

12 DR. HUDAK: Okay. Yes, we have a
13 question over here. Yes?

14 DR. SAVEL: So are we voting separately
15 on whether to include benign intracranial
16 hypertension as another adverse event -- adverse
17 effect or --

18 DR. HUDAK: Well, the vote would be on
19 the recommendation as it stands which is both
20 things, so that's why I was trying to elicit
21 comment as to whether or not one wanted to
22 separate those out.

1 DR. SAVEL: Because this is -- I'm Wael
2 Savel from pediatric GI, University of
3 Connecticut. Couple of things. The Delzicol
4 switch came about in 2014 and I remember precisely
5 where I had to change my patients from Asacol to
6 Delzicol because Asacol was no longer available.
7 So there was a sudden switch that we had to deal
8 with.

9 Number two, one of the frequency side
10 effects that we see with these patients is
11 headaches. I quite honestly believe that the
12 benign intracranial hypertension is underdiagnosed
13 in many of these patients because the usual thing
14 that we do is discontinue the medication without
15 any further testing. We just report it has
16 headaches instead of benign intracranial
17 hypertension which is probably contributing to a
18 significant portion of those patients who did
19 develop headaches.

20 Thirdly, the medications are approved
21 for pediatric patients ages 5 and above. However,
22 I quite honestly can't remember the last time I've

1 seen a 5, 6, 7 year old prescribed Delzicol or
2 Asacol. Due to the fact that the tablets are very
3 large or the capsules and they are unable to
4 swallow them, and it is not recommended to open up
5 those capsules either.

6 So therefore, we end up using off-label
7 medications we recommend for the patients to open
8 and mix with applesauce or whatever their
9 preference is and consume those medications. The
10 interstitial nephritis is a very well-known
11 adverse event that we see with these patients.
12 Diabetes insipidus, however, I've seen one case in
13 ten years of practice and it's not a very common
14 phenomenon.

15 As mentioned with those cases, once you
16 discontinue the medication the symptoms reverse,
17 at least from the case I've seen also. Thank you.

18 DR. HUDAK: Perhaps we could just
19 prepare to put up the section on the adverse event
20 labeling for these products. Does that include
21 headaches or...

22 DR. HAUSMAN: I have the label. Hold

1 on. Ethan Hausman, DMPH. Headache is listed
2 under pediatrics in adverse reactions. Section
3 6.1, so that's actually in relation to control
4 data.

5 DR. HUDAK: Dr. Campbell?

6 DR. CAMPBELL: Do you know what imagine
7 the 23 year old had with pseudotumor? Did she
8 have an MRI or other imaging?

9 DR. RADDEN: I'll defer to the safety.

10 DR. HARINSTEIN: Hi. I can respond to
11 that. So the 23 year old had a CT, MRI, and an LP
12 performed, but there was no additionally venous
13 imaging on the MRI.

14 DR. CAMPBELL: So, in general, a regular
15 MRI is sufficient to look for venous thrombosis,
16 so how did you all reach the conclusion that you
17 couldn't rule that out based on the imaging?

18 DR. HARINSTEIN: We had consulted the
19 Division of Neurology Products and the medical
20 officer there had recommended that because of the
21 imaging and the other two pediatric cases that it
22 was insufficient for a diagnosis of BIH versus

1 cerebral venous thrombosis.

2 DR. HUDAK: Dr. Hoehn?

3 DR. HOEHN: Sarah Hoehn. So I had a
4 follow up to what Dr. Campbell was saying.
5 Cerebral venous thrombosis, by definition, is not
6 benign and it's not going to resolve by itself.
7 So it wouldn't -- the fact that the treatments
8 resolved without treatment or intervention or
9 anticoagulation, to me, means it's unlikely that
10 it was venous thrombosis.

11 So it seems like the rationale given for
12 not adding it to the labeling change doesn't
13 really hold up. I would advocate adding benign
14 intracranial hypertension to the labeling change
15 the same and interstitial nephritis. I think
16 that's a really, in my opinion, a very weak
17 argument given to not add it just because they
18 didn't do an angiogram to a clot. The fact that
19 their symptoms got better. That's my thoughts.
20 But I certainly defer to Dr. Campbell.

21 DR. HUDAK: Dr. Campbell?

22 DR. CAMPBELL: Did you consult with a

1 radiologist or just a neurologist? Because I
2 haven't met a neuroradiologist who could not
3 diagnose a venous thrombosis based on a plain MRI
4 without an MRI venogram.

5 DR. HARINSTEIN: Just a neurologist.
6 However, the neurologist felt also on the case of
7 the 23 year old that the open pressure (inaudible)
8 was higher than he has typically seen, some
9 concern in the case.

10 DR. CAMPBELL: Could you clarify that
11 comment? By definition, when you have pseudotumor
12 you have an elevated open pressure with an LP.

13 DR. HARINSTEIN: The opening pressure is
14 80 centimeters of water in the case, and he felt
15 that that was higher than he's typically seen in
16 these patients.

17 DR. CAMPBELL: I don't understand how
18 that differentiates between a cerebral thrombosis
19 versus a drug induced pseudotumor.

20 DR. HARINSTEIN: It wouldn't have helped
21 to distinguish that. He was just unsure about the
22 credibility of the case.

1 DR. HUDAK: So I guess the question here
2 is do we have two or three cases of benign
3 intracranial hypertension?

4 DR. HARINSTEIN: We have three cases.
5 Two in pediatric patients, specifically. The 23
6 year old was not the pediatric patient, obviously.

7 DR. HOEHN: This is Sarah Hoehn. But we
8 have the same number of pediatric patients with
9 interstitial nephritis which we're saying we
10 should add a labeling change. We have the exact
11 same number of patients who fulfill diagnostic
12 criteria for intracranial hypertension, and we're
13 willing to not add that. That's what is troubling
14 to me.

15 DR. FISCHER: This is Gwen Fischer. I
16 would agree with that statement and also add that
17 none of the patients in these cases had other
18 signs of venous thrombosis. Typically you would
19 see signs of stroke and seizure which is fairly
20 common with those patients.

21 DR. HUDAK: Okay. So I think we will
22 separate this into two votes. The first vote

1 would be for the whole category of all the
2 mesalamine products available for pediatric
3 treatment. Whether to agree with the FDA
4 recommendation not to change the labeling
5 regarding benign intracranial hypertension with
6 this product. So we'll do that vote first.

7 So you can indicate -- so, in other
8 words, if you say yes you agree that there
9 shouldn't be any product labeling change. If you
10 say no you would suggest that there is a change
11 and then we'll sort of take the vote and see where
12 we are, so.

13 There we go, okay. So let me make sure
14 that I understand the data. So the data are, the
15 red is the no vote?

16 UNIDENTIFIED MALE: Yes.

17 DR. HUDAK: Okay. And the green is the
18 yes. Okay, so we'll go around the table and folks
19 can provide their rationale. We'll start over
20 here with Dr. Anne.

21 DR. ANNE: Dr. Anne. No.

22 DR. WADE: Kelly Wade. No.

1 DR. WHITE: Michael White. No. I think
2 that the instance of headache is quite high or at
3 least recognized as a problem and may very well be
4 related to intracranial hypertension that never
5 gets worked up.

6 DR. DRACKER: Bob Dracker. No.

7 DR. HOEHN: Sarah Hoehn. I voted no. I
8 think benign intracranial hypertension should be
9 added to the labeling change.

10 DR. CUNNINGHAM: Melody Cunningham. I
11 voted yes, but I was thinking not clearly and, no,
12 I think it does need to be added to the label.

13 DR. CAMPBELL: This is Jeff Campbell. I
14 voted no. I think when you have a kid with
15 pseudotumor we often start looking through the
16 list of drugs that cause pseudotumor, and I think
17 these two cases sound pretty compelling and it
18 would be valuable to have this on the list.

19 DR. CATALETTO: Mary Cataletto. I voted
20 no.

21 DR. CNAAN: Avital Cnaan. I abstained
22 because I felt that I didn't have enough

1 information. Hearing some additional information
2 as people went around, I will join the no.

3 DR. SHWAYDER: Shwayder. I voted yes
4 under the assumption that headache would lead
5 people to look for these other things, and it's
6 already listed as headache as a side effect.

7 DR. TURER: Christy Turer. I voted
8 no. I think -- I agree that we look for what
9 drugs cause intracranial hypertension. I think it
10 would be valuable to add this.

11 DR. HAVENS: Peter Havens. I voted no.
12 I agree.

13 DR. SAVEL: Wael Savel. I voted no. I
14 completely agree with the statements by Dr. White,
15 and I think it's an underdiagnosed side effect.

16 DR. MOON: Mark Moon. No.

17 DR. FISCHER: Gwen Fischer. No.

18 DR. HUDAK: Okay. I think that's a
19 pretty clear signal. We'll vote on the second
20 part of the recommendation, and that is whether or
21 not you agree, yes, or disagree, no, with the FDA
22 recommendation to add nephrogenic DI in the

1 post-marketing section on adverse reactions. So
2 please vote.

3 Again, a pretty clear signal. Dr.
4 Fischer, we'll start with you.

5 DR. FISCHER: Gwen Fisher. I concur.

6 DR. MOON: Mark Moon. I concur.

7 DR. SAVEL: Wael Savel. I concur.

8 DR. HAVENS: Peter Havens. Yes.

9 DR. TURER: Christy Turer. I concur.

10 DR. SHWAYDER: Shwayder. Yes.

11 DR. CNAAN: Avital Cnann. Yes.

12 DR. CATALETTO: Mary Cataletto. Yes.

13 DR. CAMPBELL: Jeff Campbell. Yes.

14 DR. CUNNINGHAM: Melody Cunningham. I
15 concur.

16 DR. HOEHN: Sarah Hoehn. Yes.

17 DR. DRACKER: Bob Dracker. I concur.

18 DR. WHITE: Michael White. I agree.

19 DR. WADE: Kelly Wade. I agree.

20 DR. ANNE: Premchand Anne. I concur.

21 DR. HUDAK: So, in summary, with these
22 two votes the committee agrees with adding

1 nephrogenic diabetes insipidus, but disagreed with
2 not adding benign intracranial hypertension. Just
3 a point of semantics that's been raised, is that
4 sufficient to be construed as a recommendation to
5 add it or do we need to take a separate vote on
6 benign intracranial hypertension?

7 DR. ALEXANDER: This is Dr. Alexander.
8 I think we got the message.

9 DR. HUDAK: Pardon me?

10 DR. ALEXANDER: I think we got the
11 message.

12 DR. HUDAK: Okay.

13 DR. NELSON: If not A doesn't mean if
14 not B.

15 DR. HUDAK: There was a question, so I
16 was just making sure. Thank you.

17 DR. LEVIN: Excuse me, Dr. Hudak? May
18 I?

19 DR. HUDAK: Yes.

20 DR. LEVIN: A couple more points.

21 Again, Bob Levin, pharmacovigilance. We will, as
22 soon as possible, take that under discussion with

1 neurology colleagues and look in more detail. The
2 other thing we can do, we'll go back and look at
3 our searches and maybe broaden our search to see
4 if we can capture such cases in a different way.

5 May I also ask Dr. Savel a question?
6 You mentioned that intracranial hypertension is
7 under recognized, underdiagnosed. Did you mean
8 broadly is that a general comment?

9 DR. SAVEL: I think broadly in patients
10 who are treated with mesalamine preparations. As
11 I mentioned earlier, they are diagnosed with
12 headaches which is one of the common side effects,
13 with or without other symptoms. Usually the
14 symptoms occur two weeks to four weeks after
15 initiation of the medication regardless whether
16 the patients are on steroids or not, on
17 concomitant steroid treatment or not.

18 Therefore, the general practice is to
19 stop the medication and see if the symptoms
20 resolve or not. Frequently, the symptoms do
21 resolve or more frequently than not. And
22 therefore, without any further testing we have

1 made the diagnosis that the patient has an adverse
2 reaction to mesalamine and we stop the medication
3 and we moved on to a different medication without
4 looking at benign intracranial hypertension.

5 I certainly have seen at least two or
6 three cases in the last five years that, for sure,
7 fit the criteria.

8 DR. LEVIN: Right, okay. That's really
9 helpful. Appreciate it.

10 DR. SAVEL: Yes.

11 DR. HUDAK: Okay. Great. So we will
12 move on, I think, to a discussion of Kepivance.
13 Dr. Radden, you have the floor again.

14 DR. RADDEN: I'll wait for the --

15 DR. HUDAK: Oh, we have a new FDA group
16 coming.

17 DR. RADDEN: Yes.

18 DR. HUDAK: Okay. If those arriving at
19 the table could introduce yourselves to us.

20 Patanavanich
,

DR. PATAVANICH: Saharat
21 safety evaluator with Division of
22 Pharmacovigilance.

1 DR. DINNDORF: Patricia Dinndorf, clinical
2 reviewer from the Division of Hematology Products.

3 DR. MISTRY: Kusum Mistry, drug use
4 analyst, Division of Epidemiology.

5 DR. RADDEN: All right. I'll get
6 started. So today I will also be discussing the
7 pediatric focused safety review for Kepivance or
8 palifermin. I'll be following the outline shown
9 here.

10 Kepivance is a mucocutaneous epithelial
11 human growth factor. It is indicated to decrease
12 the incidence and duration of severe oral
13 mucositis in patients with hematologic
14 malignancies receiving myelotoxic therapy in the
15 setting of autologous hematopoietic stem cell
16 support.

17 Dosing recommendations advise
18 intravenous injection of 60 micrograms per
19 kilogram per day for three consecutive days before
20 and three consecutive days after myelotoxic
21 therapy, for a total of six doses.

22 Kepivance was originally approved in

1 December 2004. In May 2013 data from a
2 pharmacokinetic and safety study supporting use in
3 patients 1 to 16 years of age was adding to
4 labeling which prompted this safety review.
5 Additionally, there is a pending pediatric
6 post-marketing study that is due in March 2020 to
7 evaluate survival, incidence of secondary
8 malignancies, cancer relapse, hospitalization
9 days, and treatment related complications in
10 hematopoietic stem cell transplant recipients.

11 Use of Kepivance in patients 1 to 16
12 years of age is supported by adequate and
13 well-controlled studies in adult, in additional to
14 a dose escalation, PK, and safety study of 27
15 pediatric patients with acute leukemia who
16 underwent myeloablative therapy and hematopoietic
17 stem cell transplant.

18 Subsection 8.4 of Kepivance labeling was
19 updated to describe the limited supporting use --
20 data supporting use in patients 1 to 16 years of
21 age, including the results of this PK and safety
22 study.

1 I would also like to call your attention
2 to additional label changes relevant to safety
3 which were recently completed following an
4 evaluation of the risk of infection in studies of
5 Kepivance in the transplant population. While no
6 increase incidents of infection was noted in the
7 two studies that supported approval, an increased
8 incidence of treatment emergent infections was
9 noted in a post-approval study of patients with
10 multiple myeloma who underwent autologous
11 transplantation with a chemotherapy only
12 preparative regime using high dose melphalan.

13 In this study, shorter timing between
14 pre- and post-preparative Kepivance regimens
15 compared to the two studies that supported
16 approval was noted. Additionally, findings from a
17 study of Kepivance with allogeneic transplantation
18 were evaluated. No increased risk of infection
19 was identified. However, the study also did not
20 demonstrate efficacy in decreasing the incidence
21 of severe, acute graft versus host disease. And
22 there was a higher incidence of severe mucositis

1 in Kepivance patients.

2 Based on the analyses of these studies,
3 labeling was changed to revised the dosing
4 schedule to ensure seven days between pre- and post-
5 preparative regime doses. And to add information
6 on the increased risk of infection in the
7 melphalan study.

8 Additionally, in the setting of
9 allergenic transplantation, a limitation of use
10 statement and a discussion of the increased
11 incidence of severe mucositis was included.

12 Now let's look at the use of Kepivance.
13 This table displays the nationally estimated
14 number of patients with a hospital discharge
15 billing for Kepivance from U.S. non-federal
16 hospitals from the date of the pediatric labeling
17 change in May 2013 through December 2015. Of the
18 nearly 1,400 total patients, pediatric patients
19 account age
20 to 16 years old accounted for
21 approximately 17 percent of the total Kepivance
22 use. No use in patients less than 1 year of age

1 was captured.

2 Now I'll review the safety and pediatric
3 focused adverse events associated with Kepivance
4 since the start of FAERS data collection in
5 January 1969 through March 2016. As you can see,
6 of the eight events reported for pediatric
7 patients seven were classified as serious with one
8 death.

9 Now let's walk through the selection of
10 the pediatric case series. Of the seven serious
11 pediatric reports four were found to be duplicates
12 and excluded, leaving three deaths -- I'm sorry,
13 three cases and one death. Of the three serious
14 pediatric adverse events there was one fatality,
15 one case involved the unlabeled events of cardiac
16 and hepatic failure, and one case involving the
17 unlabeled event of seizure.

18 The one fatal event involved a six month
19 old female with complicated cardiopulmonary
20 history, including severe and progressive
21 respiratory issues that was ultimately treated
22 with Kepivance off-label based on a potential

1 pulmonary benefit. She died three weeks later due
2 to respiratory insufficiency and pulmonary
3 hypertension which resulted in right ventricular
4 failure. Her demise was associated with her
5 multiple underlying medical issues and unlikely
6 related to Kepivance use.

7 The first nonfatal serious adverse
8 event involved a 13 year old male with clear cell
9 renal sarcoma treated with doxorubicin. He was
10 subsequently given Kepivance for mucosal
11 inflammation and developed cardiac and hepatic
12 failure 10 months after starting Kepivance and
13 eight months after his last dose.

14 The case is confounded by the use of
15 doxorubicin which is associated with cardio
16 toxicity. Additionally, insufficient information
17 was provided to assess causality for the hepatic
18 failure.

19 The last case involved a 4 months old
20 female with a reported past medical history
21 significant for Omenn Syndrome, a form of severe,
22 combined immunodeficiency who was taking multiple

1 medications. She developed a rash and seizures
2 two days after starting Kepivance, and three days
3 after starting cyclophosphamide prior to a stem
4 cell transplant. Note that skin rash is a labeled
5 event and the event of seizure is confounded by
6 the concomitant use of multiple medications.

7 FDA also review reports of a clinical
8 and a non- clinical study evaluating Kepivance to
9 improve pulmonary outcomes. Both post-marketing
10 studies were associated with worsened outcomes,
11 including increased risk of mortality and
12 infection with Kepivance use in these settings.
13 Additionally, use of Kepivance in these studies
14 involved dosing and/or a route of administration
15 different from approved recommendations.

16 This concludes the pediatric focused
17 safety review. Overall, the cases were either
18 related to the patients' underlying medical
19 conditions, confounded by concomitant medications,
20 or had limited information to assess causality.
21 No new safety signals were identified. However,
22 the review highlighted risks associated with off-

1 label use of Kepivance for pulmonary indications
2 which should be discouraged unless a benefit in
3 this setting is demonstrated.

4 FDA recommends continuing ongoing
5 surveillance. Does the committee concur? Again,
6 I'd like to acknowledge my colleges on this slide
7 for their assistance.

8 DR. HUDAK: Thank you, Dr. Radden. I'd
9 just comment that I think the one death you saw
10 was a incredibly last ditch effort to try
11 something that might be beneficial to a child who
12 was on death's door and was unsuccessful.

13 When was this case? Do you know? Just
14 out of curiosity.

15 DR. RADDEN: You said when was it?

16 DR. HUDAK: Yes, when was it?

17 DR. RADDEN: I'm not sure.

18 DR. HUDAK: Was it still in the era when
19 we were using a lot of chloral hydrate?

20 DR. PATAVANICH: The case was reported
21 back in 2012.

22 DR. HUDAK: 2012, okay. Hepatoblastoma

1 is something that's been linked to chloral hydrate
2 use in this children.

3 Okay. This is open for discussion.

4 DR. SHWAYDER: Using this medicine, the
5 mucous in the mouth is different from the mucous
6 in the lungs. Were they just stabbing at
7 something? Why were they using it?

8 DR. HUDAK: I have no idea, but
9 presumably that's what it was.

10 DR. DINNDORF: There was some -- as far
11 as the study in adults, they were basing it on
12 some pathophysiology where they thought that it
13 might be useful in quickening recovery of patients
14 who had acute respiratory syndromes, and it was
15 given IV. In a schedule that's not at all like
16 the schedule -- it was continuous over a number of
17 days.

18 In the animal study, the dog was given
19 intranasal into rats who were given doses of virus
20 concomitant. The dose that was delivered was
21 several orders of magnitude more than the dose
22 that would be given at the indication. Then there

1 was in the rats who had received the Kepivance in
2 addition to being -- receiving the virus there was
3 an increase mortality. It was mice, not rats. I
4 always get that mixed up.

5 DR. HUDAK: So the question is open for
6 a vote and that is the FDA recommends no label
7 changes and continue their ongoing surveillance
8 process. So vote on your machine.

9 Okay. So we'll just go around the room
10 to formalize it. So we can start with Dr.
11 Fischer.

12 DR. FISCHER: Gwen Fisher. I concur.

13 DR. MOON: Mark Moon. I concur.

14 DR. SAVEL: Wael Savel. I concur.

15 DR. HAVENS: Peter Havens. Concur.

16 DR. TURER: Christy Turrer. I concur.

17 DR. SHWAYDER: Shwayder. Concur.

18 DR. CNAAN: Avital Cnann. Concur.

19 DR. CATALETTO: Mary Cataletto. I
20 concur.

21 DR. CAMPBELL: Jeff Campbell. I concur.

22 DR. CUNNINGHAM: Melody Cunningham. I

1 concur.

2 DR. HOEHN: Sarah Hoehn. I concur.

3 DR. DRACKER: Bob Dracker. I concur.

4 DR. WHITE: Michael White. I agree.

5 Although, I'm not sure how you're going to
6 discourage off label use without making a change
7 in the label.

8 DR. WADE: Kelly Wade. I concur.

9 DR. ANNE: Premchand Anne. I concur.

10 DR. HUDAK: Okay. So in summary,
11 unanimous agreement with the FDA recommendation on
12 Kepivance.

13 DR. DINNDORF: Can I make a comment about
14 the off-label use? We tried to negotiate that
15 with the sponsor to actually include comments,
16 more detailed information about those two
17 incidences. We got push back from the sponsor,
18 and we do not have regulatory authority to make
19 them do that. we would have preferred to do that.

20 DR. WHITE: I understand that.

21 DR. HUDAK: Okay. So that concludes
22 staff product review. Are we still on schedule to

1 move to the update on EXJADE?

2 MARIEANN BRILL: Yes.

3 DR. HUDAK: So this is -- a couple
4 comments on this. This is an issue that was
5 identified from a public hearing about a year ago,
6 as you heard this morning. The FDA has been
7 working on this. This is sort of an interim, not
8 a final, sort of progress report as to the status.

9 No one on the committee, because this
10 sort of came up as a late addition has been
11 cleared for conflict of interest on this, so this
12 is for information only. So there can be do
13 opining from the committee on any of the matters
14 that are presented.

15 So I think Dr. Waldron, you're set to
16 go?

17 DR. WALDRON: Yes, I am.

18 DR. HUDAK: Anybody else at the table?
19 No, no one else at the table we need to introduce,
20 so thank you.

21 DR. WALDRON: My name is Peter Waldron.
22 I'm the representative of a group which is

1 evaluating the safety issue raised at the
2 September 2015 Pediatric Advisory Committee
3 regarding *deferasirox*.

4 Since one year has elapsed from this
5 request we want to tell the committee and other
6 interested parties how we are addressing this
7 concern. First, I will review the presentation to
8 the September 2015 PAC briefly and give a high
9 level overview of our plan. Then I will discuss
10 the safety issues of fever, dehydration, or
11 hypovolemia and renal and hepatic injury.
12 Finally, I will describe the data sources that we
13 will use.

14 The case presented at the PAC was part
15 of the scheduled review of *deferasirox*. A child
16 with a fatal outcome was identified by the review.
17 This child's mother also presented her daughter's
18 case to the PAC, and there were additional
19 comments about the child's case from the Cooley's
20 Anemia Foundation.

21 In brief, the child was a 35 month old
22 girl who had transfusion dependent thalassemia.

1 She developed an acute illness while she was
2 receiving **deferasirox**. When she presented for
3 medical attention she had kidney and liver failure
4 and metabolic acidosis. A diagnostic test for a
5 respiratory syncytial virus was positive.

6 Her immediate cause of death was
7 cerebral edema with herniation. The PAC's
8 specific request to the agency, as communicated by
9 this quote in the first bullet was to evaluate the
10 acute illness event, fever. In developing the
11 analysis plan we began the process of reviewing
12 fever as an indicator to interrupt *deferasirox*
13 dosing. However, we concluded early in this
14 process that a broader interpretation of fever to
15 mean an acute illness including fever and
16 hypovolemia was needed.

17 I will describe this evaluation in more
18 detail with the next slides. Having determined
19 this focus, then we are identifying cases from the
20 sources available to us which I also will describe
21 later. We will then analyze the events of kidney
22 and liver injury with a goal of identifying pre

1 disposing factors and potentially preventable
2 causes.

3 We are focusing on liver and kidney
4 injury because these are the organ systems that
5 are most frequently adversely affected by
6 **deferasirox**. Then, using these sources we will
7 analyze the role of interrupting or continuing
8 **deferasirox** during acute illness events. With a
9 goal of determine how the decision to continue or
10 interrupt may influence the outcome of acute
11 illness events relative to kidney and liver
12 injury.

13 As healthcare providers to children, you
14 know that when we observe a large group of
15 children over months and years a high proportion
16 will have at least one illness with fever. The
17 figure of 45 percent of pediatric subjects with
18 fever is from the sponsor's investigator's
19 brochure. This proportion represents the
20 sponsor's current aggregation of clinical trial
21 findings.

22 Since assessing fever is a part of our

1 review, we will develop our own result for the
2 proportion of children who develop fever.
3 However, acute illness, including some viral
4 infections, illnesses with hypovolemia and
5 anorexia, and acute liver injury can develop
6 without fever. Therefore, as part of our
7 evaluation we plan to assess acute illness events
8 with and without fever, and their outcomes
9 including the variable of dose interruption.

10 Hypovolemia, due to decreased intake,
11 and/or increased losses, both insensible and
12 measurable, is a common component of pediatric
13 illnesses. Clinical trials with **deferasirox**
14 establish that renal injury is a risk of
15 **deferasirox** use. The **deferasirox** label includes
16 statements about monitoring renal function and
17 dose reductions and interruptions for compromised
18 renal function.

19 Since hypovolemia can compromise renal
20 function we considered hypovolemia to be an
21 important component of acute illnesses that we
22 should evaluate. Therefore, we will determine the

1 potential for acute volume loss to produce labeled
2 renal criteria for dose modification, and the
3 potential for volume loss to produce excess
4 exposure.

5 Now, we acknowledge that unlike
6 temperature, there is not a straightforward
7 measurement in the absence of a recent baseline
8 weight to assess volume loss. Through our
9 clinical parameters that are used to develop
10 estimates of volume status, including mucous
11 membrane moisture, tear production, skin quality,
12 the appearance of eyes and heart rate, as well as
13 laboratory parameters that can be used in clinical
14 settings to make an assessment of volume status.

15 However, the FDA reviewers do not have
16 the patient and the hospital lab in front of us.
17 We are limited to the reported data, so our
18 estimates of volume status will be more limited
19 than a clinician at a bedside.

20 In summary, we identified the events
21 fever and hypovolemia as indicators of acute
22 illness. We will evaluate those events for their

1 association with kidney and liver injury. The
2 data sources that we have available to examine a
3 relationship between acute illness events and
4 subsequent adverse events are listed here. The
5 five year observational study among children ages
6 2 to less than 6 at enrollment was submitted to
7 the FDA January 29 of this year for the purpose of
8 fulfilling a post-marketing requirement.

9 The second source listed here is a
10 pooled analysis of 17 studies that included
11 pediatric AIDS subjects. The sponsor submitted
12 these and other datasets in responses to our
13 request. The FDA Adverse Event Reporting System
14 is another source that we will use to identify
15 cases of fever or hypovolemia, and finally, the
16 medical literature.

17 In conclusion, we expect to make a final
18 report the Pediatric Advisory Committee in March
19 of next year. At that time, any change to the
20 label that the agency may recommend will be
21 discussed.

22 DR. HUDAK: Thank you. Very clear

1 presentation of the issue. If anyone has any
2 questions or they want to illicit more information
3 from Dr. Waldron that's fair. But otherwise we'll
4 wait for your report in March. Thank you.

5 DR. WALDRON: Thank you.

6 DR. HUDAK: Moving on, we'll end the
7 morning with a presentation. I assume this is
8 Lieutenant Commander Dr. Dinatale coming up to
9 present on, I think a very interesting summary, on
10 the new pregnancy and lactation labeling rule.

11 DR. NELSON: So, Mark, as they're
12 getting set up let me just give a quick context.
13 So you may notice at times when we do that little
14 chart that says, here's the things that are
15 included in the review, you know, pre, what do we
16 call it, prenatal, whatever. Exposure during
17 pregnancy it sort of slides over to one side.

18 Basically, we thought it would be useful
19 to give you a sense of that labeling rule, and I
20 might call your attention when you get to it, as
21 to where the labeling changes when companies have
22 to convert to the new PLLR that there's a complete

1 review of data at that time. We're also in
2 conversations with DPMH, the Maternal side of the
3 pediatric maternal health about the review of
4 those, you know, pregnancy exposures.

5 So the feeling is that it's not part of
6 the PAC remid, if you will, in terms of
7 pediatrics. If there was an issue we would bring
8 it back, but we thought it would be useful for you
9 to see exactly what's going on, if you will, on
10 that side of the house relative to those -- I
11 mean, one of them was, like, 85. I mean, you see
12 those cases disappear. We wanted to have some
13 sense of where they're going.

14 DR. DINATALE: Okay. Good morning.
15 Thank you for that introduction. So this morning
16 we will be discussing the pregnancy and lactation
17 labeling rule, also known as the PLLR. So here's
18 my overview. We'll start with a brief
19 introduction. We'll look at the history of
20 pregnancy labeling. I'll provide you with an
21 overview of the PLLR labeling changes, and then
22 we'll go through a summary and conclusion.

1 So there are 6 million pregnancies in
2 the United States every year and 50 percent of
3 women report taking at least one medication during
4 pregnancy. Pregnant women will take an average of
5 about 2.6 medications at any time during pregnancy
6 with first trimester use of prescription drug
7 increasing by more than 60 percent.

8 Use of four or more medications in the
9 first trimester has actually tripled from about 10
10 percent to 28 percent. The source is listed
11 below, but this encompasses a

12 year study. So only a small percentage
13 of drugs are

14 contraindicated for use during pregnancy
15 and lactation. These include drugs such as
16 isotretinoin and mycophenolates. For most of the
17 drugs, labeling should provide what is known in a
18 way that will enable the prescriber to make
19 decisions for treatment. The question is, how do
20 we do this?

21 Let's take a look at a history of
22 pregnancy and lactation labeling. So if we look

1 back into the 1960s you might remember the
2 thalidomide teratogenicity and all the cases of
3 fetal limb malformations that occurred in infants
4 throughout Western Europe.

5 In November of 1960, Dr. Francis Kelsey
6 of the FDA had refused to approve thalidomide in
7 the United States, and as a result of this
8 tragedy, in 1962 Congress enacted the Kefauver Harris
9 Amendment to the Federal Food, Drug, and Cosmetic
10 Act. Whereby, manufacturers had to prove that a
11 drug was not only effective, but also safe. This
12 led to several safety reports that emerged to
13 report on this post-marketing information.

14 By the 1970s clinicians were faced with
15 a vast increase in information that they had a
16 hard time interpreting. So in 1979 the FDA
17 introduced the pregnancy labeling category which
18 provided standard regulatory statements. However,
19 in 1994 several groups, including the Teratology
20 Society, began to meet and recommended that the
21 FDA delete these pregnancy categories from drug
22 labeling, and instead replace them with narrative

1 statements that would summarize and interpret
2 available data.

3 Between 1997 and 2003 several groups
4 began to meet. There was expert input, advisory
5 committees, focus groups all met to begin to
6 decide how this rule would be written. In 2006
7 the physician labeling rule published. However,
8 the pregnancy and lactation subsections of
9 labeling that revision was deferred to a later
10 date.

11 In 2008 the draft PLLR published, and
12 that also followed a period of public comment from
13 2008 to 2013, and finally on December 4, 2014 the
14 PLLR went into effect. Or it was published.

15 So what is the problem with the
16 pregnancy letter categories? The pregnancy letter
17 category system was seen as overly simplistic. It
18 was seen as a grading system where A was seen as a
19 drug that had minimal risk and X was seen as a
20 drug that shouldn't be used.

21 In addition, a drug that had adverse
22 reactions in animals was labeled as the same

1 category that had no animal information. Those
2 were labeled Category C drugs.

3 So the intent of the PLLR is to provide
4 the prescriber with relevant information for
5 critical decision making when treating a pregnant
6 or a lactating woman. More complete statements
7 are made based on what is known of the risk.
8 Considerations are made for medical and disease
9 factors. Animal data is now put into context of
10 human exposure. When there's human data available
11 that is added into labeling, and when there are no
12 data available that's explicitly stated.

13 So the PLLR went into effect on June 30
14 of 2015. All prescription drugs will be required
15 to remove their pregnancy letter category by June
16 of 2020, and this is a gradual process.
17 Prescription drugs that are approved on or after
18 June 30 of 2001 also have that additional
19 requirement to change the content and formatting
20 of labeling, and I'll provide you with examples of
21 what this looks like.

22 In addition, PLLR reorganizes

1 information in prescription drug labeling to more
2 clearly describe the data that are available, and
3 to aid physicians and prescribers in the
4 counseling of their patients who are using
5 prescription drugs.

6 So let's look at an overview of the PLLR
7 labeling changes. If you look on the left-hand
8 side this is what labeling used to look like. You
9 had Section 8.1 known as Pregnancy, 8.2 was Labor
10 and Delivery, and 8.3 was Nursing Mothers. Now,
11 what new labeling shows, and you can see on the
12 right-hand side, 8.1 is still Pregnancy, but now
13 Labor and Delivery forms a sub-heading under
14 pregnancy.

15 8.2 is now known as Lactation, and the
16 new section is Section 8.3 known as Females and
17 Males of Reproductive Potential. This is the
18 section that will include information about
19 pregnancy, (inaudible), contraception, and
20 fertility.

21 So let's look at each of the headings in
22 a little bit more detail. Section 8.1, Pregnancy,

1 and there are four headings that would appear
2 under that. First is pregnancy exposure registry.
3 Then we have risk summary, and that's a required
4 heading. Clinical considerations and then data.

5 So in a drug label that has information
6 about a pregnancy exposure registry a following
7 statement would appear. There is a pregnancy
8 exposure registry that monitors outcomes in
9 pregnant -- monitors pregnancy outcomes in women
10 exposed to (trade name) during pregnancy. And
11 then there is specific contact information, in
12 particular, a phone number and website for the
13 prescriber to call.

14 The risk summary, this is the required
15 heading, if there is no drug systemic absorption
16 then a statement such as this would appear in
17 labeling. Mainly the (trade name) is not absorbed
18 systemically following (whatever the route of
19 administration) and maternal use is not expected
20 to result in fetal exposure to the drug.

21 In drugs that do have systemic exposure
22 the following will appear. If a drug is contra

1 indicated then this will appear first in the risk
2 summary. This section will also have a risk
3 statement based on human data. If there are no
4 human data this will specifically be stated in
5 this section. If there are human data the
6 information will come from clinical trials, if
7 there's a pregnancy exposure registry, other
8 epidemiologic studies, or a well described case
9 series. This information will be summarized in
10 this section.

11 The risk statement on animal data will
12 include specific information about the number and
13 type of species that were studied, when the drug
14 was given, what the animal doses were expressed in
15 terms of human doses, and then what the outcomes
16 were in the pregnant animals and their offspring.
17 So the human data and the animal data risk
18 statements are required.

19 Next is a risk statement based on
20 pharmacology. This is included only in products
21 where there is a well-understood mechanism of
22 action. So we've included this in products --

1 oncology products, drugs that have cytotoxic
2 potential. If you do include this statement there
3 will be a cross reference to Section 12 where the
4 prescriber can get more information.

5 The next required section here is the
6 background risk information in the general
7 population, and I'll provide you with an example
8 on a later slide. But basically this provides the
9 prescriber with what the background risk of
10 miscarriage or malformations is in the general
11 U.S. population. Then finally, if known, the
12 background risk of a miscarriage or fetal
13 malformations in the disease population.

14 So here's an example of labeling for a
15 Section 8.1, Risk Summary, where there is a risk
16 based on animal data. Now, as you can see in this
17 case there really isn't a lot of information based
18 on human data. But there is information based on
19 animals. So this drug was given orally. It was
20 given to pregnant rats and rabbits during the
21 period of organogenesis, and then you note here
22 the doses at which it was given, and then the

1 effects that were seen in the animals.

2 And then the last paragraph includes
3 that background risk statement that I told you.
4 What the estimated background risk is in the
5 indicated population, and then the background risk
6 of miscarriage and fetal malformations in the
7 general population. These numbers come from the
8 CDC and they've been stable for the past 30 years.

9 So turning our attention to the next
10 heading, and this is known as Clinical
11 Considerations. There are five optional headings
12 that would be included only if the information is
13 available. First is disease associated maternal
14 and/or embryo fetal risk. We would include this
15 section if there's any information that's related
16 to the disease. For example, in a diabetes
17 product, if a patient has uncontrolled diabetes
18 what are the pregnancy complications that she
19 faces? What are the risk to the fetus because of
20 the diabetes?

21 The second heading is known as dose
22 adjustments during pregnancy and the postpartum

1 period. This would be included if there were
2 specific dose adjustments that need to occur in a
3 pregnant woman. For example, certain anti-
4 seizure medication or an antibiotic may have a
5 dose change during pregnancy. If you include this
6 section then it would be a cross reference to
7 Section 2.

8 Third is maternal adverse reactions, and
9 you would include this if a drug has potential to
10 cause an adverse reaction in a pregnant woman.
11 The fourth section is fetal and neonatal adverse
12 reactions. This includes effects that would be seen due
13 to the drug on a fetus or a neonate. Finally,
14 labor or delivery. This was the effects of the
15 drug is taken during labor or delivery.

16 The final section under 8.1 is known as
17 Data. This is where you would have a detailed
18 description of the data that had originally been
19 summarized up above in risk summary and in
20 clinical considerations.

21 The applicant typically provides the
22 agency with a comprehensive review of any relevant

1 published literature, a review of their
2 pharmacovigilance database, and if there is a
3 pregnancy exposure registry they would provide
4 that information as well. This would help support
5 the language that we use to update the sections of
6 labeling.

7 There are two sections. You would have
8 human data and animal data. Again, the human data
9 would have a description of the studies, the type
10 of study that was done, how many subjects were
11 included, how long the study lasted, any exposure
12 information and limitations of data. Then the
13 animal data section would have specific
14 information about the animal studies that were
15 conducted.

16 Now, let's turn our attention to Section
17 8.2. This is known as Lactation. There are three
18 headings under Lactation. First is risk summary.
19 This is a required heading. Then clinical
20 considerations and data. So let's briefly look at
21 each of these headings.

22 So risk summary, if a drug does not have

1 known systemic absorption, as statements such as
2 this would appear. Basically, the drug is not
3 absorbed systemically by the mother following
4 whatever route of administration, and breastfeeding is
not expected to result in exposure of
6 the infant to the (drug name).

7 If there is systemic exposure then
8 several things need to be present. First we need
9 to know, is the drug present in milk or not? If
10 it is present, do we know what the concentration
11 milk is? Do we have the actual or estimated
12 infant daily dose? What are the effects of the
13 drug on the breastfed infants? What are the
14 effects of the drug on milk production? If
15 unknown, this would also be stated.

16 Finally, a risk benefit statement would
17 be included, and I'll provide you with examples
18 here in the next two slides, what this would look
19 like.

20 So this is an example of a drug that --
21 where the class is known to be present in human
22 milk. So although there's no specific information

1 about this drug being present in milk, this is a
2 monoclonal antibody, so we do know that they are
3 present in human milk. So I'm going to point your
4 attention to the last section here.

5 This is the risks benefits statement
6 that would be included in a drug where it would be
7 okay to use during breastfeeding. The
8 developmental and health benefits of breastfeeding
should be considered, along with the
10 mother's clinical need for the (trade name) and
11 any potential adverse effects on the breastfed
12 child from the (trade name) or from the underlying
13 maternal condition.

14 In a drug that does have safety concerns
15 where you do not want the mother breastfeeding.
16 This is what labeling would look like. I'll draw,
17 again, your attention to the last sentence where
18 the risk benefits statement is as follows.
19 Because of the potential for serious adverse
20 reactions, and you would include what those
21 particular concerns are, advise patients that
22 breastfeeding is not recommended during treatment

1 with (trade name).

2 Okay. The last two sections of
3 lactation are included only if there's
4 information, so they're not required. There's
5 clinical considerations, and you would include
6 this section if you have information on how to
7 minimize exposure to the breastfed infant, or if
8 you have any information for the prescriber on how
9 to monitor for adverse reactions. This would be
10 included here as well.

11 The next section is data, and this would
12 be included only if you have information
13 available. Again, we do required that the
14 applicant provides the agency with a comprehensive
15 review of published literature and their
16 pharmacovigilance database so that we can update
17 this section.

18 This section would describe any human
19 clinical lactation studies and provide the data
20 here. If there are no human data, if there are
21 any animal lactation studies this information
22 would be described here instead.

1 Okay. Finally, Section 8.3 is Females
2 and Males of Reproductive Potential. This would
3 be included if there are recommendations for
4 pregnancy testing, contraception, or when animal
5 and human data suggest that the drug might effect
6 fertility. Those are the three headings listed.

7 What Section 8.3 is, is a dedicated
8 labeling section that consolidates all of the
9 information from other areas of labeling. So it
10 moves recommendations for contraception and
11 pregnancy testing from Section 8.1 and 13, moves
12 it all up to 8.3. It moves human fertility study
13 descriptions and infertility considerations from
14 Section 13 to 8.3. Specific information about
15 animal fertility study descriptions will still
16 remain in Section 13, non-clinical toxicology.

17 Here's an example of labeling that ended
18 up using all three of those headings: Pregnancy
19 Testing, Contraception, and Infertility. In this
20 case there is information for the prescriber to
21 get a pregnancy test for their patients if they're
22 going to be using the product. There is

1 information about contraception advising females
2 of reproductive potential, to use effective
3 contraception during use of the drug, and then
4 for, in this case, it's two weeks after the last
5 dose.

6 Then the infertility section there are
7 concerns in animal studies that this drug has
8 caused infertility in rats. So this information
9 is relayed here that there is also potential for
10 seeing infertility in humans.

11 So in summary, the PLLR implementation
12 is a gradual process. It will take another two to
13 four years to complete this. All prescription
14 drug labeling will be required to remove the
15 pregnancy letter categories. PLLR provides a
16 clear communication of available data to assist
17 the prescriber with critical decision making when
18 treating a pregnant or a lactating woman. The
19 PLLR also notes when there are no data available.

20 Again, an overview of the sections that
21 we discussed, 8.1, Pregnancy, 8.2, Lactation, and
22 8.3 Females and Males of Reproductive Potential

1 with each of the headings underneath them. So, as
2 a conclusion, the PLLR provides a more structured
3 approach to labeling that helps provide a more
4 clearly -- just clear description of available
5 data that can be used to aid in the complex risk
6 benefit discussion between the prescriber and
7 their patient. It also includes required
8 statements when data are not available.

9 Our hope is that all stakeholders will
10 work together to proactively seek information to
11 fill these gaps. Provide you with some resources
12 if you would like more information. The PLLR
13 website. We'll provide more information about the
14 final rule. There's information about the
15 pregnancy registry website, and this is run by the
16 Office of Women's Health, so if there is more
17 information about a pregnancy registry this is
18 where you might find it.

19 Other resources, I have links to the
20 draft guidance for the PLLR, the physician
21 labeling rule, so you have all those resources to
22 obtain more information. If you are looking to

1 find product labeling, drugs at FDA, DailyMed,
2 Lactmed, and CDC are all good sources.

3 This concludes my presentation. Are
4 there any questions?

5 DR. HUDAK: Just one general question
6 that's -- I'm sorry, I won't take -- you go first
7 then.

8 DR. CUNNINGHAM: Melody Cunningham.
9 Just sort of a reminder question, but when we look
10 on 8.3 the animal fertility study descriptions
11 remain in Section 13. Kind of reminder point, but
12 I'm wondering why those remained in 13 and the
13 others were moved up?

14 DR. DINATALE: We thought it would
15 probably be better to keep the animal data in that
16 section, you know, Section 13, and to describe
17 more of the human effects in Section 8.3. There's
18 usually like a brief statement, you know, that
19 says, you know, because of animal studies, you
20 know, women might -- there might be infertility
21 noted, and then there's a cross reference, you
22 know, see Section 13.1 for more details.

1 DR. HUDAK: So I think I recognize this
2 has been a work that's taken a long time, and
3 there have been a lot of constituencies that have
4 contributed. I think this is really valuable.
5 You know, as caretakers, you know, for mothers
6 and babies we are very often confronted with the
7 need to have good information on drug effects on
8 mothers and babies.

9 Hopefully this will allow better
10 integration and congruency among all the different
11 resources we have because right now, as you know,
12 there are sometimes some significant nuances,
13 different nuances, between different sources on
14 particular drugs or agents.

15 DR. DINATALE: Right.

16 DR. TURER: I have a question regarding
17 the maternal registry. I wondered to what extent
18 it would be possible to have a registry that went
19 into the children that were exposed in utero.
20 Because my concern is that we're going to capture
21 the data through labor and delivery and that's
22 where it's going to end. But to understand the

1 longitudinal impact would be really beneficial to
2 connect what are the child outcomes of children
3 who were exposed?

4 DR. DINATALE: Right. And a lot of the
5 pregnancy registries, it depends. Some of them
6 will follow them for 12 months, some of them will
7 follow then two years, three years. I haven't
8 seen anything that's gone beyond 3 years in the
9 ones, at least, that I reviewed. But definitely,
10 you know, some good points for particular drugs
11 that might have longer effects.

12 UNIDENTIFIED MALE: Just to comment on
13 that though, but at the same time we're not
14 typically -- with a pregnancy registry, talking
15 about things that end at labor and delivery and
16 don't follow on with what happens to the infant in
17 terms of any outcomes.

18 DR. DINATALE: Right. Usually there's a
19 pediatrician that will evaluate the child. There
20 are certain -- you know, sometimes they'll follow
21 them maybe every month, every three months,
22 depending on the pregnancy registry. There's a

1 set number of months that they follow them, you
2 know, usually up to 12 months, but sometimes even
3 longer. So there is a pediatrician that is
4 evaluating them and providing feedback to the
5 registry.

6 DR. HUDAK: Dr. Havens?

7 DR. HAVENS: Dr. Havens. You're not
8 requiring the establishment of a registry for
9 every drug?

10 DR. DINATALE: Right. No, it's not
11 every drug.

12 DR. HAVENS: Nor are you requiring that
13 people enter their patients' children, perhaps,
14 into the registry? That's not required by this
15 rule?

16 DR. DINATALE: Right. No, it's not a
17 requirement. Yes. I mean, there are certain
18 drugs, you know, certain classes like, for
19 example, anti-seizure medications where there are
20 registries. So if a new anti-seizure medication
21 comes out they get entered into a registry and
22 they get followed.

1 It's not a requirement. I mean, our
2 hope is that our provider will read the labeling,
3 will see the information, and will kind of be
4 proactive. You know?

5 DR. HAVENS: I just want to compliment
6 you on a great discussion of this complex rule.
7 The rules is great and I appreciate your
8 discussion of it.

9 DR. DINATALE: You're welcome.

10 DR. HUDAK: Dr. Moon?

11 DR. MOON: Oh.

12 DR. HUDAK: You were signaling. Very
13 good.

14 DR. JONES: I just had a question. So
15 how are you going to roll this out to the public
16 and to medical providers because this is a great
17 change, but it's going to be a significant change.
18 So how are you going to work with medical
19 providers to make sure they understand the new
20 label?

21 DR. DINATALE: So over the past couple
22 of months we have been, either myself, a lot of

1 members of the maternal health team have been out
2 and speaking at difference conferences. You know,
3 so we've been working with the Office of Women's
4 Health. Either we're providing - - we're speaking
5 at these conferences or being available there at a
6 booth to answer questions. So that's one way.

7 Let's see, other ways. I know the
8 Office of Women's Health has also worked on
9 providing information to kind of get it out to,
10 you know, to the general public as well. So we
11 are working on advertising it and, you know,
12 letting people know about it.

13 DR. SHWAYDER: Dr. Dinatale, that was
14 great, and I'd like to bring this back to Henry
15 Ford Hospital. Is this PowerPoint available?

16 DR. DINATALE: I think it is, yes.

17 DR. NELSON: It's on the website as a
18 PDF which you can use, and no government work is
19 copyrighted.

20 DR. HUDAK: Dr. White, I think had a
21 question.

22 DR. WHITE: Thank you very much. This

1 will help us in fetal cardiac evaluations
2 tremendously to be able to tell the parents what
3 to expect from their exposure early. And as an
4 aside, this is another place where understanding
5 the pharmacogenetics will make a big difference as
6 evidenced by the studies with codeine and codeine
7 toxicity where the CYP 2D6.

8 DR. HUDAK: Okay. I think that's good.
9 Thanks very much for that presentation.

10 DR. DINATALE: Thank you.

11 DR. HUDAK: So I want to assure
12 everybody that we've done tremendous work here
13 this morning. We're back on the secret schedule
14 which now calls for lunch with everybody to
15 regroup at 1:00.

16 (Recess)

17 DR. HUDAK: Back into session. Marieann
18 has a couple of administrative announcements.

19 DR. BRILL: With the fiscal year ending
20 your travel reimbursements will not be posted
21 until November of this year. So if you have
22 questions please contact Euneka Joseph. Sorry

1 about that.

2 DR. HUDAK: Okay. Glad I didn't have to
3 make that announcement. All right. So we'll
4 start the afternoon session. We have some new
5 people from FDA at the table to support Dr.
6 Taylor, so maybe you can introduce yourselves?

7 DR. BRINKER: Hi. My name is Allen
8 Brinker and I'm a medical officer in DPV, and I'm
9 here today in support of colleagues who couldn't
10 be here today because they are at the Chantix AC.
11 So I'm representing the review team that looked
12 over these in the post-marketing setting.

13 DR. BAZINI: Hi. I'm Alla Bazini. I'm
14 one of the medical officers in the Division of
15 Anesthesia, Analgesia and Addiction products.

16 DR. CRISAFI: Hi. I'm Leah Crisafi.
17 I'm the team leader for the anesthesia team in
18 Division of Anesthesia, Analgesia, Addiction
19 products.

20 DR. PHAM: Hi. My name is Tracy Pham.
21 I'm a drug use analyst from the Division of
22 Epidemiology 2, Office of Surveillance and

1 Epidemiology.

2 DR. HUDAK: Okay. Very good. Dr.
3 Taylor, you've got a triple header here.

4 DR. TAYLOR: Yes.

5 DR. HUDAK: Okay. Say a few words about
6 yourself and then you can get started.

7 DR. TAYLOR: Hi. I'm Dr. Amy Taylor and
8 I'm a medical officer in the Division of Pediatric
9 and Maternal Health in CDER at FDA. I'll be
10 presenting first the Bloxiverz pediatric focused
11 safety review.

12 This is the outline of my presentation.
13 I will start with background information on the
14 product. Bloxiverz or neostigmine methylsufate is
15 a cholinesterase inhibitor approved for marketing on
16 May 31, 2013. Neostigmine has been marketed as an
17 unapproved product since 1939.

18 Bloxiverz is indicated for the reversal
19 of the effects of non-polarizing, neuromuscular
20 blocking agents after surgery for all age groups.

21 Bloxiverz is contraindicated for known hypersensitivity,
and in cases of peritonitis or

1 mechanical obstruction of the intestines or
2 urinary tract.

3 There are five warnings and precautions
4 which you see here. Next I will touch on the
5 clinical studies which supported their approval of
6 Bloxiverz. The evidence for efficacy is derived
7 from published literature. The clinical studies
8 include randomized spontaneous recovery or placebo
9 controlled studies. A total of 404 adult patients
10 and 80 pediatric patients were studied. Patients
11 had reductions in their recovery time from
12 neuromuscular blockade compared to spontaneous
13 recovery.

14 I will now discuss the drug use trends.
15 Over the cumulative time period from May 2013
16 through December 2015 nearly 654,000 pediatric
17 patients age 0 to 16 years had an inpatient or
18 outpatient hospital discharge billing for
19 neostigmine injectable products from U.S.
20 non-federal hospitals. This number translates to
21 4 percent of the total
22 million patients who were on neostigmine

1 injectable products.

2 There are limitations to the drug use
3 database which are presented here. Data from
4 children's and other stand-alones, especially
5 hospitals, federal hospitals, and VA facilities
6 are excluded in the drug use analysis.

7 I will now discuss the FAERS safety
8 data. A search of the FAERS system from May 31,
9 2013 to March 29, 2016 revealed five pediatric
10 reports, all of which were coded as serious.
11 There were no deaths. All of the reports were
12 reviewed. One reports was excluded from the case
13 series because it was a duplicate and one was
14 excluded because it was a report of a
15 transplacental exposure.

16 This leaves us with a case series of
17 three cases. The next few slide will present the
18 cases in the case series. The first is of a 1
19 year old male undergoing a diagnostic laparoscopic
20 exam, was diagnosed with pulmonary edema after
21 administration of neostigmine. This delayed his
22 extubating and he remained in the hospital for two

1 days.

2 The second case is also a 1 year old
3 male undergoing vitrectomy and lens
4 reconstruction. He was diagnosed with pulmonary
5 edema after neostigmine administration. He
6 recovered.

7 The third case is a 9 year old male
8 undergoing tonsillectomy. He demonstrated signs
9 of pulmonary edema after neostigmine
10 administration leading to re-intubation. After
11 his condition improved he was again given
12 neostigmine and, again, experienced signs of
13 pulmonary edema. After treatment with
14 aminophylline, chlorpheniramine, and theophylline
15 he recovered.

16 A search of the FAERS system prior to
17 May 31, 2013 was conducted. Two additional
18 pediatric cases were found. The first case is a
19 16 year old man with Brugada Syndrome undergoing
20 implantation of a cardioverter defibrillator. He
21 developed signs of pulmonary edema after
22 neostigmine was administered. He recovered with

1 treatment.

2 The second case is a 6 year old male
3 undergoing corneal repair. He developed signs of
4 pulmonary edema after neostigmine administration
5 and extubating. He was reintubated and recovered
6 after treatment.

7 In the five cases presented a temporal
8 relationship between neostigmine and pulmonary
9 edema was seen. However, all five cases were
10 confounded by potential airway management
11 difficulties, and two cases were confounded by
12 prior respiratory or cardiac issues. In addition,
13 we identified two literature reports of non-
14 cardiac pulmonary edema in adults post-neostigmine
15 administration.

16 This concludes the pediatric focus
17 safety review of FAERS reports. There are reports
18 of pulmonary edema after administration of
19 neostigmine. Due to the rarity of reports and
20 confounding, FDA will continue routine, ongoing
21 post-marketing safety monitoring. Does the
22 committee concur?

1 I'd like to thank these folks for their
2 help with my presentation.

3 DR. HUDAK: Okay. Thank you, Dr.
4 Taylor. So this is open for discussion. Yes, Dr.
5 Hoehn?

6 DR. HOEHN: It seems really hard to
7 tease out what would be sort of post-obstructive
8 pulmonary edema from an extubating related event.
9 So I didn't know if you had any data on the
10 incidence of pulmonary edema post-extubating
11 without neostigmine?

12 DR. TAYLOR: I don't know if the
13 division has that information or if OSE?

14 DR. BRINGER: I'm looking at my
15 colleagues here and they're shaking their heads,
16 but we, as a group, have access back at White Oak
17 where we work to more resources, including some
18 pediatric intensivists. We discussed each of
19 these cases with them, and they say that they see
20 this. This is not a truly remarkable event. That
21 you do see this from time to time.

22 I would also want to point out that

know

1 these cases have occurred -- have come to us over
2 some time, and some of them, most of them, all of
3 them are outside the U.S. And so we can't necessarily
4 how these kids were treated and what conditions
5 were going on with concern or in comparison to
6 what's contemporary American medicine.

7 So getting to the point, my colleague
8 with whom we discussed this felt like none of
9 these cases it was -- you could show -- you could
10 consider without a reasonable doubt that this was
11 neostigmine.

12 DR. HOEHN: Just a clarifying question,
13 so none of those cases were in the U.S.? They
14 were all international cases?

15 DR. BRINKER: Yes.

16 DR. HOEHN: Okay. I have no concern,
17 whatsoever, about neostigmine. That's why I think
18 it's likely something else. That's why I just
19 didn't know if there were comparisons made to what
20 the incidence was with neostigmine. Okay.

21 DR. HUDAK: So I don't know if this
22 helps or not, but in the final review on Page 16

1 it does say that noncardiogenic pulmonary edema
2 can be a consequence undergoing anesthesia. That
3 advanced airway incidences is estimated to be 0.1
4 percent.

5 I was curious looking at the -- your
6 summation that there were confounding potential
7 airway management issues. That didn't quite align
8 with the individual detail or sort of reports that
9 were given for each of these cases. So I don't
10 know what additional information you had to
11 conclude that?

12 The one case where there was the
13 reintroduction, the reoccurrence of the pulmonary
14 edema was very striking.

15 DR. BRINKER: So I can't speak for my
16 colleague who's not here today. We tried to
17 provide you with a synopsis that worked well on a
18 PowerPoint slide, and we discussed each one of
19 these cases with all the data that was available
20 to us, individually, when we worked up these
21 cases.

22 DR. HAUSMAN: Hi. Ethan Hausman. I

1 just pulled up an article, literature review from
2 2012, Annals Medical Health Science Research, and
3 the incidence overall in an unselected population
4 is 0.1 percent after general anesthesia. However,
5 if there's an underlying background of obstruction
6 the incidents can range from about 9.5 percent to
7 12 percent, in this article.

8 DR. HUDAK: Dr. White?

9 DR. WHITE: It was striking to me that
10 we don't capture use data from pediatric hospitals
11 for neostigmine? So do you have any estimate of
12 how many additional cases of neostigmine might
13 have been given if you included children's
14 hospitals? Is there any way to even estimate that
15 number?

16 DR. TAYLOR: Dr. Pham?

17 DR. PHAM: So for the drug use data any
18 data from

19 (inaudible), children hospitals, or
20 from federal facilities we don't
21 capture that. But if there's -- if
22 a hospital has a center, a

1 children's center, that might be
2 captured in our data. But we
3 wouldn't be able to obtain any of
4 the adverse event coming from the
5 data -- based on the data that's
6 available to us.

7 DR. WHITE: Well, you get the adverse
8 events. You just wouldn't get the incidents of
9 the use of neostigmine because this is the drug
10 utilization database that excludes that data. I'm
11 just curious if we have any idea of how many
12 surgical case are preformed? Any way of estimating
13 how many likely cases of neostigmine use there
14 might be in pediatric hospitals compared to other
15 hospitals.

16 I imagine most children in the country
17 that are being treated surgically are not being
18 treated surgically in children's hospitals, but
19 that -- it's a major piece of data that would help
20 us determine is this a high incidence of side
21 effects above and beyond what would be 0.01 or is it
22 much, much lower? I mean, I know it's a

1 difficulty.

2 DR. NELSON: This data is not a
3 denominator for the numerator, and so it'll be
4 higher, but I don't know if it necessarily lends
5 itself to any different interpretation. We don't
6 have database -- I mean, part of it to contact the
7 databases -- you know, that's just the nature of
8 the databases.

9 UNIDENTIFIED MALE: Yes. Typically we
10 don't have access to precise patient-level data.

11 DR. BRINKER: So there are a lot of
12 limitations with spontaneous FAERS data,
13 especially for an old drug like this, but the
14 numerator here, for the -- the domestic enumerator
15 is 0.

16 DR. HUDAK: Yes, okay.

17 DR. FISCHER: Gwen Fischer. I just want
18 to point out that at least two of these cases had
19 other things going on in the case that very much
20 increased the risk of

21 (inaudible). One being laryngeal
22 spasm and the other being

1 tonsillectomy which is one of the
2 most common pediatric procedures
3 for kids being intubated and
4 getting use of these drugs. So it
5 seems like very confounding data to
6 me.

7 DR. HUDAK: Very?

8 DR. FISCHER: Confounding data.

9 DR. NELSON: I'll just make a comment
10 too. The reason we brought this is not so much
11 because we think we can make a lot of the
12 pulmonary edema, but because we thought it was
13 remarkable, A, that there was this, but, B, wanted
14 to alert the committee that there are drugs out
15 there that are marketed unapproved drugs, and
16 here's one from 1939.

17 And so you've got however many years
18 that is. I mean, that goes back to when the Food,
19 Drug, and Cosmetic Act was first passed because
20 of, you know, we thought that was remarkable
21 enough, even with just three events, all foreign
22 with zero U.S. to just let you see it as a group.

1 DR. HUDAK: Any other thoughts or
2 comments before we vote on the question? So we
3 will vote on the question of the FDA's
4 recommendation to continue their post-marketing
5 safety monitoring and not do anything further this
6 time about pulmonary edema in terms of label.

7 So vote on your speaker. Okay. That's
8 a nice slate, so we'll go around the room starting
9 with Dr. Anne.

10 DR. ANNE: Premchand Anne. I concur.

11 DR. WADE: Kelly Wade. I concur.

12 DR. WHITE: Michael White. I agree.

13 DR. DRACKER: Bob Dracker. I concur.

14 DR. HOEHN: Sarah Hoehn. I concur.

15 DR. CUNNINGHAM: Melody Cunningham. I
16 concur.

17 DR. CAMPBELL: Jeff Campbell. I concur.

18 DR. CATALETTO: Mary Cataletto. I
19 concur.

20 DR. CNAAN: Avital Cnaan. I concur.

21 DR. SHWAYDER: Shwayder. Yes.

22 DR. TURER: Christy Turer. I concur.

1 DR. HAVENS: Peter Havens. I concur.

2 DR. SAVEL: Wael Savel. I concur.

3 DR. MOON: Mark Moon. I concur.

4 DR. FISCHER: Gwen Fischer. I concur.

5 DR. HUDAK: Okay. So the summary is
6 that the committee unanimously supports the FDA
7 recommendation on this medication neostigmine.

8 So going on to your second header,
9 doxycycline, which has been in the news because of
10 an increase in the cost of pill from 3 cents to
11 over \$5 in some places. Another issue entirely,
12 but happy to hear about the data.

13 DR. TAYLOR: Again, this is an outline
14 of my presentation and I'll start with background
15 information.

16 Doryx or doxycycline hyclate is a
17 tetracycline antimicrobial approved for marketing
18 on May 6, 2005. Doryx has multiple indications
19 which are listed here. Doryx is approved for use
20 in pediatric patients. However, it should be used
21 in patients 8 years or less only when the
22 potential benefits are expected to outweigh the

1 risks due to the effect on tooth development and
2 growth.

3 Doryx is contraindicated for known
4 hypersensitivity to tetracyclines. There are six
5 selected warnings and precautions which I've shown
6 here. I will now discuss the drug use trends.

7 This table displays the nationally
8 estimated number of patients with a dispensed
9 prescription, oral doxycycline hyclate stratified
10 by age, dispensed from U.S. outpatient retail
11 pharmacies from April 1, 2013 through December 31,
12 2015. Pediatric patients age 0 to 16 years
13 accounted for 6 percent of the total, or
14 approximately 1.2 million patients.

15 I will now discuss the FAERS safety
16 database. A search of the FAERS system from
17 January 1, 2006 to December 31, 2015 revealed 30
18 pediatric reports of which 23 were coded as
19 serious. There was one death. All of the reports
20 were reviewed. One report was excluded from the
21 case series because it was a duplicate. This
22 leaves us with a case series of 22 cases,

1 including one death.

2 Of note, all of the cases were in
3 patients aged 12 to 17 years. Most were taking
4 doxycycline hyclate for acne.

5 This slide presents the pediatric
6 adverse events which included the suicide of a 13
7 year old by gunshot. In addition, there were two
8 cases of suicide attempt, one case of anxiety, and
9 one case of anxiety and depression.

10 Given the low number of cases relative
11 to time and extensive use the prevalence of
12 anxiety, depression, and suicide in adolescents,
13 and the potential for acne to contribute to
14 psychiatric conditions such as depression, an
15 association of these events with doxycycline is
16 unlikely.

17 This slide is meant to remind us of the
18 epidemiology of youth suicide. There are
19 approximately 4,600 youth suicides each year, and
20 it is the third leading cause of death among youth
21 aged 10 to 24 years.

22 This slide lists the other series

1 nonfatal adverse events reported, including
2 intracranial hypertension which is listed in
3 Warnings and Precautions. Please note, a case may
4 have more than one event.

5 This concludes the pediatric focused
6 safety review of FAERS reports. There were no new
7 safety signals identified. FDA recommends
8 continuing routine ongoing post-marketing safety
9 monitoring. Does the committee concur? And I
10 would like to thank these people for the help with
11 my presentation.

12 DR. HUDAK: Okay. Open for discussion.
13 Dr. Havens?

14 DR. HAVENS: Peter Havens. Just to
15 point out that I really appreciate having been
16 able to read these statistical evaluation in the
17 background which shows the extent to which FDA is
18 willing to work really hard to make sure that the
19 data upon which they base their recommendations
20 are adequate. Whoever did that job gets the
21 prize.

22 DR. SHWAYDER: Tor Shwayder here. I

1 write for doxycycline probably eight times or 20
2 times a day because we use it since tetracycline
3 went off the market. I'd like to know if the data
4 reflect the doxycycline monohydrate or does it
5 just reflect the hyclate? Because I write for
6 whatever the pharmacy will fill.

7 DR. TAYLOR: Yeah. Oh, actually, I'll
8 let --

9 DR. READY: Travis Ready, drug use,
10 Division of Epidemiology. We only looked at the
11 hyclate salt.

12 DR. SHWAYDER: Do you expect any
13 difference in the monohydrate?

14 DR. READY: I would not expect any
15 difference. I'm not sure if I fully understand
16 your question though. Are you specifically just
17 thinking about the utilization as compared to the
18 hyclate?

19 DR. SHWAYDER: Yes. I write for them
20 randomly because the insurance one day will pick
21 one and not the other depending on the cost. So I
22 write on my prescription, one or the other,

1 tablets or capsules, don't call me for prior
2 authorization just fill it. Period. So however
3 it gets filled it gets filled.

4 DR. READY: Okay. I would defer back to
5 my colleagues because Doryx was what triggered the
6 PAC meeting, so therefore, we broadened the base
7 to include generic Doryx or doxycycline hyclate.

8 DR. SHWAYDER: Thank you.

9 DR. HUDAK: Dr. Dracker has a question.

10 DR. DRACKER: I just want to make a
11 comment. I wish the committee could deal with the
12 issue of availability and pricing like we've
13 eluded to. Because those have been the two
14 biggest issues with this drug, is trying to find
15 it and trying to get it paid for.

16 DR. HUDAK: Yes. Apparently, the Lyme
17 disease prone people up in Cape Cod, pharmacists
18 up there have as hard time getting adequate
19 supply, so. Anyway, so I think we're open for a
20 vote on this. We will start with Dr. Anne again.

21 Oh, do we have another question? I'm
22 sorry.

1 DR. SAVEJ: Is esophageal ulcers listed
2 as an adverse reaction on the label of the drug or
3 no?

4 DR. TAYLOR: Yes, it it.

5 DR. SAVEJ: Is it, okay.

6 DR. HUDAK: Okay. So we will --

7 DR. WADE: I have got --

8 DR. HUDAK: Dr. Wade.

9 DR. WADE: Sorry. Kelly Wade. I just
10 wanted some guidance on how to think about these
11 cases of suicide where there rarely is a direct
12 causality, you know, link, but in the review there
13 was concerns expressed by a parent of causality,
14 and in the case that, you know, ended in death
15 there was an 11 month time period, but in the
16 other cases there was a shorter time period.

17 But in general, I think, these suicide
18 issues related to drugs or whether or not they can
19 be is in the press and is at the forefront, so how
20 -- can you give us some guidance on how to think
21 about the drug related effects specifically
22 regarding suicide?

1 DR. LEVIN: Bob Levin from
2 Pharmacovigilance. Yes, it's one of the most
3 severe type of events, obviously, so in some case
4 -- well, overall, it's a thing we do struggle with
5 and we have several ongoing project to sort out,
6 at a best, try to assess causality, but how to
7 interpret the numbers too. What kind of studies
8 you need? So completing suicide is, obviously,
9 quite rare, and to really have a fully powered
10 study to detect a difference you'd really need
11 tens of thousands of patients. So it makes it
12 really tricky to study it.

13 We do know, in general, it's
14 surprisingly common how, at least suicidal
15 ideation and thoughts and non-self-injurious
16 behavior without the intent for suicide is quite
17 common through the pediatric age range.
18 Obviously, completed suicide is much more rare.

19 To look at your question broadly, like I
20 think, you're asking and pointing out. We agree.
21 It's one of the most serious adverse events to try
22 and disentangle what's causal, what's not. And as

1 far as spontaneous reports, one of the main
2 factors in whether a report is submitted is
3 whether it's a serious adverse event. So it's
4 hard to interpret exactly. There's a lot of
5 missing information from these cases.

6 Typically, I'm thinking of all sorts of
7 drugs for both adults and pediatric patients in
8 which suicide might be a risk or a potential risk,
9 it's really hard to sort out, as you might guess,
10 but we're trying. Generally, not just psychiatric
11 trials, but a lot of trials with different
12 indications are including perspective assessments
13 of suicidality, so that's one thing we're trying
14 to do with drug development. It's a really
15 difficult area, but we're trying to figure out
16 different types of study designs and
17 post-marketing data collection that can get to
18 that.

19 DR. HUDAK: Dr. Nelson?

20 DR. NELSON: Just to expand on that last
21 point, you know, Bob will probably remember, but
22 now, I guess over a dozen years ago, when the

1 question of suicidality came up with SSRIs and the
2 like that was all controlled clinical trial data,
3 and even to interpret that controlled clinical
4 trial data there was a adjudication of all the
5 cases done by Columbia and then the development of
6 a Columbia suicidality scale.

7 Specifically, unless someone else
8 develops a new scale that scale is being
9 incorporated into all ongoing clinical trials
10 where there's a concern about the ability to
11 monitor the potential for a suicidality signal
12 which includes most psychotropic, includes a lot
13 of the neurological drugs, and the Division of
14 Neurology Products and the likes.

15 So going forward, I think there is a
16 way, but out of these kind of data very difficult.
17 It was even difficult to do it in those pediatric
18 data which were, I think, on the order of 14 or 15
19 controlled clinical trials that were randomized
20 and placebo controlled, and you still needed to go
21 back and adjudicate that in order to be able to
22 ascertain whether there was or was not a signal.

1 So going forward I think there's an
2 answer. But going back to these kind of data, as
3 Bob pointed out, is very difficult to sort out.

4 DR. HUDAK: I think it is difficult. I
5 think I'd point out that, you know, among
6 adolescents, if you take adolescents from 12 to 17
7 there are probably about 25 million adolescents in
8 the United States, and through incidences, if you
9 have 4,600 suicides in this age group that's 1 per
10 5,000 adolescents, so there is, you know, going to
11 be an expectation there's going to be suicides in
12 a drug that's used widely.

13 DR. WADE: Kelly Wade again. Is it or
14 when is it or is it ever reasonable to pull in
15 case reports from the literature or case series?
16 Just because there are mood swings and side
17 effects in this drug class. So when do you invoke
18 literature review?

19 DR. TAYLOR: Really, it's our routine to
20 do that. We search the literature, almost
21 automatically, with each signal or potential risk
22 that we work up. So that's a common practice that

1 we use.

2 DR. HUDAK: Kelly, we had one
3 presentation this morning, I can't remember which
4 drug it was, but the information they presented
5 did include some literature reports. So they
6 typically do that when they go through their
7 adverse event analysis.

8 DR. WADE: Yes. I just didn't see that
9 in this case, and just doing simple searches
10 quickly it looks like there is some literature in
11 this domain.

12 DR. READY: You mean suicidality in
13 general? Yes, there's a --

14 DR. WADE: And doxycycline.

15 DR. READY: Okay. Yes, I'm not aware of
16 the specific literature for that, but that's a
17 good point. Yes, there's more and more literature
18 all the time about suicidal ideation and injurious
19 behavior and whether it's drug-related.

20 DR. HUDAK: Dr. Cope, do you have?

21 DR. COPE: Yes. I just wanted to say
22 we're all involved, the different teams, you know,

1 in the review. And, like, for example, there was
2 an article I found out of UK that was doxycycline
3 suicidality but, again, these are adolescents.
4 And, you know, I mean, at least when I did 10
5 years in clinical practice seeing
6 teenagers, I mean, sometimes the depressed ones
7 are the ones that come in for, you know, acne
8 therapy. You know? Or the ones that are being
9 treated for chlamydia have, you know, other sorts
10 of problems going on.

11 So many times the case reports will see
12 or actually be the ones that end up in our reviews,
13 sometimes. So.

14 DR. READY: Another difficult area.
15 It's especially difficult with severe skin
16 disorders. There's no question there's a greatly,
17 highly increased risk of all psychiatric events,
18 including suicide. So it makes it even more
19 difficult to try to sort our causal factors.

20 DR. WADE: I think I was just thinking
21 that in these cases of teenage suicide, you know,
22 maybe this is an area where just a short summary

1 of what's in the literature in case reviews would
2 just add to the comprehensiveness of the data put
3 before us, even though we all recognize there are
4 case reports. Would just add to the thoroughness.

5 DR. HUDAK: Okay. Thank you. So I
6 think maybe it's time to vote. So, Dr. Anne, want
7 to start with you?

8 So the question is do we agree with the
9 FDA's recommendation to continue their
10 post-marketing safety studies and not alter the
11 label.

12 DR. ANNE: Maybe should we do the
13 buttons first or?

14 DR. HUDAK: Oh, I'm sorry. Do the
15 buttons first. Okay. Now we can go around the
16 room.

17 DR. ANNE: Premchand Anne. I concur.

18 DR. WADE: Kelly Wade. I concur.

19 DR. WHITE: Michael White. I agree.

20 DR. DRACKER: Bob Dracker. I concur.

21 DR. HOEHN: Sarah Hoehn. I concur.

22 DR. CUNNINGHAM: Melody Cunningham. I

1 concur.

2 DR. CAMPBELL: Jeff Campbell. I concur.

3 DR. CATALETTO: Mary Cataletto. I

4 concur.

5 DR. CNAAN: Avital Cnaan. I concur.

6 DR. SHWAYDER: Shwayder. Concur.

7 DR. TURER: Christy Turer. I concur.

8 DR. HAVENS: Peter Havens. I concur.

9 DR. SAVEJ: Wael Savej. I concur.

10 DR. MOON: Mark Moon. I concur.

11 DR. FISCHER: Gwen Fischer. I concur.

12 DR. HUDAK: Okay. Excellent. Another

13 unanimous with the recommendation for continue

14 post-marketing surveillance.

15 The last one in your triple header. Is

16 there anybody else coming to the table for FDA?

17 Welcome.

18 DR. STARKE: I'm Peter Starke. I'm

19 medical officer and associate director for

20 labeling in the Division of Pulmonary Allergy and

21 Rheumatology.

22 MS. Kalra: Dipti Kalra. Division of

1 Pharmacovigilance.

2 DR. PHAM: Tracy Pham, drug use analyst,
3 Division of Epidemiology, OSE.

4 DR. BRINKER: And Allen Brinker, medical
5 officer DPV.

6 DR. HUDAK: Okay. Very good, Dr.
7 Taylor?

8 DR. TAYLOR: So, again, an outline of my
9 presentation starting with the background
10 information on the product. Xolair (omalizumab) is
11 an anti-IgE antibody originally approved for
12 marketing on June 20, 2003. Xolair is indicated
13 for the treatment of moderate to severe persistent
14 asthma in patients 6 years and older, and for
15 chronic idiopathic urticarial disease in adults
16 and adolescents 12 years of age and older.

17 Xolair is contraindicated for known
18 hypersensitivity. I've listed six of the warnings
19 and precautions from the labeling.

20 Next I will touch on the clinical
21 studies and subsequent labeling changes with
22 initiated this PAC review. The safety and

1 effectiveness of Xolair for the treatment of
2 chronic idiopathic urticarial was evaluated in 39
3 patients
4 to 17 years as part of two larger
5 studies, with a total of 640 adult and adolescent
6 patients.

7 The CIU indication was added to the
8 labeling, along with instructions for
9 administration of Xolair for CIU. Information on
10 adverse reactions was also added to Section 6 of
11 the labeling. Information on the clinical studies
12 in pediatric patients with CIU was added, as well
13 as a rationale for not studying patients less than
14 12 years of age. You can see that there at the
15 bottom of the slide.

16 However, the statement was subsequently
17 removed in July of this year after completion of
18 studies in patients 6 to 11 -- sorry, 6 to less
19 than 12 years with asthma. This approval of
20 Xolair for the younger age group was supported by
21 negative results in the Xolair's long-term study that
22 did not show an imbalance of malignancies in

1 patients 12 years of age and older who are being
2 treated with Xolair.

3 Information on the clinical studies for
4 CIU was added to Section 14.2. I'll not discuss
5 the drug use trends.

6 Because Xolair was mainly distributed to
7 mail order specialty pharmacies and clinics, we
8 examined Xolair utilization patterns based on a
9 sample of U.S. outpatient retail, mail order,
10 specialty, and non-retail settings. Over the
11 cumulative time period from March 20, 2014 through
12 February 2016 nearly 4,000 pediatric patients aged
13 0 to 16 years had a Xolair prescription or medical
14 claim.

15 Of these, the majority of Xolair use was
16 among patients aged 12 to 16 years. Although the
17 data suggests that there may be use in patients
18 under 12 years of age this cannot be validated due
19 to the lack of access to patient medical records.

20 These are the limitations to the Xolair
21 drug utilization analysis. I'll now discuss the
22 FAERS safety data.

1 A search of the FAERS system from August
2 1, 2011 to July 31, 2016 revealed 420 pediatric
3 reports of which 405 were coded as serious. There
4 were nine deaths. There were three additional
5 reports of pediatric deaths identified among
6 reports not reporting in age.

7 So we now have a total of 408 pediatric
8 reports with a serious outcome. All of the
9 reports were review, 285 reports, including five
10 deaths were reviewed and excluded for the reasons
11 you see here. This leaves us with a pediatric
12 case series of 123 cases, including seven deaths.

13 This slide lists the causes of death for
14 the seven cases with a fatal outcome. The
15 following factors alone or in combination,
16 negatively affected causality assessment,
17 insufficient clinical information, underlying
18 contributive disease, concomitant medications, and
19 lack of temporal relationship between omalizumab
20 administration and the event.

21 Of the 116 remaining cases which
22 describe serious, nonfatal, unlabeled adverse

1 events, 92 has alternative, plausible explanations
2 for the events, such as you see listed here.

3 Of the remaining 24 cases, 19 reported
4 adverse events classified under infections and
5 infestations. Two cases with adverse events were
6 classified under investigation. One case of
7 Stevens-Johnson Syndrome, one case of secondary
8 adrenocortical insufficiency, and one case of pain
9 in extremity.

10 This concludes the pediatric focus
11 safety review of FAERS reports. No new safety
12 signals were identified. FDA recommends
13 continued, routine, ongoing post-marketing safety
14 monitoring. Does the committee concur? And I
15 wish to thank the following folks.

16 DR. HUDAK: Okay. Thank you, Dr.
17 Taylor. This is now open for discussion. Dr.
18 Shwayder?

19 DR. SHWAYDER: So I see hyper-IG people
20 all the time. Mainly in the gaze of very bad
21 eczema, doc aid or stat-3 mutations. And beg, we
22 beg for omalizumab and we're always refused. So

1 (inaudible) of this particular committee, but some
2 way or another we've got to let the FDA know that
3 we need this medicine. Because I can count on one
4 hand the number of common idiopathic urticarial
5 I've seen in
6 years, but I see these others every day.

7 DR. HUDAK: Dr. Cnaan?

8 DR. CNAAN: You have this study that you
9 reported about in the 6 to 12 years old where my
10 understanding was that it had negative results, is
11 that correct?

12 DR. TAYLOR: No. I'll defer to Dr.
13 Stark, but I don't believe it was negative.

14 DR. STARKE: So this is Dr. Starke. So
15 the pediatric indication for use in asthma was
16 added in July of this year. We're talking about 6
17 through 11 years of age. Previously it was
18 approved for both indications, asthma and CIU down
19 to 12.

20 The reason that we allowed the
21 indication, you may recall that there was an
22 advisory committee back in 2009 that discussed the

1 pediatric studies to support and asthma indication
2 in 6 through 11 years of age. I presented at that
3 advisory committee. I was the primary reviewer.
4 The studies did support the indication, at the
5 time. But at the time we had a concern about
6 malignancy risk that had yet to be fully explored
7 that had shown up in the original adult and
8 adolescent clinical trials.

9 So the company was in the process, at
10 that time, and since completed a very large, five
11 year observational cohort study called XLs that
12 included approximately 5,000 patients treated with
13 Xolair and 2,500 patients not treated with Xolair.
14 And on the basis of the results of that study we
15 felt that it would be reasonable to reconsider the
16 indication for the 6 through 11 years of age, and
17 the company resubmitted, and we approved it. I
18 hope that explains it.

19 DR. CNAAN: Yes. Thank you. I guess I
20 was asking not so much about the asthma, but the
21 urticarial. There was no study in urticarial in 6
22 to 12?

1 DR. STARKE: Not that I'm aware of, no.

2 DR. TURER: I agree. I was not clear
3 when reviewing the data given to us if we were
4 being asked to comment on it as an indication for
5 CIU. So I wanted to understand better. Are we
6 being asked to give an approval of omalizumab for
7 CIU? Okay. Because I didn't have the data to
8 make that -- thanks.

9 DR. STARKE: This is Dr. Starke. I would
10 add that we would probably, at this point,
11 reconsider if the company wanted to do or provide
12 the data for the 6 through 11 years of age for
13 CIU.

14 DR. NELSON: Mark, given there's many
15 new members, so this committee is reviewing, sort
16 of a pediatric focus post-marketing safety which
17 is triggered by labeling changes, and so you will
18 see often when there's multiple label changes
19 things come back. But if there was a question of
20 approval on the table that would be the division-
21 specific pulmonary and allergy committee
22 supplemented, perhaps, with pediatric experts.

1 Although there are some pediatric experts.

2 So this committee does not get asked
3 those questions. We didn't appreciate the extent
4 to which that might be confusing from the
5 document.

6 DR. HUDAK: Okay. I think we're ready
7 to go around. So we'll start, Dr. Fischer. Oh,
8 buttons first. Buttons first.

9 Okay. Now we can go around the table.

10 DR. FISCHER: Gwen Fischer. I concur.

11 DR. MOON: Mark Moon. I concur.

12 DR. SAVEJ: Wael Savej. I concur.

13 DR. HAVENS: Peter Havens. I concur.

14 DR. TURER: Christy Turer. I concur.

15 DR. SHWAYDER: Shwayder. Concur.

16 DR. CNAAN: Avital Cnann. I concur.

17 DR. CATALETTO: Mary Cataletto. I

18 concur.

19 DR. CAMPBELL: Jeff Campbell. I concur.

20 DR. CUNNINGHAM: Melody Cunningham. I

21 concur.

22 DR. HOEHN: Sarah Hoehn. I concur.

1 DR. DRACKER: Bob Dracker. I concur.

2 DR. WHITE: Michael White. I agree.

3 DR. WADE: Kelly Wade. I concur.

4 DR. ANNE: Premchand Anne. I concur.

5 DR. HUDAK: Very good. So another
6 unanimous agreement with the FDA recommendation
7 for Xolair.

8 All right. Our final drug for the day
9 -- oh, okay, so we do have one recusal and who's
10 that?

11 DR. BRILL: Dr. Jones will be recused
12 from the discussions of Karbinal.

13 DR. HUDAK: Okay. So Dr. Hausman, do
14 you have anybody coming to the table in your
15 support?

16 DR. HAUSMAN: We still have Dr. Starke
17 and --

18 DR. STARKE: I'm Dr. Starke.

19 DR. HUDAK: Dr. Starke.

20 DR. STARKE: Allergy, Rheumatology. I'm
21 associate director for labeling and medical
22 officer, and I was the primary medical officer for

1 the carbinoxamine safety issues back in 2007 or
2 '08, but not for the Karbinal. But I'm here
3 representing.

4 DR. NGUYEN: Annie Nguyen, safety
5 evaluator for the Division of Pharmacovigilance.

6 DR. LEE: Joann Lee, drug use analyst,
7 Division of Epidemiology.

8 DR. HUDAK: Okay. Welcome, so Dr.
9 Hausman?

10 DR. HAUSMAN: Good afternoon. This
11 session will be about Karbinal ER and we can see
12 the outline that we'll be following today. As
13 noted on the slide, Karbinal ER is an extended
14 release oral suspension H1 histamine receptor
15 antagonist first approved in 2013. The 2013
16 approval prompted the current post-marketing drug
17 use safety review and today's presentation.

18 I may refer to carbinoxamine products
19 generally as CM and Karbinal ER and KER. As noted
20 on Slide 4, Karbinal ER is indicated for several
21 allergic indications including seasonal and
22 perineal allergic rhinitis. It's also indicated

1 as an adjunct to epinephrine and other measures in
2 the treatment of acute anaphylaxis, and as a
3 treatment for allergic complications occasionally
4 reported with receipt of blood and plasma
5 exposures.

6 So from the regulatory history, in the
7 1950s Clistin was first approved as a single
8 active ingredient carbinoxamine product of
9 treatment of allergy indications in patients 1
10 year of age and older. In the 1960s,
11 carbinoxamine alone or in combination with other
12 active ingredients was subsequently marketed for a
13 variety of unapproved indications, including, but
14 not limited to treatment of colds and coughs, and
15 these are indications for which carbinoxamine was
16 never approved. As well as some other allergic
17 symptoms in infants and young children, as well as
18 in older patients.

19 So in the 1980s and 90s marketing
20 applications for Clistin tablets and elixir were
21 withdrawn. However, this is not because of issues
22 related to efficacy or safety of the drug. So in

1 the early 2000s generic marketing applications for
2 single ingredient carbinoxamine tablets and
3 solutions were approved based on the agency's
4 prior findings of efficacy and safety from
5 Clistin.

6 In 2005 - 2006 period, FDA noted a
7 safety signal of death with the use of
8 carbinoxamine containing drug products in children
9 under the age of 2 years. We'll be discussing
10 this further on the next slide or two.

11 So the summary of the safety review and
12 actions. So from 1983 through 2006 there are 21
13 deaths reported in children younger than 2 years
14 of age. On investigation of the reports, a
15 relationship of those deaths to carbinoxamine was
16 not established. Most or all the deaths were
17 associated with the use of unapproved combination
18 products containing carbinoxamine along with
19 pseudoephedrine.

20 So for the actions, at that time, the
21 action for the approved single active ingredient
22 carbinoxamine products was to put a

1 contraindication for use in labeling for children
2 less than 2 years of age, and removal of dosing
3 information from labeling for children 1 to less
4 than 2 years of age. The actions for all
5 unapproved carbinoxamine products was removal from
6 marketing.

7 So the basis of approval for Karbinal ER
8 is listed up on the slide. Safety and efficacy of
9 Karbinal ER in patients over 2 years of age is
10 based on demonstration of bioequivalent to the
11 immediate release reference product. This is
12 reflected in Sections 6, 12.3, and 14.1 of the
13 label that you have in your background package.

14 PREA studies for patients less than 2
15 years of age were waived because there is the
16 conclusion that there was evidence that suggested
17 that there would be a safety issue in that group.
18 So representative sections of labeling on
19 presented on this slide. There's the
20 contraindication. There's also a contraindication
21 for use in nursing mothers because of a risk of
22 potential mortality in their infants.

1 Please note under Section 5, Warnings
2 and Precautions, the second bullet which is 5.5,
3 use of accurate measuring devices. This is
4 specifically noted in labeling, teaspoons are not
5 accurate. If anybody in the greater D.C. area
6 has been listening to the radio the last couple
7 days, it's my understanding that the American
8 Academy of Pediatrics is banging this drum again.
9 It's a very important issue.

10 So in Section 8.4 this reflects that the
11 deaths that have been reported in patients 2 years
12 of age and younger who were taking carbinoxamine
13 containing products. And it highlights, again,
14 the contraindication I those patients.

15 We now go to the drug utilization slide
16 and I lost my place, so excuse me for one second.
17 So this graph displays the total number of
18 pediatric patients 0 through 16 years of age who
19 received the dispensed prescription of Karbinal
20 carbinoxamine ER from U.S. retail pharmacies from
21 March 1, 2013, which is the approval, to February
22 29, 2016. Pediatric patients from 0 to 16 years

1 of age accounted for the majority of patients.

2 We'll now transition over to the safety
3 information. In an effort to capture potential
4 events reported from the 2005 - 2006 safety
5 related activities the FAERS search covered the
6 period from the 2006 review through February 2016.
7 There were 46 serious pediatric reports, including
8 43 deaths.

9 We have up on the screen now the
10 flowchart which explains how we adjudicated the
11 cases for discussion in today's presentation. So
12 you see that 46 reports were received, 28 of the
13 reports were reviewed and excluded for the reasons
14 listed on the bottom left, and this results in a
15 pediatric case series of 18 reports which included
16 15 reports of death.

17 We have a table up here which shows some
18 of the characteristics in the case series. We can
19 see that there was two cases reported in patients
20 over 2 years of age, and

21 cases were reported in patients who were
22 less than 2 years of age. In the bottom row we

1 can see that 14 out of the 15 reports -- I'm
2 sorry, 14 of the reports refer to presence of
3 pseudoephedrine.

4 So the summary of the safety review is
5 that there were no new deaths that were not
6 already accounted for in the 2006 safety review.
7 So all the current cases in the current review
8 were reported to FDA from 2007 earlier. All
9 children were less than -- of the pediatric death
10 cases, all children were less than 1 year of age.
11 However, one case did not report an age, but
12 stated that the patient was a baby.

13 Pseudoephedrine was seen in 14 out of
14 these 15 cases. In the instance the report of the
15 patient who died where pseudoephedrine was not
16 listed, this was a 3 month old infant who received
17 three doses of Karbinal ER over approximately 15
18 hours. Caregiver came in, noted that the patient
19 was in distress and not breathing, resuscitation
20 failed, and no other additional information is
21 available.

22 Slide 17 presents the non-fatal serious

1 events. We have one case of toxic epidermal
2 necrolysis arising from or with Stevens-Johnsons
3 Syndrome, and the patient also had leukopenia.

4 Please note that the patient was also
5 treated with acetaminophen which has been linked
6 to TEN and is actually in more recent labels for
7 acetaminophen. There was one patient who had an
8 undocumented seizure, and there was no additional
9 clinical information available. The final patient
10 was a 6 year old who experienced nosebleeds.

11 While nosebleeds are not labeled,
12 anticholinergics effects which can cause drying of
13 the nasal mucous is labeled.

14 So that concludes the presentation. We
15 concluded that there are no newly occurring deaths
16 since the safety related regulatory activities of
17 2005 and '06. There were no new safety signals
18 identified. FDA recommends continued, ongoing,
19 safety monitoring. Does the committee agree? I'd
20 like to acknowledge and thank the folks listed on
21 this slide?

22 DR. HUDAK: Thank you, Dr. Hausman. Any

1 comments? Questions? Observations? Thank you
2 for emphasizing the importance of accurate dosage.

3 All right. Hearing none we will vote on
4 the FDA recommendation to continue their current
5 safety monitoring by pressing buttons.

6 Okay. We will register oral votes.
7 We'll start with Dr. Fischer again.

8 DR. FISCHER: Gwen Fisher. I concur.

9 DR. MOON: Mark Moon. I concur.

10 DR. SAVEJ: Wael Savej. I concur.

11 DR. HAVENS: Peter Havens. I concur.

12 DR. TURER: Christy Turer. I concur.

13 DR. SHWAYDER: Shwayder. Concur.

14 DR. CNAAN: Avital Chann. I concur.

15 DR. CATALETTO: Mary Cataletto. I

16 concur.

17 DR. CAMPBELL: Jeff Campbell. I concur.

18 DR. CUNNINGHAM: Melody Cunningham. I

19 concur.

20 DR. HOEHN: Sarah Hoehn. I concur.

21 DR. DRACKER: Bob Dracker. I concur.

22 DR. WHITE: Michael White. I agree.

1 DR. WADE: Kelly Wade. I concur.

2 DR. ANNE: Premchand Anne. I concur.

3 DR. HUDAK: Okay. So in summary, we
4 have unanimous concurrence with the FDA
5 recommendation.

6 All right. So that brings us to the
7 conclusion of the drugs for the day. We have five
8 devices. We are scheduled for a break. Our
9 dilemma is, maybe you can help me here, who's
10 here. We have finished a half an hour before our
11 new secret schedule. So either we can, if the
12 people are here and we can get people here, move
13 up the device presentations.

14 But our dilemma is that some of the
15 folks show up at the time that the schedule said,
16 so, Skip, you have any?

17 DR. NELSON: We think we're here. We
18 think they're here, but we'll confirm. I know
19 Vasum is, but whether the presenters are all here
20 or not at this point.

21 DR. HUDAK: Okay. Why don't we do this?

22 DR. NELSON: Take a break and we'll sort

1 it out?

2 DR. HUDAK: Take a 15 minute break and
3 plan on regrouping at 2:15.

4 DR. NELSON: Get all the ducks in a row.

5 DR. HUDAK: If people are here we'll
6 start.

7 DR. NELSON: Right. Okay.

8 (Recess)

9 DR. HUDAK: We are ready to start. Let
10 me figure out who is here. I see some new faces
11 down at the end of the table for the Berlin Heart.
12 Yes? So if you can introduce yourselves and then
13 we can have Dr. Ward start.

14 MS. BAUER: Kelly Bauer. I'm a nurse
15 consultant in the Office of Surveillance and
16 Biometrics, FDA.

17 DR. LASCHINGER: John Laschinger. I'm a
18 medical officer and a cardiac surgeon, Office of
19 Cardiovascular Devices, FDA.

20 DR. HUDAK: One recusal on this case,
21 Dr. Fischer. You need to push -- excellent, okay.
22 All right. We're ready.

1 MS. WARD: Good afternoon. My name is
2 Rebecca Ward. I am an epidemiologist for the
3 Office of Surveillance and Biometrics within the
4 center for devices and radiological health at the
5 FDA. I will present a summary of the post-market
6 review for the Berlin Heart EXCOR Pediatric
7 Ventricular Assist Device or PVAD to include
8 medical device reports or MDRs, the post-approval
9 study results, and the literature review.

10 The Berlin Heart EXCOR device received
11 HDE approval on December 16, 2011. The EXCOR in
12 intended to provide mechanical support for the
13 failure of one or both ventricles as a bridge to
14 cardiac transplantation. The EXCOR consists of an
15 extra (inaudible) and pneumatically driven blood
16 bump and cannula which connect the blood pump to
17 the atrium or ventricle and to the great arteries.

18 The IKUS provides alternating air
19 pressure to the blood pumps through driving tubes.
20 It can be used to support one or both ventricles.
21 A typical biventricular pump configuration is
22 shown in the top right of the diagram.

1 The blood pump is divided into an air
2 chamber and a blood chamber by a multilayer of
3 flexible polyurethane membrane. The alternating
4 air pressure provided by the IKUS moves the
5 membrane. Thus, filling and emptying the blood
6 pump. Both the blood chamber and the polyurethane
7 connectors are transparent to allow for the visual
8 detection of deposits and for monitoring the
9 filling and emptying of the blood pump.

10 There were 279 devices sold in the U.S.
11 from November 30, 2014 to November 20, 2015.
12 Fifty five patients were implanted with one or
13 more IKUS blood pumps in the U.S. in the same
14 timeframe. All implants were in pediatric
15 patients.

16 Next, I will discuss the MDR review.
17 The FDA searched the MDR database for all MDRs
18 associated with Berlin Heart EXCOR from June 1,
19 2015, the cutoff date from the previous year's
20 summary, through May 31, 2016. The query resulted
21 in the identification of 32 MDRs. Here is an
22 overview of the data for reporting country,

1 patient gender, and patient age as identified in
2 the MDRs.

3 There were 31 pediatric patients ranging
4 in age from 1 month to 15 years with an average
5 age of 3.4 years. Additionally, there was one
6 adult MDR. This slide identifies the event type
7 of the 32 MDRs. There were zero deaths, six
8 serious injuries, and 26 malfunctions. The shaded
9 column highlights the 31 pediatric patients.

10 This chart depicts the primary reported
11 problem in the 32 MDRs. The pediatric patients
12 are identified in blue and the one adult patient
13 is identified in red. The most commonly reported
14 problem is related to defects with the pump
15 membrane in 18 MDRs. In (inaudible) or
16 hemorrhagic CDAs and driving tube leaks were the
17 next two most frequently reported problems with
18 three MDRs reported for each.

19 This table further characterizes the
20 primary reported problem by event type and time to
21 event occurred which is represented in months.
22 Blood pump membrane defects results in three

1 injuries and 15 malfunctions occurred between 1
2 and 8.9 months. As indicated in the executive
3 summary, the firm incrementally implemented a
4 number of changes from 2013 to 2015 to mitigate
5 membrane layer defects.

6 Pumps manufactured after June 2015
7 include all of the changes. Only one of the 18
8 reports of membrane defects involves a pump
9 manufactured after all of the changes were
10 implemented. This device problem will continue to
11 be monitored over the coming year.

12 There were three injury CVA events which
13 occurred between 0.3 and 1.7 months.
14 Additionally, there were two events in the same
15 patient involving arterial outflow cannula leaks
16 which occurred at 1.7 and 2.8 months. Microscopic
17 analysis of the first case identified a small cut
18 or incision on the outer service of the tubing,
19 allowing a drop of blood to leak through. The
20 second device was discarded and not evaluated.

21 Based on the investigation of both
22 events, it was determined that the 1 year old

1 patient was chewing on the cannula connecting set
2 and likely caused the leak. According to the IFU
3 and physician's manual, clinicians are instructed
4 on the appropriate cannula length, proper
5 maintenance and assessment of the cannulas and
6 blood pump, and avoiding kinking or bending of the
7 cannulas.

8 The IFU was updated in 2015 to include
9 stronger precautions on cannula care and activity
10 restrictions. This added statement included the
11 potential for injury or death if cannula damage
12 occurs. The FDA is continuing to monitor this
13 issue. All of the events reported in the MDRs are
14 further described in the executive summary.

15 The table compares the reported problems
16 from this year's analysis to the number of MDRs
17 from the 2015 PAC analysis. Note, that this table
18 is not an exhaustive list and therefore, does not
19 include all reported problems from last year's
20 analysis. And the totals will not equal 100
21 percent. As you can see, the top reported
22 problems are consistent with last year's analysis.

1 To summarize key points, the injury and
2 malfunction MDRs related to CVA, membrane defects
3 and driving tube leaks are similar to reported
4 events from the previous year and in the IDE. The
5 firm has made design and manufacturing changes to
6 mitigate membrane defects and driving tube leaks.

7 FDA will monitor for additional events
8 over the coming year. The IFU was updated in late
9 2015 with stronger language regarding care of the
10 cannula and patient activity restrictions. There
11 are no other safety concerns at this time.

12 I will now present an update of the
13 post-approval study and the systematic literature
14 review. Upon approval of the EXCOR HDE in 2011
15 FDA required one post-approval study as a
16 condition of approval. The post-approval study is
17 an all comers perspective registry of patients
18 implanted with the EXCOR device. The primary
19 purpose of the study was to evaluate the safety of
20 this device by demonstrating that the series
21 adverse event rate or SAE rate is not greater than
22 the rate observed in the IDE study.

1 Enrollment and obtainment of the primary
2 endpoint of interest was complete prior to last
3 year's PAC meeting, and clinical outcomes for all
4 39 subjects were reported. That's the light grey
5 shaded box on the top left.

6 The safety endpoint was also met. The
7 SAE rate in the post-approval study was lower than
8 the SAE rate overserved in the IDE study by a
9 statistically significant margin. The
10 post-approval study continued after the obtainment
11 of the primary endpoint of interest. All 27
12 subjects that survived to successful heart
13 transplant or weening were eligible for continued
14 follow up for an additional 24 months.

15 The purpose of continued follow up of
16 the surviving study subjects is to assess lower
17 term functional outcomes and quality of life that
18 may be associated with use of the EXCOR device.
19 In addition, FDA thought to obtain more
20 information regarding the evolution of neurologic
21 outcomes for patients surviving stroke that
22 occurred while on EXCOR support.

1 Twenty five subjects have contributed
2 continued follow up data and 20 of those have
3 completed their 24 month post-EXCOR or
4 post-transplant visit. Additionally, late
5 neurologic and clinical outcomes for the five
6 subjects who survived following a strike while on
7 EXCOR were assessed.

8 The most complete functional outcome
9 assessment was collected using the FS-II. The
10 FS-II assesses general health and life stage
11 specific factors for the child over a two week
12 period. Children ages 0 months to 11 years can be
13 evaluated. The questionnaire is completed by the
14 primary caretaker, and scoring is calculated as
15 the percentage of the maximum number of points for
16 a specific age range with higher scores being
17 better.

18 This assessment was completed for the
19 majority of study subjects at baseline and 12
20 months post-EXCOR or transplant. As shown in the
21 grey, highlighted column, total scores, general
22 health scores, and responsiveness, activity,

1 interpersonal functioning scores showed
2 statistically significant improvement from
3 baseline to 12 months post-EXCOR or transplant.
4 The 24 month results are provided in your
5 executive summary and showed similar score
6 improvement from baseline.

7 The pediatric stroke outcome measure of
8 PSOM is used to assess outcomes after strokes in
9 pediatric patients. Specifically, PSOM scores
10 deficits for five domains, summarized on this
11 slide. Each of these five domains can be scored
12 from 0 to 2 with 0 indicating no deficit, and the
13 score of 2 indicating severe deficit. A total
14 maximum or worse possible score across all five
15 domains is a score of 10.

16 Scores may change over time with
17 progression, a regression or neurologic deficits.
18 And a total score of 2 or greater is indicative of
19 a severe deficit.

20 Five subjects that experienced the
21 stroke while on EXCOR support survived, two, a
22 successful transplant or a weening. The patients'

1 clinical neurological status allowed for
2 performance of a transplant in 80 percent of those
3 affected and surviving. In three of the five,
4 regression of the severity of the neurologic
5 deficit was observed.

6 The firm also provided brief clinical
7 notes on the current health status of these
8 subjects, shown on the grey, highlighted column on
9 the right. Based on these clinical summaries,
10 four of the five subjects are doing well or
11 showing some improvement.

12 Summarizing the PAS update. Survival
13 after transplant or successful weening is high.
14 Subjects that survive to a transplant after a
15 stroke are reportedly improving or doing well.
16 While limited data are available regarding the
17 longer term quality of life and functional
18 outcomes for study subjects, the assessment with
19 the most complete data shows statistically
20 significant improvement in functional outcomes
21 from baseline to 12 months post- transplant or
22 EXCOR.

1 No additional concerns are raised from
2 the longer term follow up of subjects than this
3 post-approval study. A literature review was also
4 conducted to update the probable benefits and
5 risks of the device. In June 2016, a search off
6 the PUMA database for articles published since
7 last year's search was performed using the same
8 search terms and limits as last year.

9 These search terms and limits are
10 included in the executive summary. The
11 inclusion/exclusion criteria on flow chart for the
12 literature reviewed are displayed here. Of 15
13 potentially relevant articles, five fit the
14 criteria for qualitative synthesis. Five
15 retrospective cohort studies were identified, and
16 the majority of these cohorts were European.

17 One study included both pediatric and
18 young adult populations. The four other studies
19 were pediatric only populations. The median age
20 of patients in these studies with pediatric only
21 populations range from 23.8 months to 9.1 years.
22 Patients included in these retrospective studies

1 were implanted with an EXCOR device as early as
2 1990 and as last as 2014.

3 Survival while on EXCOR ranged from 65
4 to 90 percent and survival to transplant ranged
5 from 61 to 81 percent. Time on device and time to
6 transplant varied by patient. Average time on
7 EXCOR device, and average time from EXCOR to
8 transplant was not consistently reported in these
9 studies.

10 Two studies were designed to evaluate
11 survival in subpopulations that may have more
12 inherent risk. In both of those studies the
13 patient sub-groups with potentially more inherent
14 risk, single ventricle patients on one study, and
15 patients needing multiple, mechanical, circulatory
16 support modalities in the other study had similar
17 survival compared to their study counterparts.
18 The commonly report complications in the
19 literature are neurologic adverse events including
20 hemorrhagic CVA and thromboembolic events, as well
21 as thrombosis and infection.

22 Neurologic adverse events were

1 heterogeneously reported across studies. The
2 proportion of subjects experiencing hemorrhagic CV
3 and thromboembolic neurological adverse events was
4 highest in (inaudible) 2016. That study had data
5 on patients implants with an EXCOR device as early
6 as 1990. The authors noted that post-implantation
7 anticoagulation therapy was modified in the year
8 2000. However, the authors did not break down
9 stroke rates by time period.

10 Device related infection was also
11 reported in two studies, and the proportion of
12 subjects with these events varied greatly. The
13 highest proportion of subjects with device related
14 infections was also reported in (inaudible). The
15 authors noted that 67 percent of patients had skin
16 infections around the EXCOR cannula.

17 To summarize the literature reviewed
18 this year, EXCOR continued to be associated with a
19 relatively high rate of survival while on device
20 and survival to transplant. Use of EXCOR also
21 continued to be associated with neurologic adverse
22 events and infection. However, the adverse events

1 observed in this year's literature search are
2 similar across what was observed in last year's
3 literature search, the IDE study, and the
4 post-approval study.

5 In summary, FDA's review team has
6 identified no new safety concerns since the 2015
7 PAC meeting, and concludes that the probable
8 benefit/risk profile of the device for the
9 pediatric population continues to support the HTE
10 for which the exemption was granted. FDA will
11 continue surveillance and report updates of the
12 following to the PAC in 2017: the MDR review, the
13 mandated post-approval study review, and the
14 literature review.

15 FDA would like to ask the committee,
16 does the committee agree with FDA's conclusions
17 and proposed approach? Thank you.

18 DR. HUDAK: Thank you. So this is, for
19 members on the committee who have been here the
20 past few years, this comes up annually, so this is
21 a new annual update and open for discussion.

22 It's nice to see that the membrane issue

1 has been addressed. But, I guess, maybe the
2 reporting is lagging behind as some of the old
3 units are being deployed. So, Dr. White?

4 DR. WHITE: Just quickly, how many of
5 the older units remain in inventory that can be
6 used going forward? Do we have that information
7 or did they replace all the units in inventory
8 across the spectrum?

9 MS. BAUER: There are still older units
10 out.

11 DR. WHITE: Do we have any idea why?
12 How many and why, actually?

13 DR. KEPPLER: (inaudible).

14 DR. WHITE: Pardon? I'm sorry. We
15 can't --

16 DR. KEPPLER: Sorry. The sponsor will
17 get back to us about that.

18 UNIDENTIFIED MALE: Is it possible to
19 just change out the membrane in the device? No.

20 DR. WHITE: Is there a reason not to
21 replace the units in inventory, other than costs,
22 if they're a safer device?

1 MS. BAUER: I do know that it does take
2 quite a bit of time to manufacture one pump. I
3 think it's over a month, as well, so I think
4 that's cost and the availability. Cost and
5 availability, but they are working on more pumps.

6 DR. WHITE: Thank you.

7 DR. HUDAK: Okay. Dr. Havens and then
8 Dr. Hoehn.

9 DR. HAVENS: Peter Havens. I just had a
10 data clarification issue. Table 1 in the
11 backgrounder suggests that there was no change
12 from the 2015 analysis to the 2016 analysis in the
13 membrane defect data, but you said, starting in
14 July 2015 we're down to one. I just didn't
15 understand. At least that's what I understood you
16 to say. So I'm just trying to understand what the
17 answer is.

18 Then, if there's really only one since
19 2015 what's the denominator? So Table 1 has an
20 MVR count, in the 2015 analysis of 22 in that 2016
21 analysis of 18 -- this is just for the membrane
22 defect. But then the statement was that since the

1 change a year ago there's been one membrane
2 defect, and I'm not clear why the numbers don't
3 add up? Then one out of how many implanted is the
4 question.

5 DR. LASCHINGER: Yes. I think what it
6 meant is that there's only -- of the membrane
7 defects that are listed on that table only one
8 came from a device that was manufactured with all
9 the changes. As you just heard --

10 DR. HAVENS: Got it, okay.

11 DR. LASCHINGER: -- all the changes --
12 all the devices with changes have not yet been
13 distributed throughout the whole system and
14 there's still old devices in the system.

15 DR. HAVENS: I understand. So in Table
16 1 there are old devices that have the old
17 membranes.

18 DR. LASCHINGER: Mm-hmm.

19 DR. HAVENS: In the new membranes, how
20 many new -- therefore, the question is, how many
21 devices with the newer membranes serve the
22 analysis with one in the numerator.

1 DR. LASCHINGER: I don't know the answer
2 to that question as far as how many of the new
3 devices have been implanted as of yet, in the U.S.
4 market.

5 DR. KEPPLER: In this dataset that she's
6 showing we didn't do that analysis. I hear you
7 asking what the denominator was for devices that
8 had all the changes compared to the one that had
9 an issue and we didn't prepare that together with
10 FDA for this meeting.

11 DR. HAVENS: Thank you.

12 DR. KEPPLER: If I heard you right.

13 DR. HAVENS: Yes, no. That's the
14 question. It sounds like the membrane was
15 identified as a problem. The defects in the
16 membrane have been changed. In the changed
17 membranes there's only been one reported problem
18 associated with the membrane. But then the
19 question is how many of the new membranes have
20 been used that serve as the denominator for that
21 estimate of one in the numerator.

22 Yes, ma'am?

1 DR. KEPPLER: Yes. I understand your
2 question.

3 DR. HAVENS: Well, good. Okay.

4 DR. KEPPLER: We'll have to look at that
5 with you in the future.

6 DR. HAVENS: Okay.

7 MS. BAUER: Because we can't get at that
8 in the next couple minutes.

9 DR. KEPPLER: NDRs don't have that
10 denominator data.

11 DR. HAVENS: We'll ask for that specific
12 number in the response.

13 DR. LASCHINGER: Thanks.

14 DR. HUDAK: Dr. Hoehn?

15 DR. HOEHN: My question's corollary to
16 that. I was also confused about the 2015 membrane
17 data. Because it looks like there were 18 cases
18 where there was still a malfunction and then they
19 differentiated 18 that malfunction and three
20 injury, so I wanted some clarify. What was the
21 injury to the patient? Because I think there's a
22 difference when the device malfunctions and it has

1 to be switched out to a new one or the membrane
2 has to be changed versus what the impact is with
3 the patient?

4 So I didn't know if you could elaborate
5 on the differences between the three injuries that
6 occurred from out of the 18 membrane issues.
7 Because it certainly sounds like there's still old
8 membranes in use. Does that question make sense?

9 DR. LASCHINGER: Injuries are things
10 that result in either hypertension, tamponade type
11 physiology for the pump. So when you get the
12 membrane defect, basically, it's a space occupying
13 lesion occurs due to, depending which layer
14 ruptures, due to air or blood inside the device.
15 So in some of them you get the need for another
16 procedure to change the pump out, where the
17 patient becomes briefly hypotensive.

18 Two of those three that was done without
19 difficulty or effect on the patient. The third
20 patient had a low cardiac output, and they also
21 had the pump exchanged and at some point later,
22 due to poor status overall, it was decided to

1 remove support. But it wasn't directly as a
2 result of that incident. That incident certainly
3 didn't help things along as far as taking care of
4 the patient, but the demise of the patient wasn't
5 directly a result of that event. So those are the
6 three injuries.

7 DR. HOEHN: So just to --

8 DR. LASCHINGER: It's in the summary, so
9 you can actually read them, but those are the
10 three injuries.

11 DR. HOEHN: Okay. But if there's a
12 membrane problem you don't switch out the
13 membrane? You can't just - -

14 DR. LASCHINGER: No. You switch out the
15 whole pump.

16 DR. HOEHN: -- switch out one membrane.
17 You switch out the whole pump?

18 DR. LASCHINGER: Yes.

19 DR. HOEHN: Okay.

20 DR. LASCHINGER: In the same way --

21 DR. HOEHN: I was just trying to
22 clarify.

1 DR. LASCHINGER: The same with pump
2 thrombosis, when you see a thrombus in the pump.
3 It's a clear pump, so you can see it and thrombus
4 tends to occur in some patients, especially near
5 the inflow and outflow valves. When you see that
6 you can change out the pump electively.

7 The membrane rupture occurs a little bit
8 more suddenly and has more hemodynamic effects,
9 depending on how much pressure there is on the sac
10 as far as allowing it to expand fully. So that
11 kind of occur more acutely.

12 DR. HOEHN: Okay. But the injury was
13 more from the fact that the pump's not working
14 there. So it's everything related to health
15 failure from their underlying condition?

16 DR. LASCHINGER: Yes, yes.

17 DR. HOEHN: And then the emergent
18 process to change out the pump?

19 DR. LASCHINGER: Yes.

20 DR. HOEHN: Okay. Thank you. I just
21 wanted to be sure I understood.

22 DR. LASCHINGER: Mm-hmm.

1 DR. HUDAK: I will take Dr. Shwayder and
2 then Dr. Cunningham. But could the speaker from
3 the audience stand up again and introduce yourself
4 and your name for the record?

5 DR. KEPPLER: I'm Mary Beth Keppler from
6 Berlin Heart.

7 DR. HUDAK: Okay. Thank you. Okay, Dr.
8 Shwayder?

9 DR. SHWAYDER: So I'm looking at Table 3
10 in the Berlin 2015 update. Because I was curious
11 how long these are left in because they're a
12 bridge to transplant, and I noticed that most are,
13 like, 0 to 79 days, but there are a few outliers.

14 I'm curious if the system failures of
15 the pump are related to age that they are
16 operating? Does that make sense? If you have
17 that data because it doesn't show up in the other
18 tables.

19 DR. LASCHINGER: I'm looking to see one
20 thing.

21 DR. SHWAYDER: In other words, is there,
22 like, four months out we should think about

1 switching these things out?

2 DR. LASCHINGER: No. There's been
3 nothing that we've seen as far as the time period
4 that would recommend changing out the device. The
5 devices are examined several times a day as matter
6 of routine to look for thrombus and to look for
7 problems like this. But there's not been a
8 specific time period where a recommendation's been
9 made to change out the device because it increases
10 the chance of membrane rupture. No.

11 DR. HUDAK: Dr. Cunningham?

12 DR. CUNNINGHAM: Sure. One other
13 question related to the three injuries. Are any
14 of the three injuries or several of them with
15 patients who got the device with the new changes?

16 DR. LASCHINGER: Not that I'm aware of,
17 no.

18 DR. HUDAK: Dr. Campbell?

19 DR. CAMPBELL: So it looked like in the
20 original patients there was a 33 percent stroke
21 risk. Is there

22 any way to -- is there any surveillance

1 to understand whether or not that risk is rising
2 or falling since that's one of the clear safety
3 risk?

4 DR. LASCHINGER: Yes. It was --

5 DR. CAMPBELL: It's one of the clear
6 safety risks.

7 DR. LASCHINGER: It was 30 percent in
8 the PMA. I'm sorry, the HDE application, I'm
9 sorry. It's been about
10 percent consistently in the literature
11 throughout. The one study, actually most of these
12 children have been anticoagulated using what's
13 called the Edmonton Protocol that uses both
14 anticoagulant and two antiplatelet agents.

15 There is some promising work being done
16 out of Stanford, but it's only been published so
17 far in abstract form. But I can tell you that
18 with that they've been able to affect an 80
19 percent reduction in both stroke rate and bleeding
20 complications using a revised anticoagulation
21 protocol. That's only at one center so far.
22 Whether that pans out when it's expanded to more

1 centers or is due to something about the local
2 care of those patients we won't know until they do
3 it.

4 But, certainly, I think there's some
5 work to be done on the anticoagulation protocol
6 with these devices to make it more effective.
7 Both from preventing thrombolytic complications
8 and bleeding complications, both.

9 DR. CAMPBELL: Is the new protocol, is
10 that a higher dose of anticoagulation --

11 DR. LASCHINGER: Yes.

12 DR. CAMPBELL: -- or a lower dose.

13 DR. LASCHINGER: A higher dose of
14 antiplatelet agents, same dose of anticoagulants,
15 but a higher fixed dose of antiplatelet agents
16 that are not based on, you know, bench testing of
17 their effectiveness, but rather on fixed higher
18 doses.

19 DR. MOON: Are we assuming that all the
20 intracranial bleeds then were from an embolism,
21 and then became an intracranial bleed?

22 DR. LASCHINGER: No. That's not true.

1 Some were intracranial.

2 DR. MOON: Spontaneous?

3 DR. LASCHINGER: Yes.

4 DR. HUDAK: Dr. Havens?

5 DR. HAVENS: Is it possible to address
6 the issue about taking the old membrane devices
7 off the market and replacing them all with new
8 membrane devices or is that not a possible part of
9 the discussion?

10 DR. HUDAK: I think someone from FDA can
11 discuss that.

12 DR. NELSON: I would let Dr. Pierce,
13 perhaps address, whether that's doable in the
14 threshold for

15 (inaudible) to be able to do that.

16 But since there's some new folks
17 around the table let me just give
18 you a quick framework about the
19 device reviews.

20 If you look at MDRs, so it's basically
21 2007 the committee receives these reports of these
22 adverse events and basically then we obtain any

1 recommendation as to whether there should be any
2 action taken in response to those adverse events.
3 And so that's what it specifically says, including
4 obtaining any recommendations of such committee
5 which gives you all about actions to take. So
6 that's the language, in a very general way.

7 So if you think you all want to make a
8 recommendation, I don't know if that's actually
9 doable and what the threshold is for doing that.
10 Folks from CDRH, perhaps, could address that.

11 DR. LASCHINGER: The removal of the
12 devices though from general use for this purpose
13 without the ability to place them all and all the
14 size ranges would result in a shortage of the
15 devices and an inability to use them. So although
16 that would be the ideal solution, without the
17 ability to replace the devices easily and
18 simultaneously it would result in some shortages
19 that would be detrimental to overall patient care.

20 DR. HUDAK: So I would suggest that we
21 do not have data yet on the whether or not the
22 rate of membrane defects per membrane month has

1 changed. So I think making any sort of a
2 recommendation without those data would be
3 premature.

4 DR. MOON: Does the redo have to -- is
5 this a redo sternotomy? To put the new device --
6 you can just change it out in the pocket?

7 DR. LASCHINGER: It's on the outside.
8 It's external.

9 DR. MOON: So that negative of having to
10 change out a bad membrane is really not that big
11 of a deal?

12 DR. LASCHINGER: No. And it's the same
13 process that's done for changing out a device when
14 there's thrombus in the pump as well. So it's a
15 device that every center knows how to do. That
16 every center can do well.

17 The only difference would be in if there
18 was an acute hypomanic event with the membrane
19 rupture that caused a hemodynamic problem. The
20 devices are three layers on purpose so that you
21 don't -- there's never been an event where you got
22 air in the systemic circulation because of a three

1 membrane rupture which is what it would take.

2 So really what it does cause is just
3 space between the membranes to enlarge, causing a
4 tamponade like effect either from air or from
5 blood, depending which membrane ruptures.

6 DR. MOON: And that doesn't create
7 potential for clotting and stroke?

8 DR. LASCHINGER: No. No, it just
9 basically decreased the forward output of the
10 pump.

11 DR. MOON: So I would suggest that that
12 negative wouldn't rationalize creating a
13 deficiency in devices.

14 DR. LASCHINGER: Yeah. No, yeah, yeah.
15 Right.

16 DR. MOON: I think that negative
17 shouldn't force us to pull every device off so
18 that we don't have enough of.

19 DR. LASCHINGER: Yes, I would agree.

20 DR. HAUSMAN: Just to add to this
21 discussion, I think to reiterate what Dr.
22 Laschinger mentioned. It would be a significant

1 public health and deficiency and deficit to
2 actually pull these devices off and not have them
3 available for use when necessary. Especially
4 considering the relatively low rate of the
5 membrane ruptures. Just want to clarify that.

6 It would also be for us to consider a
7 recall issue, and that would also be a very
8 different process.

9 DR. HUDAK: Dr. White?

10 DR. WHITE: Michael White. Is it fair
11 to say that the performance of the device has not
12 changed significantly since we approved it, and
13 this is simply an improvement to lower the risk of
14 the device? So we're not really saying the device
15 is more dangerous than we expected when we put it
16 on the market?

17 DR. LASCHINGER: Yes.

18 DR. WHITE: We're just looking for ways
19 to improve the outcomes. Is that a fair
20 assessment?

21 DR. LASCHINGER: Yes. I think that's
22 true. I think we knew about all these problems

1 when we approved it. The problem was is,
2 obviously, when there's no other device to treat
3 children in this age range at this point in time.
4 So with all the warts and all, I guess, I don't
5 know what I -- you know, we approved this knowing
6 that, obviously, things could be improved.

7 I think the company has been very
8 forthright in trying to improve the defects we saw
9 with the mechanics of the device, things like
10 membranes and things. And I think other
11 researchers are very aware and very concerned
12 about the risk of stroke and things like that, and
13 are working actively on different anticoagulation
14 regimes that would address that.

15 There has been a study of the patients
16 in the IDE study looking at their anticoagulation
17 regimes, their various lab measurements along the
18 way to see if there were any predictors of stroke
19 that could be identified in advance to tell people
20 when they would need to either be aware that a
21 clot might be close to forming or be at risk of
22 forming, and nothing has been identified that

1 would allow that prediction.

2 So I think changes in the
3 anticoagulation regime which are being looked at
4 now are probably the most efficient and promising
5 way to go.

6 DR. HUDAK: Two more questions. Dr.
7 Cunningham and then Dr. Hoehn.

8 DR. CUNNINGHAM: So we're stating that
9 this is an improved device. I would say it's a
10 new device, but since we have no idea of the
11 denominator I don't think we can say it's an
12 improved device. I don't know what our
13 recommendation would be in terms of how soon you
14 would come with that data of the denominator so we
15 could make some real judgement.

16 DR. HOEHN: Sorry. One last technical
17 question just to be sure I understand. So when
18 the membrane ruptures you change the pump, but all
19 the cannulas stay the same?

20 DR. LASCHINGER: Yes.

21 DR. HOEHN: Okay. Thank you.

22 DR. LASCHINGER: Yes. And the pump is

1 totally on the outside of the body.

2 DR. HUDAK: Dr. Nelson?

3 DR. NELSON: Just a point of
4 clarification. A humanitarian use device is an
5 approved device. It's under the humanitarian use
6 device exemption, so from that standpoint the
7 evaluation of safety, I think is, you know,
8 knowing the denominator is a separate question.
9 So I'm not sure what you mean by approve the
10 device.

11 DR. CUNNINGHAM: I think I didn't speak
12 clearly enough. I said improved, not approved.
13 So we're saying it's an improved device, but I
14 don't think we can state that until we know the
15 denominator.

16 DR. NELSON: Thank you for the
17 clarification

18 DR. LASCHINGER: Yes. We agree. You
19 know, we approved the changes in the device based
20 on bench testing and those things that might
21 predict better longevity for the device and the
22 membranes. But until we have the clinical

1 evidence we don't know either, and it's too early
2 in its use to make statements about whether or not
3 it's improved or not. So I think you're right.

4 DR. HUDAK: Dr. Moon, will you have the
5 last word?

6 DR. MOON: Yes, I've got one last
7 question that might take all afternoon to answer.
8 In your review of the literature you had stroke
9 rates of 3 percent in one study and 47 percent in
10 the other study. That just doesn't make any sense
11 to me. Do you have an explanation for that? Is
12 somebody not reporting them? Because we really
13 can't make any conclusions based on that.

14 MS. BAUER: I completely agree.
15 (inaudible) study with the higher rates were both
16 infection and stroke had patients enrolled as
17 early as 1990 and followed our HUD patients
18 enrolled as late as 2014. The Sandica study, if
19 I'm remembering correctly, their earliest subject
20 was implanted in 2008, and their latest subject
21 was implanted in 2014.

22 So I would assume that there would be

1 differences in both the device and the, as the
2 author noted, the anticoagulation therapy over
3 time. It's possible that the stroke rates were
4 higher earlier in the (inaudible) study, and that
5 may attribute to the higher rate observed here.
6 But, I agree that they're vastly different and
7 it's very hard to make any kind of conclusion from
8 that.

9 UNIDENTIFIED MALE: I'm just going to
10 add to that, just to clarify, because you brought
11 up a very poignant issue when you asked the
12 question about the change in the anticoagulation
13 regime. The anticoagulation regimes are revolving
14 with respect to use of the device.

15 You also pointed out whether all these
16 strokes that we experienced in these patients are
17 related to a thromboembolic event versus a
18 spontaneous, quote/unquote, occurrence. Because,
19 certainly, spontaneous occurrences can be
20 exacerbated by increased or overdone
21 anticoagulation. So, again, all of these issues
22 are evolving in terms of managing the pump and the

1 patient at the same time.

2 DR. LASCHINGER: I think the rates that
3 we're seeing in studies that we've done are
4 probably the most accurate due to the way that
5 they were all, you know, assessed and adjudicated.
6 The other studies are doctor reported strokes, and
7 they're not assessed or adjudicated the same way.

8 The Hesper Study, in particular, involved
9 both adults and children and stretched over a
10 period of almost 25 years. So, you know, but
11 overall, I think you can say there probably is
12 about a 30 percent stroke rate, as we've seen,
13 to 33 percent. That one third of those
14 are probably hemorrhagic. The other two-thirds
15 are thromboembolic, and that stroke does
16 contribute to death. We know that. But if the
17 patients survive their stroke most of them actually
18 go on to transplant.

19 Once the patients do end up going on a
20 transplant, which about two-thirds do, survival is
21 the same as any other transplant patient long
22 term, so. In general, those are the conclusions

1 you get from reading the entire literature.

2 DR. HUDAK: Dr. White, last question.

3 DR. WHITE: Your reporting was so great
4 on percent. That percentage is not key to time on
5 pump. It's not keyed to any other indication.
6 It's just the percentage of patients that had that
7 complication.

8 MS. BAUER: Yes.

9 DR. WHITE: Unless we have some other
10 means of assessing the stroke, 3 percent may have
11 been because the kids were transplanted very
12 rapidly. I don't have that study to look at to
13 see if those rates mean anything.

14 MS. WARD: Time to transplant and time
15 on device varied by study. I don't remember a
16 large variation between the time on device and
17 time to transplant between the studies. I have
18 the numbers over there. I can get them for you.

19 I agree, it would be much better to have
20 rates, but this was what was provided in the
21 literature.

22 DR. WHITE: Thank you.

1 DR. LASCHINGER: Yes. And in the IDE
2 study they did report the adverse events in terms
3 of events per days of patient support. So those
4 have all been reported and they're publicly
5 available.

6 We do require the sponsor to report
7 events as events per patient day of support.

8 DR. WHITE: When we look at the
9 literature, if we could put that number in when
10 you bring this back next year, because I know you
11 will.

12 MR. LASCHINGER: Okay.

13 DR. WHITE: It would be helpful to us
14 for our deliberations if we had an event rate per
15 days, patient days or something like that to help
16 us make this determination. Thank you.

17 DR. HUDAK: So let me just summarize. I
18 think really what a couple of the committee
19 members are asking for are more sophisticated
20 analysis of event versus time which you don't
21 really get at by events per patient day. So that
22 requires some statistical tour de force analysis

1 on existing data, but I think that would be useful
2 to look at.

3 If you can bring up the slide, the last
4 slide, the summary slide, so we can get to the
5 recommendation. So with your buttons, we'd like
6 to vote on the question here, the recommendation
7 that the FDA will present to us in 2017 the
8 results of their next review which includes new
9 patients and literature findings, and maybe I can
10 also add into that a little bit more information
11 on, sort of, this time event analysis. Also, a
12 better discrimination of the events on the old
13 membrane pump versus the new membrane pump.

14 Okay. So we'll go around the room. I
15 think. Dr. Anne, you're up. Come around this
16 way.

17 DR. ANNE: Premchand Anne. I concur.

18 DR. WADE: Kelly Wade. I concur.

19 DR. WHITE: Michael White. I concur.

20 And I would ask that you try to stratify the data
21 that you present to us for events based on the
22 size of the device, and some discriminator of how

1 time to events -- I'm not sure of the best way to
2 do that, but help us come up with a better
3 descriptor.

4 DR. DRACKER: Bob Dracker. I concur.

5 DR. HOEHN: Sarah Hoehn. I concur.

6 DR. CUNNINGHAM: Melody Cunningham. I
7 concur.

8 DR. CAMPBELL: Jeff Campbell. I concur.

9 DR. CATALETTO: Mary Cataletto. I
10 concur.

11 DR. CNAAN: Avital Cnaan. I concur. I
12 would also suggest looking at the subject year
13 exposure when you compare old to new.

14 DR. SHWAYDER: Shwayder. Concur.

15 DR. TURER: Christy Turer. I concur.

16 DR. HAVENS: Peter Havens. I concur.

17 DR. SAVEJ: Wael Savej. I concur.

18 DR. MOON: Mark Moon. I concur.

19 DR. HUDAK: Okay.

20 DR. LASCHINGER: Can I just make one?

21 DR. HUDAK: Yes.

22 DR. LASCHINGER: For pure MDR reporting

1 we don't have a -- I just want to make sure the
2 committee understands that we do not have a
3 denominator, so we can't tell you what the rate is
4 based on the entire U.S. experience. We can only
5 tell you what MDRs we have, and in Table 2 in your
6 summary, the time to event for each of those MDRs
7 is noted.

8 So for those noted MDRs we can give you
9 a time to event. But how that compares to
10 patients, it doesn't take into account the
11 patients who didn't have those MDRs, and so it's
12 going to be a very -- it's not going to be
13 representative of patients overall, but only for
14 the patients who had that MDR.

15 If we can get that data to you. Just so
16 you know.

17 DR. HUDAK: Sure. But can I ask a naïve
18 question then?

19 DR. LASCHINGER: Sure.

20 DR. HUDAK: So there are relatively few
21 of these devices actually in use.

22 DR. LASCHINGER: Mm-hmm.

1 DR. HUDAK: Are you reporting on a
2 complication rate of 33 percent of strokes, so
3 there aren't that many devices that are out there
4 in use for which complications have not been
5 reported. So it seems to be a relatively simple
6 matter of working with the company, perhaps, and
7 finding out which patients for how long have been
8 on these pumps and factoring that information,
9 which is all negative data. It's just going to --
10 I mean, pretty straightforward it seems to be.
11 But I guess the consensus is to do the best you
12 can with what you've got.

13 DR. LASCHINGER: No, I understand. We
14 intend to do that.

15 DR. HUDAK: Yes, right.

16 DR. LASCHINGER: I just wanted to point
17 out the shortcomings of the reporting systems that
18 we have available to us.

19 DR. HUDAK: Okay. Good.

20 DR. LASCHINGER: I don't want to have
21 unrealistic expectations.

22 DR. HUDAK: All right. We'll do a

1 question after the vote.

2 DR. HOEHN: It was another clarifying
3 question about what you said because I guess I
4 incorrectly assume that because it was a
5 humanitarian exemption of an IND that every time a
6 Berlin Heart was used it was reported to the FDA.
7 So you're saying that's not true? Only the
8 adverse events are reported to the FDA? And
9 there's not some database somewhere similar to
10 (inaudible) where use is tracked?

11 There's no one person out there other
12 than the company who could tell you how many times
13 a Berlin Heart's been used in the last 365 days?

14 DR. LASCHINGER: We can get some of that
15 information through annual reports and things like
16 that, yes. But, yes, we can get a lot of that
17 information that way, so.

18 DR. HUDAK: Okay. Well, thank you very
19 much. We will move on to the next topic which is
20 CONTEGRA, pulmonary valve conduit. Are we
21 changing anybody out at the table? Yes, we're
22 changing out. Okay.

1 So if you could introduce yourselves?

2 MS. CHIH-HSIN LIU: This is Jenny
3 Chih-Hsin LIU. Nurse consultant in CDRH and
4 Biometrics.

5 DR. KURTZMAN: Dr. Steven Kurtzman. I'm
6 a cardiologist in the division of cardiovascular
7 devices in the center for devices.

8 DR. HUDAK: Okay. Dr. Aggrey, you're
9 on.

10 DR. AGGREY: Good afternoon. My name is
11 George Aggrey. I'm an epidemiologist at the
12 Office of Surveillance and Biometrics, CDRH. I
13 will present CDRH and our review for the CONTEGRA
14 HDE, including a review of the medical device
15 reports and the published literature since our
16 last PAC briefing in 2015.

17 The CONTEGRA pulmonary valve conduit was
18 approved in November 2003 with indications shown
19 on the slide. The HDE annual distribution number
20 for the CONTEGRA device is 4,000. Since the last
21 PAC review one year ago, a total of 428 have been
22 implanted with the majority in the pediatric

1 population.

2 Next I will present information related
3 to the medical device reports received by the FDA.
4 Since the last PAC review, as noted in our
5 executive summary, a total of 79 MDRs related to
6 the CONTEGRA device have been received by FDA in
7 the one year period since our last update.

8 However, the number of unique reports
9 after removing events tied to published literature
10 which was covered at previous PAC meetings, which
11 will be discussed in our literature review in a
12 couple of minutes, is 58. Fifty three of those 58
13 MDRs provided information about a patient's age,
14 and of those 48 were for pediatric subjects. The
15 mean age in these reports was approximately 9
16 years.

17 This slide, which also appears in your
18 executive summary breaks out the 48 pediatric
19 reports by primary event type. As seen on the
20 slide, stenosis was the most commonly reported
21 adverse event and accounted for 50 percent of the
22 pediatric events. Of note, all of these cases

1 required device replacement or conduit and
2 angioplasty. An additional

3 MDRs reported device placement, but did
4 not specifically mentioned stenosis as the reason.

5 Three of those cases were situations
6 where the patient outgrew their device, and the
7 remaining MDRs provided no specific reason for the
8 replacement. As can be seen on the two right-hand
9 columns. The mean time to stenosis or device
10 replacement for the (inaudible) set of MDRs was
11 approximately 75 months. Stenosis and device
12 replacement reflect anticipated long-term events
13 given the young age of the majority of the
14 pediatric patients at the time of CONTEGRA
15 implants.

16 When comparing MDRs for this year's PAC
17 report to that presented in 2015, the types of
18 events reported, regardless of patient age, are
19 similar. Although, as would be expected with the
20 passive reporting system, the absolute numbers and
21 percentages varied. In summary, the MDRs received
22 since the last PAC meeting identified no new types

1 of safety issues.

2 I will now present the results of FDA's
3 literature review. A search of the (inaudible)
4 and databases were conducted using the same search
5 terms as last year's search and is discussed in
6 your executive summary. This slide shows the
7 article selection process which resulted in a
8 total of 11 articles for final review. These 11
9 publications are discussed in detail in your
10 executive summary, and I'll only be highlighting
11 some of the more relevant points in the next few
12 slides.

13 Three of the studies and all case
14 reports included only pediatric patients. In the
15 next two slides I'll present data from the two
16 publications which contain more than one CONTEGRA
17 recipient. Sarikouch et al published a recent
18 retrospective study which compared outcomes of
19 patients who received CONTEGRA and sterilized
20 pulmonary homografts or (inaudible) homografts.

21 Each group consisted of 93 patients, and
22 the mean follow up ranged from 5 to 7 years for

1 the three cohorts. The highlighted numbers
2 represent outcomes (inaudible) a significant
3 difference between CONTEGRA and the sterilized
4 pulmonary homograft or (inaudible) homografts.
5 (inaudible) from implantation and peak pressure
6 gradient of 50 mmHg or more was (inaudible) for
7 CONTEGRA.

8 However, the failure for insufficiency
9 and endocarditis were comparable in all three
10 conduit types. As studies by Kido et al and
11 routine pediatric patients who have received small
12 caliber CONTEGRA device. The patient population
13 included young patients with low body weight and
14 patients who have persistent pulmonary
15 hypertension with post-operative pressure gradient
16 about 60 mmHg.

17 Through 10 months of follow up, the
18 mortality rate was 15.4 percent, and the rate of
19 freedom from re-operation was approximately 54
20 percent. The office concluded that low body
21 weight at operation and persistent pulmonary
22 hypertension may have contributed to early graft

1 failure and re-operation in the study patients.
2 As such, results contained two studies which
3 included both pediatric and adult recipients of
4 the CONTEGRA.

5 The percentage of pediatric patients
6 aged less than 18 years in one study was 92
7 percent. Unfortunately, we're unable to determine
8 the percentage of pediatric subjects aged less
9 than 18 years in the other study.

10 In this first study, (inaudible)
11 colleagues analyzed patients who underwent
12 placement with evolved conduit, including 208
13 pulmonary homografts, 121 aortic homografts, 245
14 CONTEGRA grafts, and 137 porcelain homografts.
15 After a median follow up of 7 years the CONTEGRA
16 was the only graft observed to be associated with
17 a lower risk of reintervention and replacement
18 when compared to pulmonary homografts.

19 The same study also reported rates of
20 freedom from endocarditis of 10 years. As can be
21 seen on the slide, fewer CONTEGRA recipients were
22 free of endocarditis when compared to patients who

1 had received any of the other three conduit types.
2 The use of CONTEGRA was observed to be associated
3 with a nine time greater risk of endocarditis
4 compared to homografts, as shown on the slide.

5 In the second study, (inaudible)
6 evaluated 444 CONTEGRA conduit and 267 homografts
7 implanted in patients and stratified their results
8 by age group. This slide shows

9 (inaudible) for freedom from
10 explantation stratified by age
11 group, compared by conduit type
12 using log rank tests.

13 The office reported that the freedom
14 from explantation was significantly better for
15 CONTEGRA compared to homografts in patients
16 younger than 1 year, the top left on the slide,
17 and in patients 1 to 6 years, top right on the
18 slide. In patients 25 to 40 years the results
19 were similar.

20 This slide summarizes the rare adverse
21 events that were noted in either of the studies or
22 case reports. One case of each event was

1 reported, namely, coronary artery compression,
2 thrombosis, (inaudible) section, and protrusion of
3 the device between (inaudible) due to size
4 mismatch. More details on these events are
5 provided in the executive summary. These rare
6 events, including size mismatch, are already
7 included in the instructions for use.

8 The ability to draw conclusions from the
9 literature review is limited by the following
10 factors. Majority of the studies were
11 retrospective. Thus, covariates were not balanced
12 in comparing CONTEGRA to homograft or post-line
13 heterograft in at least one study. Therefore,
14 the study result may not be as robust as for a
15 randomized, controlled trial.

16 Follow up time varied in comparing
17 CONTEGRA to other conduits which could influence
18 the observed rates. The CONTEGRA conduit when
19 implanted over a long timeframe, 1999 to 2014, and
20 the standard of care may have changed during this
21 period of time. The literature findings are not
22 consistent across studies. In the studies with

1 (inaudible) patients only, the literature showed
2 that compared to homografts, the CONTEGRA has
3 lower rate of freedom from explantation and peak
4 pressure gradient of 50 millimeters of mercury or
5 more.

6 Comparable rates of freedom from
7 moderate insufficiency, and comparable rate of
8 freedom from endocarditis. In the studies with
9 pediatric and adult population, compared to
10 homografts or other conduit the CONTEGRA showed
11 lower risk of reintervention and replacement.
12 Higher rate of freedom from explantation in
13 patients younger than 1 year and in patients 1 to
14 6 years, and lower rates of freedom from
15 endocarditis.

16 CDRH concludes that there are no new
17 (inaudible) regarding the safety of the device
18 identified since the last PAC meeting. The
19 endocarditis was consistent with the data
20 previously reported in the literature that was
21 presented to the PAC in the past. The ADN for this
22 device remains appropriate for the pediatric

1 population for which it was granted.

2 FDA recommends that we continue
3 surveillance and report similar information to the
4 PAC in 2017. Does the committee agree with CDRH
5 conclusion and recommendation? This ends FDA's
6 presentation. Thank you.

7 DR. HUDAK: Thank you, Dr. Aggrey. So
8 this is open for discussion. Dr. Fischer?

9 DR. FISCHER: I was just wondering if we
10 have more information about the dissection that
11 was reported in 2016? Whether there was an
12 evaluation of the explanted device? Whether
13 physical or structural evaluation?

14 DR. AGGREY: Well, regarding the
15 literature, from what was reported in the
16 literature we do not have any -- the information
17 we have from the literature was that the
18 dissection occurred about 5 millimeters
19 approximate to the
20 (inaudible) stenosis. Essentially
21 that was the information that was
22 provided. The CONTEGRA was

1 explanted and replaced with a
2 homograph.

3 DR. FISCHER: But there weren't any
4 further evaluations of the explanted device
5 looking for a structural defect that led to the
6 dissection, as far as we know, it sounds like?

7 DR. AGGREY: We did not get that from
8 the literature. Thank you.

9 DR. HUDAK: Dr. Moon?

10 DR. PEIRIS: Just as an addition to that
11 question that was asked. Sorry, I don't think I
12 ever introduced myself. Vasum Peiris. I'm the
13 chief medical officer for Pediatric Special
14 Populations at CDRH.

15 But in addition to the point about the
16 dissection, it was also unclear whether there
17 could have been potentially a surgical issue,
18 meaning inappropriate scalpel going across the
19 conduit area. So none of those issues were clear.
20 So I don't want to make the point that this is
21 specific to a fidelity, integrity problem of the
22 conduit itself.

1 DR. HUDAK: Dr. Moon?

2 DR. MOON: Two things. One, can you go
3 to the slide before because it's hard to answer
4 that question without knowing what you're -- no,
5 what your recommendations were. Yes, right.

6 One of those studies you said had a 10
7 month, 50 percent reoperation rate? That's
8 horrible.

9 DR. AGGREY: Yes. That is true.

10 DR. MOON: That was all in very young
11 patients or was it?

12 DR. AGGREY: That is true. That was in
13 very young patients. The mean -- the median, body
14 weight for the patients was about 5.5. The total
15 population was 13, only

16 patients.

17 DR. MOON: That was a single center
18 that...

19 DR. AGGREY: That was a single sector.
20 And the patients also included other -- the others
21 mentioned patients who had were very -- had a very
22 small body weight, and they also had severe

1 pulmonary hypertension, and they believe that it
2 could be attribute -- the pulmonary hypertension
3 could have contributed to the graph failure.

4 DR. MOON: And the mortality rate was?

5 DR. AGGREY: The mortality rate was 15.4
6 percent. And that was --

7 DR. MOON: And that wasn't an operative
8 mortality rate? That was a mortality at 10 months
9 or...

10 DR. AGGREY: The mortality was two out
11 of 13 patients.

12 DR. MOON: Okay.

13 DR. AGGREY: One patient died one month
14 after the procedure, and the other patient died
15 two months after the procedure.

16 DR. MOON: Well, it will be interesting
17 to see what that group has as their results in the
18 next 13 patients because that -- those are very
19 bad. I don't know if it's grouped dependent on
20 the surgical group that was doing the procedure or
21 the -- it doesn't sound like it was the device
22 because nobody else has had that bad of results.

1 DR. PEIRIS: Just to help clarify as
2 well, because this might be a nuance of the
3 pediatric cardiology subspecialty, but the younger
4 the patient is when these devices are placed,
5 which may already be assuming that more rapidly
6 the conduit likely will need to be changed due to
7 increases in body surface area and flow demands.

8 DR. HUDAK: Dr. Anne?

9 DR. ANNE: Just to follow up on the
10 point that Dr. Moon had which was what were the
11 causes of death for the two patients that died in
12 that particular group?

13 DR. AGGREY: One patient died of septic
14 shock related to necrotic enterocolitis. The
15 second patient died of severe (inaudible) failure.
16 The patient also had chromosome anomaly, and it
17 was believed that severe pulmonary hypertension
18 may have been related to the chromosomal
19 abnormality.

20 DR. ANNE: Okay. Thank you.

21 DR. HUDAK: Dr. Cunningham?

22 DR. CUNNINGHAM: Thank you. Just one

1 clarifying. So in your literature summary in the
2 limitations, if we look at the last one, the
3 CONTEGRA were implanted over longer periods of
4 time, that actually fortifies the data about less
5 re-operation and explantation, but it does favor
6 that, perhaps, the increased rate of endocarditis
7 in the CONTEGRA, so. It was probably obvious to
8 everyone else, but.

9 DR. PEIRIS: These are all very good
10 questions and definitely worth considering and
11 pointing out.

12 DR. HUDAK: Dr. Hoehn?

13 DR. HOEHN: Sorry. I had another
14 question. We're all fixating on the Kido study.
15 Was that an American study? I can't find it
16 online. The one where half the people were
17 reoperated and there's the 15 percent mortality.

18 DR. AGGREY: The Kido study I think it
19 was from OMAN. That's an OUS study.

20 DR. HOEHN: It was where?

21 DR. AGGREY: OUS study.

22 UNIDENTIFIED MALE: Outside the U.S.

1 DR. AGGREY: Sorry, outside the U.S.

2 DR. HUDAK: Dr. Anne?

3 DR. ANNE: You know, I did not see any
4 mention of, like, pseudo-aneurism reported in this
5 particular, you know, the literature search and
6 whatever else. Was that included as one of the
7 other diagnoses by any chance?

8 DR. AGGREY: Yes. The papers did not --
9 as you can see, there are three papers for the
10 pediatric only population and two papers for the
11 adult and pediatric population, so it was only
12 five studies. This number is small compared to
13 what we presented previously.

14 The previous papers have reported
15 (inaudible) and dilation. These papers did not
16 report data on pseudo-aneurysm.

17 DR. SHWAYDER: I just had the simple
18 question, is this placed with sternotomy or can
19 you do it by endoscopic?

20 DR. PEIRIS: Sternotomy.

21 DR. SHWAYDER: Sternotomy.

22 DR. PEIRIS: The conduit can be minimally

1 dilated and potentially mitigated from replacement
2 via transcatheter balloon, quote/unquote,
3 angioplasty dilation.

4 DR. HUDAK: Okay. I think we're at a
5 point where we can do a button vote on the FDA
6 recommendation to continue current procedures with
7 reporting in 2017.

8 Okay. We'll do a voice recording
9 starting with Dr. Fischer.

10 DR. FISCHER: Gwen Fischer. I agree.

11 DR. MOON: Mark Moon. I agree.

12 DR. HAVENS: Peter Havens. I agree.

13 DR. TURER: Christy Turer. I agree.

14 DR. SHWAYDER: Shwayder. Agree.

15 DR. CNAAN: Avital Chann. I agree.

16 DR. CATALETTO: Mary Cataletto. I
17 agree.

18 DR. CAMPBELL: Jeff Campbell. I agree.

19 DR. CUNNINGHAM: Melody Cunningham. I
20 concur.

21 DR. HOEHN: Sarah Hoehn. I agree.

22 DR. DRACKER: Bob Dracker. I concur.

1 DR. WHITE: Michael White. I agree.

2 DR. WADE: Kelly Wade. I agree.

3 DR. ANNE: Premchand Anne. I concur.

4 DR. HUDAK: Thank you, Dr. Aggrey. So
5 conclusion, the committee does recommend
6 unanimately continue current monitoring of the
7 CONTEGRA device.

8 Okay. Next up is Pleximmune. Okay.
9 Great. All right. I think we're ready. If you
10 all could introduce yourselves down there.

11 DR. VELIDEDEOGLU: Ergun

12 Velidedeoglu
, medical officer. Division of

13 Transplant and Ophthalmology Products, CDER.

14 DR. WIENEKE: Hi, good afternoon,
15 Jacqueline Wienke, medical officer, Division of
16 Chemistry and Toxicology Devices.

17 DR. LIAS: Courtney Lias, director of
18 Division of Chemistry and Toxicology Devices.

19 DR. HUDAK: Okay. Dr. Kelm?

20 DR. KELM: Hello. Good afternoon. My
21 name is Kelly Kelm and I'm the branch chief of
22 Cardio Renal Diagnostic Devices in the Division of

1 Chemistry and Toxicology Devices. Today we'll be
2 talking to you about Pleximmune.

3 This is our second time presenting, so
4 last year was the first. So I think because IVDs
5 are still novel for this committee that we sort of
6 kept our brief overview of IVDs to present to the
7 committee before we get into the regulatory
8 history and information about the device and
9 update you on the literature review and MDRs over
10 the last year.

11 You may have already heard this from the
12 previous presentations on HDEs, but for HDEs we're
13 looking for probably benefit outweighing the risk
14 of injury of illness from the use of the device.

15 So briefly, what is an IVD or in vitro
16 diagnostic device? IVDs are reagents,
17 instruments, or systems intended for use in the
18 diagnosis of disease or other conditions,
19 including a determination of the state of health
20 in order to cure, mitigate, treat, or prevent
21 disease or its sequela in man, and further, IVDs
22 are also for use in the collection, preparation,

1 and examinations of specimens from the human body.

2 So as part of a pre-market submission
3 IVDs must establish adequate analytical
4 performance that supports the claims made in the
5 intended use that the sponsor provides us.
6 Sponsors should show that their device accurately
7 measures the analyte and that it does so reliable
8 and reproductively when taking into account all
9 analytical steps of the assay.

10 In addition, they establish other device
11 characteristics such as the lowest concentration
12 of input sample that yields a reliable and
13 accurate result. They assess whether any
14 compounds interfere with the testability to
15 generate an accurate result, and provide
16 information on the methods for control and
17 calibration of the assay, information on software,
18 if there is any used within the device.

19 So sponsors should also establish the
20 clinical performance or clinical validity of the
21 test. The clinical performance may be based on
22 existing clinical data, new clinical trial data,

1 or review of information in the literature.
2 Lastly, IVDs have their own labeling regulations
3 that require the package insert to include
4 adequate instructions for use, the intended use,
5 any warnings, limitations, and finally,
6 instructions on how to interpret the test results
7 and a summary of the analytical and clinical
8 performance characteristics.

9 So most of the time a test's
10 effectiveness for a particular intended use is
11 expressed as sensitivity and specificity or as
12 predictive value. Sensitivity tells you how
13 likely the test is positive in someone who has the
14 disease. Specificity tells you how likely the
15 test is negative in someone with the disease.
16 Sensitivity and specificity must be evaluated
17 together as they are dependent on each other.

18 Similarly, we consider positive and
19 negative predictive values together. Positive
20 predictive value tells how likely someone is to
21 have the disease if they have a positive result.
22 Negative predictive value tells how likely someone

1 is to not have the disease if they have a negative
2 result. Positive and negative predictive values
3 are often preferred because the information is
4 more reflective of the decision a clinician must
5 make when they receive a lab report. Predictive
6 values also depend highly on the prevalence of the
7 disease in the population.

8 So here's the regulatory history for the
9 Pleximmune test. It was granted humanitarian use
10 designation of HUD back in June 2009. HDE approval
11 was granted in August of 2014. I just wanted to
12 note, there was no post-approval study for this
13 HDE.

14 So we're going to present to you the
15 indications for use for this test and it spans two
16 pages, so bear with me. Pleximmune test is
17 intended to be performed at a single laboratory to
18 measure the CD-154 expression on T cytotoxic
19 memory cells in patients peripheral blood
20 lymphocytes. It is a qualitative prognostic test
21 intended to be used in patients less than 21 years
22 old with liver or small bowel transplantation.

1 It is an aid in the evaluation of the
2 risk of acute cellular rejection or ACR, and must
3 be used in conjunction with biopsy, standard
4 clinical assessment, and other laboratory
5 information. So this test is highly adjunctive
6 and a clinician would not use this test alone, as
7 said here, it's used with biopsy and other
8 assessments that the clinician is performing.

9 I just wanted to reiterate that the aid
10 in the evaluation of the risk means that this is a
11 prognostic marker, so it's not necessarily use as
12 a aid of diagnosis, but sort of a piece of
13 information that a doctor would use when they're
14 assessing whether or not a patient is at risk for
15 ACR.

16 So the Pleximmune test is intended for
17 use at the following time periods. So during the
18 pre-transplantation period, the test can predict
19 the risk of transplant rejection within 60 days
20 after transplantation, and during the early and
21 late post-transplantation period, for blood
22 samples collected within 60 days after

1 transplantation, and for blood samples collected
2 200 or more days after transplantation the test
3 predicts the risk of transplant rejection within
4 60 days after sampling.

5 So in both cases it's predicting 60 days
6 after either transplantation or sampling, and
7 we've underlined that because those are distinct.
8 These time periods, we acknowledge the gap, is
9 based on the data that was provided to us by the
10 sponsor during pre-market review.

11 So here is a brief description of the
12 Pleximmune test and what it is intended to
13 measure. So here we've simplified in a picture
14 the recipients immune response to donor cells, and
15 this is the mechanism that the Pleximmune test is
16 measuring. So the first event on the left is
17 antigen sensing which is the presentation of the
18 donor antigen to the T-cell by the antigen
19 presenting cell.

20 The T-cell can either accept the donor
21 antigen by undergoing apoptosis, in the top right,
22 or can attack the donor by mounting a donor

1 specific inflammatory response. The Pleximmune
2 test measures the inflammatory immune response of
3 the recipient to the donor by measuring those T-
4 cells which express the inflammatory marker
5 CD-134, also known as CD40 ligand.

6 So the Pleximmune test is based on
7 lymphocyte co- culture between recipient and donor
8 peripheral blood lymphocytes. You also need to
9 measure the background reaction which is the
10 recipient T-cells which were expressed CD-134, and
11 there's the reference reaction with measures
12 recipient T-cells expressed CD-134 in response to
13 simulation with other unrelated or third-party
14 cells. So these three reactions are all measures
15 by flow cytometry which is pictured in the bottom.
16 And so you're looking for CD-134 expression in
17 these three reactions.

18 The results of the Pleximmune test are
19 an immunoreactivity index which is a ratio of the
20 recipient's inflammatory response to donor cells
21 expressed as a fraction of his or her inflammatory
22 response to the third party cells.

1 If the donor-induced response exceed the
2 response of the third-party then the individual is
3 at increased risk for ACR. There are two cutoffs
4 used. One for pre- transplant and one for
5 post-transplant samples. Here's the description
6 of the activity response and shows you the two cutoffs
of pre- and post-transplant cut offs.

8 So here is the clinical evaluation study
9 that was presented to us in the HDE. So a total
10 of 122 specimens were evaluated from 87 individual
11 pediatric transplant patients. Of these, 97
12 samples consisted of 33 pediatric pre-transplant
13 subjects and 64 post-transplant samples from
14 pediatric samples were also analyzable.
15 This is a combination of 30 from the early
16 post-transplant period and
17 from the later post-transplant period.

18 So here on one slide is the overall study results.

19 But I'm going to walk you through them
20 in detail in the next two slides. So this is the
21 summary for the pre-transplant samples. So the
22 test predicted correctly the increased risk of ACR

1 80 percent of the time and gave 20 percent false
2 positive results. The test predicted correctly
3 decreased risk of ACR 74 percent of the time, and
4 gave 26 percent false negative results.

5 For the post-transplant samples which,
6 as I said, was the early and late post-transplant
7 periods together. The test predicted correctly
8 the increased risk of ACR 64 percent of the time
9 and gave 36 percent false positive results, and
10 the test predicted correctly decreased risk of ACR
11 92 percent of the time, and gave 8 percent false
12 negative results.

13 So this is the annual distribution
14 number for this device is 4,000 tests per year.
15 This is the actual device distribution over the
16 period of time from June 1, 2015 to May 31, 2016.
17 Plexicion informed us that they performed a total
18 of 254 Pleximmune tests for a total of 210
19 patients at their laboratory. All of these
20 specimens were post- transplant samples. They
21 have them in testing on the pre- transplant
22 specimens.

1 And as you can see among the 210
2 patients it was split fairly evenly amongst males
3 and females, and then the average of these
4 patients is 10.4 years with an age range from 4
5 months to 20.95 years old. Then we have the
6 description of the type of transplants that they
7 had received there at the bottom.

8 So we performed a literature review to
9 look for potential safety issues for this test.
10 We looked over the time period of June 1, 2015 to
11 May 31, 2016. I have a description of the method
12 up here in terms of where we looked and how we did
13 the literature search.

14 Over this time period there were no
15 publications that indicated any safety issues with
16 the test. We also used two methods to try and
17 identify if any adverse events or complaints were
18 issued over this time period for Pleximmune. We
19 did a search of the MAUDE or the new PRIMO
20 database for the same time period, June 1 of last
21 year to May 31 this year. You can see our search
22 criteria here indicated for the brand name and

1 other key words. We did not find any MDRs.

2 We also received information from the
3 sponsor, upon our request, that indicated that
4 they had not received any MDRs or complaints over
5 that time period.

6 So in conclusion, over the time period
7 June 1, 2015 to May 31, 2016 Plexicion performed a
8 total of 254 Pleximmune tests for 210 patients at
9 their laboratory. A review of the published
10 literature and MDRs since the time of approval and
11 over the last year has not identified any new or
12 unexpected risks for the pediatric population when
13 compared to the pre-market data.

14 FDA concludes that the benefit risk
15 profile of the Pleximmune for its indications for
16 use continues to support the HDE for which the
17 exemption was granted. FDA recommends continued
18 surveillance and will report to following to the
19 PAC in 2017: the annual distribution number, our
20 literature review, and our MDR review.

21 So the question for the PAC is does the
22 committee agree with FDA's conclusions and

1 recommendations? Thank you very much.

2 DR. HUDAK: Thank you, Dr. Kelm. So
3 this is open for discussion. Dr. Hoehn?

4 DR. HOEHN: Sorry, I have another
5 question. Sarah Hoehn. Was there a reason why it
6 was only used for small bowel and liver
7 transplantation and wasn't used for any other kind
8 of transplantations?

9 DR. VELIOLEOLEOGLU: No, and I can't
10 think of a specific reason why this wasn't used
11 for other types of organ transplantations, but
12 that was the study population. I mean, this may
13 also turn out to be useful if it's tried in kidney
14 transplantation, but I don't think we have data on
15 that yet.

16 DR. HUDAK: So I do have a general
17 question in terms of how well this has been
18 received clinically. Just looking at the numbers
19 you present, personally, if I were to look at a
20 result I would have sufficient uncertainty as to
21 what the result meant.

22 DR. VELIDEDEOGLU: Can you please

1 repeat the last part of your question? The last
2 sentence?

3 DR. HUDAK: Yes. I was saying that
4 depending what the result was, whether it was
5 positive or negative, I'd be uncertain as to what
6 it really meant. Because it could be positive and
7 not be correctly positive. It could be negative
8 and not be correctly negative. So how do people
9 use this an synthesis this information into
10 clinical care?

11 DR. VELIDEDEOGLU: Well, we had a
12 similar discussion last year, and I fully
13 understand the purpose of the question. In the
14 transplant world, especially in the case of liver
15 transplantation, the diagnosis of acute rejection
16 may be very challenging at times. As you might
17 all appreciate, I mean, if you give the same
18 pathological specimen or the same slide to two
19 different pathologists you may end up with
20 different results. That's not often the base, but
21 it may happen.

22 And in the case of liver

1 transplantation, especially among the many
2 confounders, especially in the case of hepatitis C
3 patients, sometimes even the biopsy may not be
4 helpful. It may be very challenging to decide if
5 it's recurrent Hep C or acute rejection. So what
6 I'm trying to say is that it's the diagnosis of
7 reject is arrived after considering multiple
8 factors. The clinical course, the time point
9 after transplant, the origin of disease, the
10 results of other imagining studies, and, of
11 course, the biopsy is considered to be the gold
12 standard. But biopsy itself may sometimes be also
13 be misleading, especially if it's a protocol
14 biopsy performed in the absence of liver
15 dysfunction.

16 So the main problem, one of the main
17 issues in the transplant world now is how much
18 immunosuppression is the right amount? And nobody
19 knows the answer and that applies to all types of
20 transplantation. So this adjunct tool is, I
21 believe, I personally believe, is a step in the
22 right direction in helping the efforts of defining

1 the optimum immunosuppression in these patients.

2 As specified on the label, it's never
3 the main diagnostic tool. It should not be used
4 as the main diagnostic tool, but I believe it's a
5 useful adjunct, and it's -- we are hoping that
6 it's going to developed further.

7 DR. WIENEKE: I'd also like to add we
8 sometimes hear some feedback about how people are
9 receiving tests. We don't have that type of
10 feedback for this test. I think the only
11 information we really have is that about 250 tests
12 were ordered last year.

13 DR. HUDAK: So maybe, Dr. Kelm, could
14 you bring up the slide again from the beginning
15 about the pre-transplant numbers?

16 DR. KELM: For this year or for the
17 original study?

18 DR. HUDAK: Whatever you've got.

19 DR. WIENEKE: Do you mean the predictive
20 values?

21 DR. HUDAK: So the pre-transplant set,

22 33 --

1 DR. WIENEKE: And that's the top?

2 DR. HUDAK: Right.

3 DR. WIENEKE: Mm-hmm.

4 DR. HUDAK: So those numbers are, they
5 are what they are, and that's my question, so I'm
6 confused, but okay.

7 Yes?

8 DR. JONES: This is Bridgette Jones.
9 For the post-transplant predictive values were you
10 able to look at to see if the best performed
11 better when measuring then early versus late
12 post-transplant? Because initially you mentioned
13 that can be measured, I think, 60 days and 200
14 days out. Does the test perform better depending
15 on when you measure it?

16 DR. KELM: We looked at all of that
17 during the review. I'm not sure we have that data
18 with us. Let's see if I've got it here.

19 DR. WIENEKE: No. These presentation
20 hasn't pooled.

21 DR. KELM: I don't recall whether --
22 that we saw a difference. Sharon, do you

1 remember?

2 DR. HUDAK: Please come to the
3 microphone and identify who you are and who you
4 represent.

5 DR. KELM: Unfortunately, we didn't
6 prepare to present the pre-market approval
7 decision information.

8 DR. MARFATIA: Yes, I don't know why,
9 but I think there were no major differences and
10 number of samples were very small to make that
11 kind of (inaudible).

12 My name is. Shirin Marfatia

13 DR. HUDAK: You represent?

14 DR. MARFATIA: I was the lead reviewer
15 when it actually was reviewed.

16 DR. HUDAK: Okay. You're with the
17 agency.

18 DR. MARFATIA: Mm-hmm.

19 DR. HUDAK: Great. Dr. Turer?

20 DR. TURER: I wondered to what extent
21 the response depends on what immunosuppressive
22 drugs and what doses patients are on, so that, you

1 know, could the sensitivity and specificity
2 change? Because you're looking at the recipients'
3 inflammatory response to donor cells.

4 DR. LIAS: So when we have test come
5 into us we do have them look at interferences, and
6 part of that is that the -- we look at what the
7 test is measuring and we assess, also, the patient
8 population, and along with the sponsor, try to
9 develop a list of potential interfering compounds.
10 A lot of times we ask that they test drugs that
11 the patient population would typically be on at
12 the levels or a little, you know, maybe even
13 higher levels to find out whether or not that
14 might be likely to analytically interfere with the
15 assay.

16 So that testing was done and we did not
17 see significant interference. Now, that being
18 said, part of the reason that we do surveillance
19 is to try and find out whether or not there are
20 new interfering compounds that are identified
21 through, you know, real life testing. And we have
22 not heard from the company that they've had any

1 scenarios where they've identified that yet.

2 DR. HUDAK: Dr. Cunningham?

3 DR. CUNNINGHAM: Thank you. So if the
4 goal of using this along with the other clinical
5 data is to either increase or decrease
6 immunosuppression based on your worry about the
7 risk of rejection, and the goals are to prevent
8 rejection, but also to minimize immunosuppression
9 and post-transplant lymphoproliferative disease
10 wouldn't it help us if we're evaluating the safety
11 of this test to know what those data are in
12 relation to when this test is used?

13 DR. VELIOLEOLEOGLU: Are you saying that
14 further safety evaluation needs to be done in the
15 post-marketing setting? Is that what?

16 DR. CUNNINGHAM: Yes. Maybe I'm
17 misunderstanding, but it seems like if we know the
18 rate of post-transplant lymphoproliferative
19 disease when this is and isn't used, graph
20 rejection when this is and isn't used, if there's
21 a higher than if we use this test of the
22 clinicians use this test, and there's a higher

1 rate in this group of post- transplant
2 lymphoproliferative disease doesn't it tell us
3 that this test is sending them down the wrong
4 road?

5 Wouldn't those data be important for us
6 not to just analyze whether the test works, but in
7 the clinical realm how it affects decision making,
8 and then how it affects outcomes?

9 DR. VELIDEDEOGLU: Well, certainly it
10 can be the subject of another clinical study, but
11 as you have seen, the numbers are quite small, and
12 we have only, like, 250 samples within the last
13 year. And, in fact, the pediatric liver
14 transplant patient population and small bowel --
15 pediatrics small bowel patient populations are
16 quite small patient populations. But this can
17 certainly be the subject of an upcoming study.

18 DR. CUNNINGHAM: And just looking -- go
19 ahead.

20 DR. PEIRIS: I just want to, maybe, try
21 to contextualize a little bit of this because
22 these same issues came up in previous reviews, and

1 I think the concern is, you know, the decision
2 that went into approving the device versus our
3 current issue, (inaudible) safety of the device.

4 And when we think about the safety of a
5 device of this nature we're thinking about the
6 safety of utilizing this specific test. Not
7 necessarily how it will be interpreted and what
8 the management will be afterwards. That tends to
9 get into that issue of the practice of medicine
10 that always has that clear distinction. However,
11 we, all being physicians, have been in that exact
12 same situation where we wonder what is the
13 pre-test probability before we order a test, and
14 what will our decision be in terms of managing the
15 patient after the test?

16 The FDA's responsibility was to figure
17 out whether this test actually works the way that
18 it's actually intended to work. The clinical and
19 analytical validity of the test.

20 DR. CUNNINGHAM: Duly noted.

21 DR. HUDAK: Any other thoughts? If not
22 we can bring up the question slide. So this has

1 been updated over the past year with additional
2 information and the question is, does the
3 committee agree with the FDA's plan to do
4 continued surveillance and report again in 2017?
5 So, use your buttons.

6 Okay. So we'll amplify with some verbal
7 comments starting with Dr. Anne.

8 DR. ANNE: Premchand Anne. I concur.

9 DR. WADE: Kelly Wade. I concur.

10 DR. WHITE: Michael White. I agree.

11 DR. DRACKER: Bob Dracker. I concur.

12 DR. HOEHN: Sarah Hoehn. I concur.

13 DR. CUNNINGHAM: Melody Cunningham. I
14 agree.

15 DR. CAMPBELL: Jeff Campbell. I concur.

16 DR. CATALETTO: Mary Cataletto. I
17 agree.

18 DR. CNAAN: Avital Cnaan. I agree.

19 DR. SHWAYDER: Shwayder. Agree.

20 DR. TURER: Christy Turer. I agree.

21 DR. HAVENS: Peter Havens. I agree.

22 DR. MOON: Mark Moon. I agree.

1 DR. FISCHER: Gwen Fischer. I agree.

2 DR. HUDAK: Okay. Thank you, Dr. Kelm.
3 Okay. We'll do another change out. We'll move on
4 to the Enterra Therapy System.

5 Okay. For this discussion, I think Dr.
6 Moon is recused. And the new people at the table
7 are?

8 DR. VENKATARAMAN-RAO: My name's Prea
Venkataraman-Rao

9 . I'm a medical officer in the
10 Gastroenterology Devices Branch.

11 DR. FORNAGER: My name's Ryan Fornager.
12 I'm a chemical engineer and reviewer in the
13 Division of Reproductive, Gastro Renal and
14 Urological devices.

15 DR. MIN: Lauran Min, epidemiologist
16 in the Division of Epidemiology.

17 DR. HUDAK: Okay. Thank you. Cathy,
18 you have the floor.

19 MS. RICKETTS: Good afternoon, my name
20 is Catherine Ricketts. I'm a nurse analyst in the
21 Division of Post-market Surveillance in the Office
22 of Surveillance and Biometrics at the FDA. I will

1 be presenting the summary of the results of the
2 FDA's annual safety review of post-market data for
3 the Enterra System.

4 Today's presentation will consist of
5 this basic outline. Enterra consists of
6 surgically implant neurostimulator, intramuscular
7 leads, and an external clinical programmer.
8 Enterra's indicated for chronic intractable nausea
9 and vomiting, secondary to gastroparesis of
10 diabetic or idiopathic etiologies in patients 18
11 to 70 years of age.

12 The annual distribution of Enterra
13 during the last reporting period has not exceed
14 the allowable ADN of 4,000. There were 103 neuro
15 stimulators implanted in pediatric patients.

16 I will now present the summary of the
17 results of our review of MDRs with a focus on the
18 pediatric MDRs. Similar to last year's methods,
19 the database search identified all MDRs related to
20 the Enterra Therapy System, resulting in an
21 initial results of 351 MDRs, 17 of which were
22 pediatric patients, 112 MDRs were considered

1 indeterminate age reports because no information
2 about the patient's age was provided.

3 This table shows the number of MDRs by
4 event and age group. Of the original 351 reports
5 identified, 35 were accounted as duplicate reports
6 for a unique event. One MDR was excluded from
7 this analysis since the event was reported in a
8 journal article, discussed under the literature
9 review of this presentation. Therefore, there
10 were 315 unique events reported, zero deaths, 203
11 injuries, and 112 malfunctions. I'll be focusing
12 on the 17 pediatric MDRs.

13 This table shows the time to event
14 occurred in 129 MDRs, including 10 of the 17
15 pediatric patients. The pediatric time to event
16 occurred were within the first year of implant and
17 included lead erosion and pocket infections,
18 return of symptoms and inappropriate shocking.

19 This table identifies the pediatric MDR
20 occurrences of the most common problems, both
21 patient and device combined, and clinical issues
22 in comparison to last year's findings. Similar to

1 last year's complaints were electric shock or
2 nerve stimulation undesired, nausea, vomiting, or
3 complaints ill defined, and pain and discomfort.
4 Each resolved with program adjustments and/or
5 system replacements and attributable to high or
6 low impedance issues commonly associated with
7 battery depletions or lead malfunctions.

8 Different this year is the complaint of
9 infections and erosion and device leads. However,
10 root causes were not mentioned in the reports.

11 Overall, both patient and device
12 problems observed for pediatric patients were
13 similar to those observed for adult patients and
14 for reports with indeterminate age. While these
15 issues are known inherent risks for the device,
16 and do not represent any new or previously unknown
17 concern regarding patient safety, there were more
18 issues of impedance this year directly related to
19 battery issues and/or lead placement. In most
20 instances, these devices were not returned for
21 evaluation by the manufacturer.

22 I will now present a summary of our

1 review of the published literature. FDA conducted
2 a systematic literature review on the safety and
3 probable benefits of Enterra in the pediatric
4 population. This is an update from the literature
5 review presented at last year's PAC meeting.

6 The purpose of the literature review was
7 to address the following questions in pediatric
8 patients younger than 22 years of age. What are
9 the probable benefits of Enterra for improvement
10 in upper GI symptoms, reduction in the need for
11 nutritional support, and improve gastric emptying
12 time? What adverse events are reported in the
13 literature after treatment with Enterra?

14 A similar search to last year's PUBMED
15 and MBASE were conducted using the listed terms
16 for Enterra, and limited to articles of clinical
17 studies of pediatric patients published in English
18 between May 1, 2015 and April 30, 2016, yielding
19 132 citations.

20 After assessment of the abstracts and
21 full text articles for eligibility, two articles
22 remained for full review and assessment. Reasons

1 for exclusion are provided in the executive
2 summary.

3 I will start by presenting the results
4 of the first included article. The study by Islam
5 et al is a retrospective review and included 67
6 pediatric subjects with medically refractory
7 gastroparesis implanted between 2004 and 2014 and
8 followed for an average of three and a half years.
9 The mean age was 13.7 with a range of 2 to 19
10 years,

11 percent were female and 85.6 percent
12 were Caucasian. This study's probably benefit
13 result of Enterra

14 included improved reports of symptoms,
15 food intake, and reduced need for parenteral
16 nutrition at 1 to 12 months compared to baseline,
17 with a decreased follow up rate after the first 6
18 months. In 11 subject symptom scores could not be
19 obtained.

20 The following adverse events were
21 reported in the Islam study. Device explant in
22 10 patients for lack of symptom improvement,

1 improved symptoms which no longer required
2 stimulation, intra matic disruption of the pocket,
3 device replacement in 13 patients due to an expire
4 battery, lead repositioning in five patients due
5 to early symptom reoccurrence and long term
6 failure of stimulation.

7 Lead erosion through that gastric mucosa
8 in two patients, seroma development in one patient
9 one month after device implantation, four deaths,
10 three from progressive respiratory insufficiency,
11 and one with no information provided.

12 The second paper by Hecker et al
13 involved 151 GP patients, both pediatric and adult
14 implanted with Enterra and followed for 12 months.
15 This study did not, however, report data
16 separately for pediatric and adult subjects.

17 The Hecket's study reported 75 percent
18 of patients had improved overall symptoms, noted
19 to be greater in diabetics than in idiopathic
20 patients. With the greatest improvement in
21 nausea, early satiety, and loss of appetite.
22 Symptoms with the least improvement included

1 constipation, diarrhea, and abnormal distention.

2 The Heckert study did not report on
3 changes in need of for nutritional support or
4 gastric emptying time following Enterra placement.
5 The Hecker et al study did not report an event
6 occurred in a pediatric or adult patient because
7 the age was not provided. The most common adverse
8 event reported in 15 or 138 patients was pain or
9 sensation at the stimulator site after placement.

10 Two diabetic patients had Enterra
11 removed for infection. There as one death of a
12 diabetic patient for unrelated causes.

13 The two studies included in our
14 systematic literature review suggest improved
15 upper GI symptoms after treatment with Enterra.
16 Although the patients may require additional
17 surgery. The effects on the need for nutritional
18 support and GET are less clear. Our results for
19 the studies should be interpreted in light of the
20 following key limitations.

21 Our review included only two papers
22 meeting the search criteria whose quality of

1 evidence was relatively low. The Islam et al
2 study was a retrospective analysis focused on the
3 pediatric population and subject to bias in which
4 the true safety and probable benefits of Enterra
5 may have been over estimated since it evaluated a
6 select group of patients who had previously
7 responded favorably to temporary treatment.

8 The Heckert et al study was a larger
9 study of 151 pediatric and adult subjects.
10 However, it was not clear if the reported benefits
11 or adverse events were experienced specifically by
12 pediatric subjects. For these reasons, we are
13 limited in our ability to make any conclusions
14 about the probably benefits and safety of Enterra
15 in the pediatric population.

16 These findings are consistent with the
17 results of the Enterra Systematic Literature
18 reviews presented in the previous 2014 and 2015
19 PAC.

20 In conclusion, no new adverse event
21 types have been reported in the MDRs or in the
22 literature over the past year. Given the results

1 presented, the FDA believes that Enterra should
2 remain an HDE device. We recommend continued
3 surveillance and will report our findings to the
4 Pediatric Advisory Committee in 2017.

5 Does the Pediatric Advisory Committee
6 agree with our conclusions and recommendations?

7 DR. HUDAK: Thank you. This is open for
8 discussion. Dr. Havens?

9 DR. HAVENS: It seems like this device
10 has been on the market for quite a long time, if I
11 understand what you said. Since 1999? And it's
12 got a humanitarian device exemption which means
13 that -- which I interpret to mean that finally
14 when it gets shown to be useful it will bump out
15 of this category as humanitarian use and actually
16 get into the real world of real use. Am I missing
17 something?

18 So then the question is, how long do you
19 have to show marginal or no benefit before you
20 stop being eligible for humanitarian use?

21 DR. PEIRIS: So, forever. You can
22 actually stay within the HUD/HDE system. As Dr.

1 Nelson mentioned earlier, the device has been
2 approved by the FDA. If the sponsor wishes to
3 consider another pathway, such as PMA, they can
4 certainly come to use for that reason. Unless
5 they begin to have use above the ADN there is no
6 current legislative regulatory authority that
7 forces a manufacturer to actually -- or a sponsor
8 to change out of the HUD HDE. The device is
9 approved and continues to be available for as long
10 as they would like within that pathway.

11 DR. HAVENS: Thank you very much.

12 DR. HUDAK: Dr. Hoehn?

13 DR. HOEHN: I have one question about
14 the two cases between April of 2015 to May of 2016,
15 about the two infection erosion cases. My two
16 questions related to those two cases were. Number
17 one, do we know if they had any comorbid
18 conditions that put them at risk, and do we know
19 what the interventions were for the erosion? Did
20 they have to have the thing removed? Do we know
21 what happened?

22 MS. RICKETTS: As far as I know, when I

1 was reviewing the MDRs I did not have information
2 that told me whether or not they had any
3 comorbidities that would have made them at risk
4 for that. I do believe that for the infections
5 they were -- the devices were usually treated with
6 aggressive antibiotics.

7 I think, if I remember right, there
8 might be one where they actually took the device
9 out and replaced it, but most often it was just
10 the aggressive antibiotic treatment. There really
11 wasn't any report of whether or not there was
12 resolution behind that. It was just that's the --
13 that was the treatment.

14 DR. HOEHN: Yes, specifically I wondered
15 if there were any long term negative effects to
16 the erosion? Because, presumably, you have to do
17 something more than antibiotics if it eroded
18 through the skin.

19 MS. RICKETTS: Right. With the erosion
20 cases, more often than that those leads that were
21 eroded were taken out and replaced. You know,
22 that was the only -- that's as far as they gave us

1 with what happened afterward.

2 DR. HOEHN: Okay.

3 MS. RICKETTS: As far as follow up.

4 DR. HUDAK: Dr. Anne?

5 DR. ANNE: With regards to the four
6 deaths that you saw there, you know, three of
7 which are progressive respiratory insufficiency.
8 Was that due to some other comorbidity or was that
9 associated with somehow or other with the Enterra
10 implantation?

11 MS. RICKETTS: The three deaths that
12 you're referring to were reported in the Islam et
13 al paper, and they provided very limited
14 information on those stats. The only information
15 that we have are that the three patients died of
16 progressive respiratory insufficiency. Two are
17 post lung transplant and one had severe cystic
18 fibrosis.

19 The paper also noted that Enterra had
20 provided relief of their GP symptoms prior to
21 their death. That's the only information that we
22 got.

1 DR. ANNE: Okay.

2 DR. HUDAK: Dr. Cunningham?

3 DR. CUNNINGHAM: Just one other quick
4 thing. So we've reviewed this a number of years
5 in a row and it's been fine. Remind me, do these
6 have to be reviewed annually? Is that our
7 mandate? Okay.

8 DR. HUDAK: Okay. Any other question?
9 Comments? If not, we can proceed to vote with the
10 buttons on the recommendation to continue the
11 present course with monitoring and reporting.

12 Okay. So I think we'll start, Dr.
13 Fischer, with you.

14 DR. FISCHER: Gwen Fischer. I concur.

15 DR. HAVENS: Peter Havens. I approve.

16 DR. TURER: Christy Turer. I concur.

17 DR. SHWAYDER: Shwayder. Approve.

18 DR. CNAAN: Avital Cnann. I concur.

19 DR. CATALETTO: Mary Cataletto. Concur.

20 DR. CAMPBELL: Jeff Campbell. Concur.

21 DR. CUNNINGHAM: Melody Cunningham.

22 Concur.

1 DR. HOEHN: Sarah Hoehn. Concur.

2 DR. DRACKER: Bob Dracker. I concur.

3 DR. WHITE: Michael White. Agree.

4 DR. WADE: Kelly Wade. Concur.

5 DR. ANNE: Premchand Anne. I concur.

6 DR. HUDAK: Okay. Recommendation is to
7 continue the current monitoring and reporting.

8 Thank you, Cathy.

9 I guess we come to the last presentation
10 of the day on the Elana surgical kit. We have
11 some new folk coming.

12 DR. ANDERSON-SMITS: Might just be me.

13 DR. HUDAK: Might just be you?

14 DR. ANDERSON-SMITS: Yes.

15 DR. HUDAK: Okay. You've got good back
16 up there. All right. So if it's just you, Colin,
17 you can get started.

18 DR. ANDERSON-SMITS: Last one and the
19 shortest, so you guys are in the home stretch.
20 Good afternoon. My name is Colin Anderson-Smits
21 and I'm the branch chief of Epidemiology, Office
22 of Surveillance and Biometrics at the Center for

1 Devices and Radiological Health. I'll be
2 presenting the annual update on the Elana Surgical
3 Kit.

4 Since the last PAC meeting a year ago,
5 there has been no reported sales or use of this
6 device within the U.S. There have been no MDRs
7 reported in the past year associated with Elana,
8 and there have been no peer review publications
9 studying the use of Elana that involved human
10 subjects since the last PAC meeting.

11 As a result, the FDA has identified no
12 new safety concerns since the last year's PAC
13 meeting. The FDA concludes that the probably
14 benefit risk profile of Elana for the pediatric
15 population continues to support the HDE. The
16 mandated post-approval study has been placed on
17 hold due to nonuse over the past few years within
18 the U.S.

19 The FDA will continue to monitor sales
20 and use, and should device use resume the mandated
21 post-approval study will be reinstated.

22 The FDA will continue surveillance and

1 report the following to the PAC in 2017, an
2 updated MDR review, an update of the mandated
3 post-approval study status, and results, should
4 the study be reinstated, and an updated literature
5 review.

6 The PAC will now be asked the following.
7 Does the committee agree with the FDA's conclusion
8 and proposed approach?

9 DR. HUDAK: So I do believe this is a
10 record.

11 DR. ANDERSON-SMITS: I did it last year
12 too.

13 DR. HUDAK: We did last year too? Okay.
14 Well, anyone have any questions, other than the
15 obvious, why?

16 DR. SHWAYDER: Why what?

17 DR. HUDAK: Why --

18 DR. ANDERSON-SMITS: Why is there no
19 use?

20 DR. HUDAK: Why are we discussing it?

21 DR. NELSON: The legislation says annual
22 review. We are in conversations about whether we

1 can develop flexibility in the device arena, but
2 those conversations are ongoing. But, basically,
3 the way the legislation was written is it requires
4 annual review by the PAC independent of the data
5 at this point.

6 DR. HUDAK: Dr. Nelson, if you have
7 devices like this that come up and there's
8 absolutely no use or activity --

9 DR. NELSON: I'm not saying it's
10 rationale. We're discussing whether there are
11 ways we can discuss some flexibility like we've
12 applied in drugs, but that's a continuing
13 conversation.

14 DR. HUDAK: So my question was, why is
15 there no use?

16 DR. ANDERSON-SMITS: Well, I'm not a
17 pediatric neurosurgeon, but I would say that hypho
18 bypass surgeries have just become obsolete. Most
19 of them are treated endovascular these days.

20 DR. PEIRIS: This is one of those key
21 issues in the pediatric populations and small
22 populations where when new therapy has come about,

1 even when a device is approved based off of
2 historical data, and the time that it takes to
3 collect that data, by the time of approval and
4 then marketing, whether that therapy still remains
5 the most optimal therapy. And others may have
6 already leap frogged about that therapy. So this
7 is a classic example of that.

8 DR. HUDAK: Okay. Just wanted to get
9 that in the record. Okay. So I think there are
10 probably no other questions. We will press the
11 buttons and go around the table.

12 DR. SHWAYDER: Show me the question one
13 more time on the slide before.

14 DR. HUDAK: It happened so quickly you
15 didn't take it in, I know.

16 Okay. We'll go around the table, and
17 Dr. Anne, you have the honors.

18 DR. ANNE: Premchand Anne. I concur.

19 DR. WADE: Kelly Wade. I concur.

20 DR. WHITE: Michael White. I agree.

21 DR. DRACKER: Bob Dracker. I concur.

22 DR. HOEHN: Sarah Hoehn. Concur.

1 DR. CUNNINGHAM: Melody Cunningham.

2 Concur.

3 DR. CAMPBELL: Jeff Campbell. Concur.

4 DR. CATALETTO: Mary Cataletto. Concur.

5 DR. CNAAN: Avital Cnaan. Concur.

6 DR. SHWAYDER: Tor Shwayder. I concur,
7 but I'd add if there's no more sales next year you
8 put it on some sort of suspension notice.

9 DR. ANDERSON-SMITHS: Can you repeat the
10 question? I'm sorry.

11 DR. SHWAYDER: I had said, if there's no
12 sales in the next year that you just put it on
13 suspension and not waste the committee's time with
14 it in the future.

15 DR. NELSON: We don't plan to. We have
16 options on mind.

17 DR. TURER: Christy Turer. Concur.

18 DR. HAVENS: Peter Havens. Concur.

19 DR. FISCHER: Gwen Fischer. Concur.

20 DR. HUDAK: Okay. So the summary for
21 this is that we agree with your continued
22 observation of a null set.

1 So we've come to the end of the meeting
2 we have done, I think, nine drugs and two
3 vaccines, and five devices, and heard a couple
4 other presentations. I think I would be remiss if
5 I didn't once again note that I think the process
6 of providing the information and interpreting it
7 and summarizing it by the FDA and the committee
8 has been superb once again, and very efficient
9 meeting and presentation, and thank the committee
10 for some unanticipated, but excellent insights
11 into some of these drugs and biologics.

12 So I think with that, Skip, you want to
13 have a final word? I think that Marieann might
14 have an announcement about some things for
15 tomorrow, transportation and all that. Just to
16 make sure.

17 DR. NELSON: Yes. I just wanted to
18 remind, for those of you who are members of the
19 committee and will be staying for the next two
20 days, I guess Euneka's meeting folks at 6:30.
21 Part of the reason for that is you're not getting
22 any special privileges to get through security,

1 and they won't -- you know, so you'll get in line
2 and we want to make sure you're in line in time to
3 actually get to the meeting room in time to start
4 the meeting. So that's why an early time. The
5 meeting starts at 8:00.

6 Just for those who are not invited, I
7 mean, just explain that so it's not like the in
8 crowd and, you know, you're not part of the in
9 crowd. This is a three committee meeting to look
10 at opioids. When there's three committees around
11 the table, generally, unless you have special
12 expertise in opioids they invite the regular
13 standing members of the committee and not those
14 who are invited as special SGEs for the purpose of
15 a specific drug or device review. So a number of
16 you are standing members of the committee, a
17 number of you are not, so that's what it's a
18 function of. It's not that we have, you know, the
19 cool kids and the uncool kids that we invite.
20 Just to explain that process in case you were
21 wondering.

22 But thank you very much for the day and

1 I think it's been a productive discussion.
2 Marieann, I don't know if there's anything else
3 you have to add?

4 DR. BRILL: Yes. I just want to say
5 please check your emails. Euneka has reserved a
6 van and the van will be downstairs tomorrow
7 waiting for you. Please be there no later than --
8 or please be there between 6:30 and 6:45 a.m.
9 Once you get into White Oak, Shivana and Sheila
10 will be waiting for you as well so that they can
11 show you where you're supposed to go.

12 So hopefully this will be a seamless
13 process. Thank you.

14 DR. HUDAK: So just to amplify, they say
15 that the van will depart exactly at 6:45 and there
16 is a \$30 roundtrip cost. They prefer cash. Just
17 forwarding.

18 Okay. So I think we're adjourned.
19 Thank you.

20 (Whereupon, at 4:23 p.m., the
21 PROCEEDINGS were adjourned)

22 * * * * *

1 CERTIFICATE OF NOTARY PUBLIC

2 COMMONWEALTH OF VIRGINIA

3 I, Carleton J. Anderson, III, notary
4 public in and for the Commonwealth of Virginia, do
5 hereby certify that the forgoing PROCEEDING was
6 duly recorded and thereafter reduced to print under
7 my direction; that the witnesses were sworn to tell
8 the truth under penalty of perjury; that said
9 transcript is a true record of the testimony given
10 by witnesses; that I am neither counsel for,
11 related to, nor employed by any of the parties to
12 the action in which this proceeding was called;
13 and, furthermore, that I am not a relative or
14 employee of any attorney or counsel employed by the
15 parties hereto, nor financially or otherwise
16 interested in the outcome of this action.

17

18 (Signature and Seal on File)

19 Notary Public, in and for the Commonwealth of
20 Virginia

21 My Commission Expires: November 30, 2016

22 Notary Public Number 351998

