



U.S. Food and Drug Administration

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of the Peripheral and Central Nervous
System Drugs Advisory Committee and the Drug Safety
and Risk Management Advisory Committee

Wednesday, November 3, 2010

8:03 a.m. to 4:29 p.m.

Hilton, Washington D.C./North Gaithersburg
The Ballrooms
620 Perry Parkway
Gaithersburg, Maryland

PRESENT:

Britt Anderson, M.D., Ph.D., Chair

Diem-Kieu H. Ngo, Pharm.D., BCPS, Designated Federal
Official

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PRESENT: (CONTINUED)

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PRESENT: (CONTINUED)

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1 P R O C E E D I N G S

2 (8:03 AM)

3 MS. NGO: Good morning. I would like to
4 first remind you to please silence your cell phones,
5 BlackBerry, and other devices if you have not already
6 done so. And please also place your BlackBerrys away
7 from the microphone, as that may interfere with the
8 audio system.

9 Is Ms. Aisha Eaton here, please? Our press
10 officer, again, when she arrives. I know she's
11 running a little bit behind.

12 MS. NGO: Dr. Anderson?

13 **Call to Order and Opening Remarks**

14 DR. ANDERSON: Good morning, everyone.
15 Thank you, all, for coming. It's a big meeting, so,
16 it's usually our custom to go around the table and
17 identify ourselves and our role on the committee and
18 sort of where we come from. So, could we start with
19 you, Dr. Twyman, since I can't read the sign but I
20 know who you are. Could you begin, please?

21 **Introductions**

22 DR. TWYMAN: Hi, my name is Roy Twyman. I'm

1 the industry rep. I'm with J & J.

2 DR. SNODGRASS: My name is Wayne Snodgrass.
3 I'm a pediatrician and clinical pharmacologist,
4 University of Texas.

5 MR. HOVINGA: Collin Hovinga, University of
6 Tennessee. I'm a pediatric neuropharmacologist.

7 DR. SOLOW: Brian Solow. I'm the medical
8 director at Prescription Solutions. We're a national
9 PBM with United Health Care for about 14 million
10 members across the country.

11 COMMANDER LEE: I'm Commander Michael Lee.
12 I'm with the Indian Health Service of the Public
13 Health Service with the National P & T Committee.

14 LTCOL SPRIDGEN: Good morning, I'm LtCol.
15 Stacia Spridgen. I'm the DoD representative, and I
16 serve as the DoD Pharmacoeconomics director.

17 DR. CAVAZOS: Jose Cavazos, University of
18 Texas Health Sciences Center in San Antonio and the VA
19 Center there.

20 DR. BALISH: Marshall Balish, Georgetown
21 University and Washington, D.C. Veterans' Hospital.

22 DR. SCHACHTER: Steve Schachter, an adult

1 neurologist, Beth Israel Deaconess Medical Center,
2 Harvard Medical School in Boston.

3 DR. ROGAWSKI: Michael Rogawski. I'm a
4 pharmacologist and neurologist. I'm professor of
5 Neurology at the University of California, Davis, in
6 Sacramento, California.

7 DR. CHAPMAN: I'm Kevin Chapman. I'm a
8 pediatric neurologist at Barrow Neurological Institute
9 in Phoenix, Arizona.

10 DR. PEARL: I'm Phillip Pearl. I'm division
11 chief of Child Neurology at Children's National
12 Medical Center in George Washington University School
13 of Medicine here in Washington.

14 MS. MARDER: Ellen Marder, neurologist,
15 Dallas VA.

16 DR. KHATRI: Pooja Khatri, neurologist,
17 University of Cincinnati.

18 DR. KINDLER: Dean Kindler, neurologist,
19 Kalamazoo, Michigan.

20 DR. LU: Ying Lu, biostatistician at Palo
21 Alto VA Medical Center.

22 DR. FOUNTAIN: Nathan Fountain at the

1 University of Virginia, where I'm a neurologist and
2 epileptologist.

3 MS. NGO: Commander Diem-Kieu Ngo,
4 designated federal official for this meeting.

5 DR. ANDERSON: Britt Anderson, I'm a
6 neurologist. I live in Waterloo, Ontario, Canada.

7 DR. GREEN: Mark Green, I'm a professor of
8 neurology and anesthesia at Mount Sinai School of
9 Medicine in New York.

10 DR. FRANK: Samuel Frank. I'm a neurologist
11 at Boston University, and I am the consumer
12 representative.

13 MS. KANDELL: Ellen Kandell. I'm a patient
14 representative, and by training, I'm a lawyer.

15 MR. WOODS: Mark Woods. I'm the clinical
16 pharmacy coordinator with Saint Luke's Hospital in
17 Kansas City, Missouri.

18 DR. COOPER: I'm Bill Cooper at Vanderbilt
19 University. I'm a pediatrician and a
20 pharmacoepidemiologist.

21 DR. WOLFE: Sid Wolfe. I'm an internist at
22 Public Citizen Health Research Group.

1 DR. NELSON: Lewis Nelson. I'm an emergency
2 physician, medical toxicologist from New York
3 University School of Medicine.

4 DR. HUFF: Steven Huff, emergency physician,
5 neurologist, University of Virginia.

6 DR. SILBERGLEIT: Robert Silbergleit,
7 Emergency Medicine, University of Michigan, and I do
8 status epilepticus clinical trials.

9 DR. NAIDECH: I'm Andrew Naidech. I'm a
10 neurology-based intensivist at Northwest University in
11 Chicago.

12 DR. VARELAS: Panayiotis Varelas. I'm a
13 neurologist and neuro-intensivist at Henry Ford in
14 Detroit, Michigan.

15 DR. SLEATH: I'm Betsy Sleath, professor and
16 chair of the Division of Pharmaceutical Outcomes and
17 Policy at the University of North Carolina.

18 DR. AVIGAN: Hi, I'm Mark Avigan in the
19 Office of Surveillance in Epidemiology at the FDA.

20 DR. HERSHKOWITZ: Norm Hershkowitz. I'm a
21 medical team leader in Division of Neurology Products
22 at the FDA.

1 DR. KATZ: I'm Russ Katz, director of the
2 Division of Neurology Products, FDA.

3 DR. TEMPLE: Bob Temple, director of the
4 Office of Drug Evaluation I.

5 DR. ANDERSON: Well, welcome to everyone
6 again. I have some remarks that I'm to read.

7 DR. ANDERSON: For topics such as those
8 being discussed at today's meeting, there are often a
9 variety of opinions, some of which are quite strongly
10 held. Our goal is that today's meeting will be a fair
11 and open forum for discussion of these issues, and
12 that individuals can express their views without
13 interruption. Thus, as a gentle reminder, individuals
14 will be allowed to speak into the record only if
15 recognized by the Chair. We look forward to a
16 productive meeting.

17 In the spirit of the Federal Advisory
18 Committee Act and the Government and the Sunshine Act,
19 we ask that the Advisory Committee members take care
20 that their conversations about the topic at hand take
21 place in the open forum of the meeting. We are aware
22 that members of the media may be anxious to speak with

1 the FDA about these proceedings. However, FDA will
2 refrain from discussing the details of this meeting
3 with the media until its conclusion. Also, the
4 committee is reminded to please refrain from
5 discussing the meeting topic during breaks or at
6 lunch.

7 Thank you.

8 **Conflict of Interest Statement**

9 COMMANDER NGO: I will now read the meeting
10 statement.

11 The Food and Drug Administration is
12 convening today's meeting of the Peripheral and
13 Central Nervous System Drugs Advisory Committee and
14 the Drug Safety and Risk Management Advisory Committee
15 under the authority of the Federal Advisory Committee
16 Act of 1972. With the exception of the industry
17 representative, all members and temporary voting
18 members of the committees or special government
19 employees or regular federal employees from other
20 agencies and are subject to Federal Conflict of
21 Interest Laws and regulations.

22 The following information on the status of

1 this committees' compliance with Federal Ethics and
2 Conflict of Interest laws covered by, but not limited
3 to, those found at 18 U.S.C. Section 208 and Section
4 712 of the Federal Food, Drug, and Cosmetic Act is
5 being provided to participants in today's meeting and
6 to the public.

7 FDA has determined that members and
8 temporary voting members the committees are in
9 compliance with Federal Ethics and Conflict of
10 Interest laws. Under 18 U.S.C. Section 208, Congress
11 has authorized FDA to grant waivers to special
12 government employees and regular federal employees who
13 have potential financial conflicts when it is
14 determined that the agency's need for a particular
15 individual's services outweighs his or her potential
16 financial conflict of interest.

17 Under Section 712 of the FD and C Act,
18 Congress has authorized FDA to grant waivers to
19 special government employees and regular federal
20 employees with potential financial conflicts when
21 necessary to afford the committee essential expertise.

22 Related to the discussion of today's

1 meeting, members and temporary voting members of these
2 committees have been screened for potential financial
3 conflicts of their own, as well as those imputed to
4 them, including those of their spouses or minor
5 children and for purposes of 18 U.S.C. Section 208,
6 their employers. These interests may include
7 investments, consulting, expert witness testimony,
8 contracts, grants, CRADAs, teaching, speaking,
9 writing, patents and royalties, and primary
10 employment.

11 At today's meeting, the committees will
12 discuss a number of safety concerns with intravenous
13 administration of the anti-seizure drugs Phenytoin and
14 Fosphenytoin, including the condition known as Purple
15 Glove Syndrome and recommending with regulatory
16 actions, if any, are necessary to diminish the risk.

17 This is a particular matter's meeting during
18 which specific matters related to Phenytoin and
19 Fosphenytoin will be discussed. To ensure
20 transparency, we encourage all standing committee
21 members and temporary voting members to disclose any
22 public statements that they have made concerning the

1 products at issue.

2 With respect to FDA's invited industry
3 representative, we would like to disclose that Dr.
4 Roy Twyman is participating in this meeting as a non-
5 voting industry representative, acting on behalf of
6 regulated industry. Dr. Twyman's role at this meeting
7 is to represent industry in general and not any
8 particular company. Dr. Twyman is employed by Johnson
9 & Johnson.

10 We would like to remind members and
11 temporary voting members that if the discussions
12 involve any other products or firms not already on the
13 agenda for which an FDA participant has a personal or
14 imputed financial interest, the participants need to
15 exclude themselves from such involvement, and their
16 exclusion will be noted for the record. FDA
17 encourages all participants to advise the committees
18 of any financial relationships that they may have with
19 the firms that make the products at issue.

20 Thank you.

21 DR. ANDERSON: At this point, we're going to
22 have a series of presentations from the FDA, and Dr.

1 Katz is going to introduce the presentations.

2 **Award Presentation in Recognition of Distinguished**
3 **Service**

4 DR. KATZ: Thanks very much, Dr. Anderson,
5 and welcome to everybody.

6 Actually, we're going to deviate from the
7 agenda. This is unknown to you, Dr. Anderson. Just
8 briefly because three of our PCNS Advisory Committee
9 members are rotating off the committee in the very
10 near future and this is the last meeting that they
11 will attend under the auspices of the Division of
12 Neurology Products with whom they have worked very
13 closely. Because we don't pay you very much, we want
14 to at least publicly acknowledge your service, and
15 it's a great service, it's a great help to us and to
16 the country, really. That's why we're here, and it's
17 hard to be an Advisory Committee member. You give up
18 time away from home and other work obligations, and
19 we've been increasingly taking issues at the
20 committee.

21 So, there have been more meetings recently,
22 and Advisory Committee members have to answer tough

1 questions publicly, which is not so easy and, in fact,
2 sometimes, it's quite courageous when it's an
3 unpopular position. So, we did want to very much
4 thank you for your service, and the three members who
5 are rotating off are Dr. Anderson, who, in particular,
6 has served as chair of the committee for the last
7 little while, and that's a particularly thankless task
8 and difficult at times, but he's done it remarkably
9 well.

10 So, the three folks who are rotating off in
11 January are Dr. Anderson, Dr. Green, and Dr. Lu, all
12 of whom, over the years, have really provided
13 excellent advice, thoughtful advice, and have really
14 been terrific to the division, and, again, to the
15 public who we serve.

16 So, let me just read. I think probably the
17 plaques all say the same thing except for the names,
18 of course.

19 (Laughter.)

20 DR. KATZ: So, let me present the first one
21 to Dr. Green, and it says, you can't see this, "The
22 Advisory Committee Service Award presented to Mark

1 Green, M.D., in recognition of distinguished service
2 to the people of the United States of America," and I
3 think that's accurate. That's very accurate. So, Dr.
4 Green.

5 (Presentation and Applause.)

6 DR. KATZ: And, for Dr. Lu, the same thing,
7 "in recognition of distinguished service to the people
8 of the United States of America." Thank you very
9 much.

10 (Presentation and Applause.)

11 DR. KATZ: And last, but certainly not
12 least, to Dr. Anderson, who actually works in Canada,
13 but we thank you for your service to the people in the
14 United States.

15 (Laughter.)

16 (Presentation and Applause.)

17 **FDA Introductory Remarks**

18 DR. KATZ: All right. Well, let me start.
19 First of all, thanks, everybody, for coming. You can
20 see we have a particularly large group. This is a
21 combined meeting of the Peripheral and Central Nervous
22 System Advisory Committee and the Drug Safety

1 Committee, but, as you know, we have supplemented the
2 committee today with many, many experts who bring a
3 wealth of expertise in many of the areas that we think
4 are relevant for discussing today's question. So, we
5 thank you all very much. We really appreciate your
6 time and your effort.

7 Let me state at the outset why we are here
8 primarily. We, of course, have included a list of
9 questions that we would like you to vote on at the end
10 and some to discuss and to vote on, but really, the
11 primary reason we've asked you to come here today is
12 to address the question of whether or not it's
13 appropriate to continue the marketing of intravenous
14 Phenytoin, and let me just say at the outset because I
15 will lapse and refer to Phenytoin and not intravenous
16 Phenytoin through the course of the day, I'm sure.

17 We are talking only about intravenous
18 Phenytoin, unless we otherwise talk about it, we don't
19 mean the oral product. We are really focusing on the
20 intravenous product. And the question of the
21 propriety of continuing to market intravenous
22 Phenytoin came to us actually from the outside from at

1 least initially an eminent epileptologist asked us why
2 we should continue to market Phenytoin, given its
3 association with some particularly serious
4 complication.

5 In particular, Purple Glove Syndrome, when,
6 in fact, a drug which is essentially a substitute for
7 Phenytoin, Fosphenytoin, was on the market and was at
8 least believed at the time not to be associated with
9 Purple Glove Syndrome. So, let me just give you a
10 little bit of the relevant background to the main
11 issue that we want you to discuss. And I'll say at the
12 outset that everything I mention, I'm just going to
13 briefly touch on some of the main issues, but
14 everything that I'm going to talk about is going to be
15 discussed in considerably more detail by the
16 subsequent agency presenters.

17 So, just to go back from a point of view of
18 regulatory history, intravenous Phenytoin was approved
19 in 1956 and was at the time and is still approved for
20 the control of grand mal status epilepticus and the
21 prevention and treatment of seizures occurring during
22 neurosurgery. And over the years, its use has been

1 associated with numerous serious adverse events.
2 Again, most notably, arrhythmias, hypotension, and, in
3 particular, Purple Glove Syndrome.

4 So, Purple Glove Syndrome, the definition,
5 as you know, vary considerably, but basically, it's
6 considered to consist at least of sort of a clinical
7 triad of pain, swelling, and discoloration. Typically
8 in the limb in which it is administered. So,
9 typically, the symptoms emerge in a few hours after
10 administration, and they progress distally, in
11 particular over the next day or so, and then in the
12 typical case, over time, the symptoms resolve.

13 In some cases though, there are
14 complications and surgical procedures may be
15 necessary, including debridement and fasciotomies and
16 even as far as we know in rare cases, amputations.
17 So, just to give you an idea, I'm just going to show
18 you a few slides of purported cases of Purple Glove
19 associated with IV Phenytoin. You can see the
20 symptoms are primarily in the digits. It may be very
21 difficult to see here, but you can clearly see--well,
22 maybe you can't clearly, but this is clearly

1 discolored and swollen, and I guess maybe it's not
2 coming out too clear. It's hard for me to see from
3 here, but, again, a very swollen, very discolored
4 significant complication.

5 So, those are some cases, but, of course, it
6 can be milder, as well. The etiology of Purple Glove
7 is not really known. It's not know for a fact that
8 it's due to extravasation of the administered drug,
9 although, that's certainly one theory. There is a
10 belief that certain aspects of the Phenytoin product
11 itself, in particular, it contains propylene glycol,
12 which is considered possibly to be acting here, and it
13 has a very high pH. The pH is 12. And those together
14 are considered to contribute to the occurrence of PGS,
15 although, again, none of that is known for sure.

16 Fosphenytoin is a phosphate prodrug of
17 Phenytoin. It was approved for marketing in 1996, and
18 it's approved for the same indications as Phenytoin,
19 and, in addition, it's also approved for use in those
20 occasions when other means of Phenytoin administration
21 are not possible, in particular, oral.

22 When the two products are given at the

1 appropriate rates, Fosphenytoin produces essentially
2 identical free Phenytoin levels as does IV Phenytoin,
3 and, in fact, Fosphenytoin was approved on the basis
4 of a showing of bioequivalence to Phenytoin, and there
5 were no controlled trials of Fosphenytoin. As far as
6 I know, there haven't been.

7 Because Fosphenytoin has a lower pH, which
8 is somewhere between eight and nine and does not
9 contain propylene glycol, it was believed at the time
10 it was approved that it might not be associated with
11 some of the serious complications, in particular
12 Purple Glove Syndrome that are associated with IV
13 Phenytoin, but there was no real data that spoke to
14 that question at the time. It is worth noting though
15 that when Fosphenytoin was approved, there was no
16 statement placed in labeling about Purple Glove
17 Syndrome. It was silent on the case, whereas that
18 language describing the occurrence of Purple Glove
19 Syndrome does appear in the Phenytoin label.

20 So, we thought that in order to adequately
21 consider the primary question of whether or not IV
22 Phenytoin should stay on the market, that it was

1 important to compare before we asked you to make a
2 decision about that or advise us about that, it was
3 important to compare the pluses and minuses of both
4 drugs across the entire spectrum of toxicities that
5 they can cause and not just focus in on Purple Glove
6 because these drugs do other things.

7 So, the first thing we did is try to call
8 our databases to see how many cases there were of
9 Purple Glove with Phenytoin or at least how many cases
10 reported, how many cases, if there were any,
11 associated with Fosphenytoin. So, agency staff looked
12 at the post-marketing spontaneous Adverse Event
13 Reporting System, AERS, to see if we had cases for
14 either, looked at the literature to see what the
15 literature--said about this, and we had also asked
16 Pfizer to do their own assessment of the issue, and
17 Pfizer is the manufacture of Cerebyx, which is brand-
18 name Phenytoin. Currently, both products are marketed
19 by multiple generic companies.

20 So, regarding the literature, there are
21 numerous of case reports of Purple Glove Syndrome in
22 the literature associated with IV Phenytoin and there

1 numerous reports of studies looking at this question
2 with IV Phenytoin using various methodologies. And,
3 again, you'll hear more about these later.

4 The literature, depending upon the
5 definition used and the type of studies that were done
6 yields estimates of the incidents of Purple Glove of
7 somewhere between zero to 6 percent or so with rates
8 of complications, serious sequelae of somewhere
9 between zero and 0.7 percent.

10 As far as we can tell, there are no
11 literature reports related to the occurrence of Purple
12 Glove Syndrome with Fosphenytoin, either case reports
13 or studies of any kind that are reported and
14 associated with Fosphenytoin. In our spontaneous
15 reporting system, in the AERS System, there are a
16 little over 40 cases of PGS that can reasonably be or
17 potentially be associated with the use of IV
18 Phenytoin, and you'll hear more about what case
19 definition was used to generate these numbers.

20 There were four possible cases in AERS of
21 Fosphenytoin-related PGS cases. There were another
22 four in AERS that didn't really meet the definition,

1 but that appeared to be possibly serious cases. Some
2 of them were treated with Silvadene cream, which is
3 used to treat burns. So, and the sponsor identified
4 in another case that we didn't have. There were nine
5 possible cases of Fosphenytoin-associated PGS. One of
6 the presumed Fosphenytoin cases did require
7 debridement.

8 Of course, these are spontaneous reports.
9 There are many vagaries associated with trying to
10 interpret the data, not the least of which is the fact
11 that many of these cases are incompletely described.
12 So, it's very difficult to necessarily in any given
13 case or in many of these cases to determine whether or
14 not we really think it is a case, and then attributing
15 causality is always an issue. It's very difficult to
16 actually know much about the actual incidents.

17 We know there's underreporting, and it's
18 very difficult to make comparisons of incidences, even
19 if you think there are cases with Fosphenytoin between
20 the two drugs because of many reasons, at the least
21 which is Phenytoin has been on the market since 1956.
22 Fosphenytoin has been on the market only since 1996,

1 and many other reasons. So, but I think a primary
2 task we will ask you to address is whether or not you
3 think that there are bona fide cases for Purple Glove
4 Syndrome with Fosphenytoin, and then if you think
5 there are, to at least try to grapple with the
6 question of whether or not there's anything we can say
7 about the relative incidents between the two products.

8 So, as I say, we think it's important when
9 considering the primary question to examine not just
10 the incidents of Purple Glove, but also, the full
11 panoply of other toxicities associated with each.
12 You'll hear again more about this, but we have looked
13 through our AERS Database, and it seems as if the
14 array, the type of adverse events that occur, serious,
15 significant adverse events that occur are pretty much
16 the same with Fosphenytoin and Phenytoin, and, again,
17 you'll hear more about that. But again, it's very
18 difficult to try to figure out what the true
19 comparative rates of those things are.

20 There are other problems that we have seen
21 with both of these drugs over the years. In
22 particular, both products are associated with

1 medication errors although they come from very
2 different causes. In Fosphenytoin, we've seen dosing
3 errors related to two main reasons. One had to do
4 with misreading of the label on the vial so that folks
5 thought there was much less drug in a vial than there
6 really was, and so, this has led to massive overdoses
7 and even some deaths, particularly in pediatrics.

8 Another type of dosing error is related to
9 how Fosphenytoin is to be prescribed, and it's to be
10 prescribed in milligrams of Phenytoin equivalence.
11 It's an extraordinarily unusual way to express the
12 potency of a drug, or mg PE, as it's referred to, and
13 we did that when it was approved because to obviate
14 the need to make some complicated, molecular, weight-
15 based dosing when switching from Phenytoin dose and
16 dosing with Phenytoin is well-known, to Fosphenytoin,
17 so, 1 mg of Phenytoin is equal to 1 mg of Phenytoin
18 equivalent for Fosphenytoin. We thought that would
19 make things much easier for prescribers, but it has
20 led to confusion over the years and many reports of
21 dosing errors.

22 Over time, we have attempted to address both

1 of these issues with changes in labeling, for example,
2 on the vial as well as product labeling to inform
3 people how better to dose and the incidents of these
4 events has dropped considerably, although for the
5 errors related to the mg PE issue, there are still
6 some reports. In the recent years, there have been no
7 reports of overdoses due to misreading the label on
8 the vial. No reports. That doesn't mean it isn't
9 happening, but we've tried to get a handle on those
10 through making various changes.

11 There have also been medication errors with
12 Cerebyx related to the name and confusion between
13 Cerebyx and Celebrex. There have also been dosing
14 errors with Phenytoin, including errors related to the
15 intravenous administration of oral suspension of
16 Phenytoin. There is no oral suspension available for
17 Fosphenytoin. So, that sort of thing can't happen
18 with Fosphenytoin.

19 And also, errors related to using
20 inappropriate infusion rate. So, that happens with
21 Phenytoin. And there are other differences between
22 the products. I'm just going to briefly go through

1 some of them that we think are relevant if we're
2 trying to make a fair comparison of the two products.

3 And supporting the use of Phenytoin, it's
4 worth nothing that Fosphenytoin needs to be
5 refrigerated and Phenytoin doesn't. So, this may have
6 implications for the use in many settings, perhaps
7 especially in the settings in which the treatment has
8 to be available immediately, let's say on crash carts
9 or in ambulances. So, that's something to consider.

10 Phenytoin labeling includes recommendations
11 for pediatric dosing, including down to infants. The
12 labeling is very old and it's not entirely clear where
13 those dosing recommendations came from, but they are
14 in labeling and they're paid attention to.

15 Fosphenytoin is used widely in the pediatric
16 population, but there are no dosing recommendations in
17 the label for pediatric patients in Fosphenytoin.
18 We've looked at the data on pediatric dosing, and it's
19 very variable. We don't think that we can actually
20 write valid dosing recommendations for pediatric
21 population for Fosphenytoin. But, again, as I say,
22 it's used widely in pediatric patients.

1 There is also a current shortage of
2 Fosphenytoin, and so, the possibility of a shortage of
3 one or the other products, in this case, an actual
4 shortage is another factor that we might want to
5 consider when we're evaluating the question of whether
6 or not one product ought to come off the market.

7 And it's also worth noting that at least
8 when it was approved; Fosphenytoin was much more
9 expensive than IV Phenytoin. That's changed
10 considerably. They are now more or less equally
11 priced, undoubtedly related to the appearance of
12 generics. And again, you'll see all of this data in
13 more detail.

14 And there are several considerations that
15 favor an increased use of Fosphenytoin compared to
16 Phenytoin. Fosphenytoin can be used with most
17 standard intravenous fluids. Phenytoin can't be given
18 with commonly-given dextrose solutions. It's given
19 through a filter. Fosphenytoin can be given
20 intramuscularly, although the label for IV Phenytoin
21 talks about intramuscular administration, I think it's
22 generally considered to be an inappropriate route of

1 administration.

2 There is this view out there that one of the
3 advantages of Fosphenytoin is that it can be given
4 faster than Phenytoin, and this is apparently an
5 advantage, and it's technically true. You can
6 actually infuse it faster than you can infuse
7 Phenytoin, but given the identical plasma
8 concentration time curves of the two when they are
9 given at an appropriate infusion rate, we have no
10 reason to expect that the onset of action will be any
11 different with those two infusion rates. So, the fact
12 that technically it can be given faster doesn't
13 necessarily imply that it will work faster than
14 Phenytoin.

15 Phenytoin is used to treat numerous off-
16 label conditions. We don't hear too much about the
17 off-label use of Fosphenytoin, but, again, given the
18 essentially identical plasma concentration time curves
19 of the two products, there is no reason to believe
20 that where Phenytoin works, Fosphenytoin wouldn't.

21 So anyway, those are sort of the major
22 issues I think we'll touch on today, and again, you'll

1 hear much more about them starting in a minute.

2 I just wanted to say also, we have a
3 somewhat unusual aspect of the program that is not
4 only FDA presenters, but we have asked two academic
5 folks to come and sort of give a point/counterpoint.
6 So, we're very happy to have today with us Dr. William
7 Coplin of Wayne State and Dr. Thomas Bleck of Rush
8 Medical College, who will present respectively the
9 case for keeping Phenytoin on and removing Phenytoin
10 from the market. I should say that the order of their
11 presentations was determined by coin toss.

12 (Laughter.)

13 DR. KATZ: So anyway, we're looking forward
14 to your input on these issues. As I say, we've
15 outlined the issues that we would like you to talk
16 about. If there are any other issues obviously that
17 you feel are relevant that we have not brought up,
18 please, of course, we want to hear about those, as
19 well.

20 So again, with that, let me thank you for
21 the work you've done in preparing and for the work
22 you're about to do today. And, with that, I'll turn

1 it back to Dr. Anderson.

2 DR. ANDERSON: Well, actually, I think it's
3 now for the continuation of your FDA presenters. And,
4 so, now we'll have Dr. Grace Chai. Thank you very
5 much.

6 **FDA Presentations:**

7 **Utilization Patterns of Fosphenytoin and IV Phenytoin**
8 **in the U.S., Years 2004-2009**

9 DR. CHAI: Good morning. My name is Grace
10 Chai, and I am with the Division of Epidemiology in
11 the Office of Surveillance and Epidemiology. Today I
12 will be presenting the utilization patterns of
13 Fosphenytoin and IV Phenytoin in the U.S. years 2004
14 to 2009.

15 The following is an outline of my
16 presentation. My objective today is to describe the
17 extent of Fosphenytoin and IV Phenytoin use in the
18 U.S. from years 2004 to 2009. I will do so using
19 sales data as well as inpatient data in terms of
20 utilization and hospital characteristics followed by
21 limitations and conclusions.

22 First, I will present the sales data. Sales

1 data for this presentation were obtained from IMS
2 Health, IMS National sales perspectives.

3 IMS Health measures the volume of products
4 sold from manufacturers to retail and non-retail
5 channels of distribution. These data can be used to
6 determine the distribution of products to settings of
7 care. In year 2009, 99 percent of IV Phenytoin and
8 Fosphenytoin vials were distributed to non-retail,
9 pharmacy settings, primarily to inpatient, non-federal
10 hospitals. Assuming that facilities purchase
11 according to use, these sales data may be utilized as
12 a surrogate for use, however, it is not a direct
13 estimate of use.

14 The following figure shows the number of
15 vials sold for Fosphenytoin and IV Phenytoin from
16 years 2004 to 2009. Sales of IV Phenytoin have
17 decreased from 5.3 million vials in year 2004 to 3
18 million vials in year 2009, while Fosphenytoin sales
19 have slightly increased from 2.1 million vials sold in
20 2004 to 2.3 million vials sold in 2009.

21 The following is a figure showing the
22 average cost of vial sold for Fosphenytoin and IV

1 Phenytoin during the years 2004 to 2009. During that
2 period, the average cost per vial Fosphenytoin fell
3 from \$29.49 to \$2.61, while the average cost per vial
4 of IV Phenytoin remained relatively stable. Generic
5 Fosphenytoin was approved in August 2007, coinciding
6 with the decreasing costs.

7 Here are the proportion of vial sales by
8 manufacturer of Fosphenytoin and IV Phenytoin for the
9 most current year to date, January 2010 to August
10 2010. Hospira sold the largest proportion of
11 Fosphenytoin, while the majority of IV Phenytoin was
12 sold by Westward. Cerebyx, a Pfizer product marketed
13 by Eisai accounted for 1 percent of the market share
14 of Fosphenytoin in the most current year to date.

15 Next, I will present the inpatient data
16 analyses of Fosphenytoin and IV Phenytoin. The two
17 databases utilized for these analyses were Premier
18 RxMarket Advisor for the inpatient utilization data
19 and SCI inpatient health care utilization systems for
20 the hospital characteristics data.

21 Premier RX Market Advisor is an inpatient
22 health care utilization database that provides data on

1 all patients from about 590 acute, short-stay, non-
2 federal hospitals in the U.S. The data are abstracted
3 from hospital discharge billing data. The data
4 include drugs used, patient demographics, diagnoses,
5 and procedures. The inpatient utilization data on
6 pediatric patients are from a subset of 37 children's
7 hospitals within Premier's network. The data are
8 nationally projected; however, national projections
9 for pediatric use are not available and are presented
10 as unprotected numbers. Additionally, emergency room
11 data was not available in the analysis of Premier
12 data.

13 This figure shows the projected number of
14 discharges for IV medications billed for discharges
15 with the primary diagnosis of status epilepticus.
16 It's for the years 2004 to 2009. IV lorazepam was the
17 most common IV medication billed on inpatient
18 discharge records for status epilepticus among the
19 selected IV medications. The number of discharges
20 billed for Fosphenytoin with the diagnosis of status
21 epilepticus increased over IV Phenytoin from years
22 2007 to 2009 to become the second most commonly-billed

1 medication with this diagnosis code in year 2009.

2 This figure shows the nationally-projected
3 number of discharges in unique patients with the
4 hospital billing for Fosphenytoin and IV Phenytoin
5 regardless of diagnosis from years 2004 to 2009. Over
6 the study period, Fosphenytoin use increased 6 percent
7 from 197,000 discharges to 210 while IV Phenytoin use
8 decreased 46 percent from 275,000 to 149,000
9 discharges. Trends in the projected number of unique
10 patients reflected trends in discharges.

11 This figure shows the actual un-projected
12 number of inpatient discharges within the Premier
13 network of hospitals with the billing for a
14 Fosphenytoin and IV Phenytoin by patient age from
15 years 2004 to 2009. Un-projected data was analyzed
16 due to the stratification of data by patient age.
17 National projections for pediatric use are currently
18 unavailable in the Premier database.

19 Patient age 17 to 64 years accounted for the
20 majority of discharges for both products, followed by
21 patients aged 65 years and older. There was a shift
22 in utilization in patients 17 years and older from

1 majority IV Phenytoin use to Fosphenytoin use from the
2 year 2007 to 2008. However, use of Fosphenytoin
3 accounted for the majority of use in the pediatric
4 population age zero to 16 years throughout the examine
5 time period.

6 This figure shows the proportion of
7 pediatric discharges with the hospital billing for
8 Fosphenytoin and IV Phenytoin by patient age for year
9 2009. Of the pediatric population, the greatest
10 proportion of discharges for Fosphenytoin and IV
11 Phenytoin were for patients aged 3 to 12-years-old in
12 year 2009. Patients aged zero to 1 month accounted
13 for 8 percent of pediatric Fosphenytoin discharges and
14 19 percent of IV Fosphenytoin discharges in year 2009.
15 Although these pie charts show the proportional use
16 within the pediatric population by product, the actual
17 numbers of discharges were higher for Fosphenytoin
18 than IV Phenytoin in the pediatric population as seen
19 in the previous graph.

20 Another inpatient database SDI in patient
21 health care utilization system was utilized to
22 describe the characteristics of hospitals reporting

1 use of Fosphenytoin and IV Phenytoin. The inpatient
2 data from SDI were found to be comparable to inpatient
3 data from Premier; however, SDI includes data on
4 emergency room discharges, which was not included in
5 the analysis from Premier.

6 SDI's data source is Hospital Charge
7 Master/Charge Data Master. This database provides
8 data from over 600 hospitals representing acute care,
9 short-term hospital inpatient sites and their
10 associated hospital emergency departments. There were
11 over 7 million annual hospital inpatient encounters
12 and over 60 million outpatient encounters, including
13 ED visits. The database includes information on data
14 similar to the inpatient data previously described for
15 Premier's database. SDI's datasets are geographically
16 representative.

17 These figures show the proportion of
18 discharges for Fosphenytoin and IV Phenytoin by the
19 location of a hospital setting where the drug was
20 billed for year 2009. Analysis of discharges by
21 location of service showed that intensive care units
22 followed by general inpatient units were the most

1 common locations of service for both products. There
2 was also comparable use of both products in the ER at
3 4 percent and 3 percent. These figures illustrate
4 similar patterns of use of Fosphenytoin and IV
5 Phenytoin within the hospital setting.

6 This figure represents the proportion of
7 hospitals reporting use of IV Phenytoin alone,
8 Fosphenytoin alone, or the use of both products. The
9 majority of hospitals report a utilization of both
10 products at their facilities in year 2009.

11 These figures show the projected number of
12 discharges for Fosphenytoin and IV Phenytoin by
13 hospital characteristics for year 2009. The figure on
14 the left shows a number of discharges by drug, by the
15 bed size of the hospital, while the figure on the
16 right shows discharges by hospitals with pediatric
17 and/or NICU units. These figures illustrate
18 comparable use of Fosphenytoin and IV Phenytoin by
19 these hospital characteristics.

20 This figure shows utilization by geographic
21 region of the hospital. There was a difference in the
22 magnitude of use by geographic region with greater IV

1 Phenytoin use in the mid-Atlantic region and greater
2 Fosphenytoin use in the southwest central regions.
3 However, these findings illustrate that, in general,
4 there is use of both products regardless of geographic
5 region.

6 Some of the limitations of the data
7 presented were that the inpatient utilization data
8 from Premier did not include use in emergency
9 department. However, ER data was presented in the
10 hospital characteristics portion of my presentation.
11 Inpatient analysis by patient age may not be
12 nationally representative, especially among the
13 pediatric population as the data is only available as
14 un-projected numbers from a subset of hospitals.

15 In conclusion, there has been a general
16 decrease in the use of IV Phenytoin and an increase in
17 Fosphenytoin use during the examine time. The cost of
18 Fosphenytoin may be a major contributor to the changes
19 in use trends. Fosphenytoin has accounted for the
20 majority of use in the pediatric population throughout
21 the examined time. No major differences were found in
22 the locations or hospital characteristics for the use

1 of Fosphenytoin or IV Phenytoin. The majority of
2 hospitals report a utilization of both Fosphenytoin
3 and IV Phenytoin.

4 Thank you.

5 DR. ANDERSON: Thank you very much. We have
6 time to ask clarifying questions to the agency after
7 all the presentations have been done. So, we can move
8 to the next one, which is from Dr. Jasmine Gatti.

9 **Broad Profile of Adverse Events:**

10 **Fosphenytoin Versus IV Phenytoin**

11 DR. GATTI: Good morning. My name is Dr.
12 Jasmine Chen Gatti. I'm a medical reviewer in the
13 Division of Pharmacovigilance. This is a general
14 presentation entitled "Broad Profile of Adverse Events
15 Excluding Purple Glove Syndrome: Fosphenytoin versus
16 IV Phenytoin," and compares the safety of these two
17 drugs for adverse events.

18 This is not intended to be a comprehensive
19 and detailed survey of the current adverse event
20 profile of Fosphenytoin and IV Phenytoin. Rather, its
21 intent is to highlight the review of AERS data of
22 these two drugs and highlight and sample the different

1 venues of current clinical use.

2 Questions can be addressed specifically to
3 the reviewer listed in the next slide as the Office of
4 Surveillance and Epidemiology, abbreviated OSE,
5 presentations proceed this morning. Purple Glove
6 Syndrome will be abbreviated as PGS.

7 This is an outline of the topics covered in
8 my presentation. Much of it sets the backdrop for the
9 other presentations to follow. The reviewers listed
10 beside each topic can provide details, if needed. It
11 includes drug properties, which Dr. Dimova (sic) can
12 address in detail. Current approved labeling,
13 spontaneous reporting, published literature, clinical
14 considerations, and conclusions.

15 I will provide more detail in the AERS
16 database for the non-PGS adverse events and published
17 literature about clinical use of both drugs.

18 Let's begin with drug properties. This
19 slide offers a side-by-side comparison of Fosphenytoin
20 and IV Phenytoin's drug properties. It's important to
21 keep in mind that drug properties influence clinical
22 safety. Let's talk about IV Phenytoin first. It's

1 very alkaline pH at 12, may cause local skin
2 irritation and possible tissue necrosis. It also
3 causes difficulty in preparation and administration of
4 the drug. For instance, since IV Phenytoin is not
5 compatible with most IV fluids, including dextrose,
6 propylene glycol was added to increase its solubility.
7 The propylene glycol, in turn, was thought to be the
8 culprit in causing CV, or cardiovascular and
9 hypotensive adverse events, but what you will see is
10 that it's not the only possible causative agent of
11 cardiovascular events, which will be simplified as CV
12 events throughout the rest of the talk.

13 Historically, in attempts to reduce these
14 complications, Fosphenytoin was developed at a lower
15 pH of 8.6 to 9.0, making a less locally irritating as
16 a prodrug of Phenytoin and a disodium phosphate ester
17 is more water-soluble and compatible with IV fluids,
18 making filters flushes and slow infusion rates less
19 essential.

20 Other features to bear in mind is that the
21 active pharmacologic agent of both products is
22 Phenytoin. Phenytoin is a sodium channel blocker that

1 can lead to cardiac irritability. So, it's not
2 surprisingly that both Fosphenytoin and IV Phenytoin
3 have cardiovascular AEs. IV Phenytoin's embedded use
4 as an anti-seizure medication since 1956, and its use
5 as a Class 1AB anti-arrhythmic drug, according to the
6 Vaughan-Williams classification, puts it in the same
7 class as Lidocaine.

8 Now let's talk about Fosphenytoin.
9 Initially, Fosphenytoin was touted as having less
10 cardiovascular and hypotensive toxicity. Fosphenytoin
11 is the prodrug, and unbound, Phenytoin is the active
12 moiety. The half life of Fosphenytoin's conversion is
13 7 to 15 minutes. No drug is known to effect its
14 conversion to Phenytoin. Fosphenytoin is highly bound
15 to plasma protein and displaces Phenytoin from its
16 protein-binding sites. Fosphenytoin also during this
17 competitive displacement fluctuates and make
18 increased, unbound Phenytoin up to about 30 percent.
19 Monitoring of both drugs is based on free plasma
20 Phenytoin levels.

21 Now we are going to discuss labeling. Now,
22 this slide shows key features in approved labeling.

1 Labeling reveals very little specific information
2 about dosing for pediatrics. There's a warning for IV
3 Phenytoin in neonates. It states that the rate of
4 administration is not to exceed 1 to 3 mg/kg, but,
5 otherwise, for Fosphenytoin, there's no mention of
6 stratification of age with dose. It's not approved
7 for children. No extensive pediatric nor geriatric
8 studies have been performed. One small pediatric
9 study found no signal of difference in concentration
10 type profile from adults. In the geriatric
11 population, doses may be lowered to avoid toxicity.

12 Both drugs are used for status epilepticus
13 or SE, and in the treatment of prevention of seizures
14 in neurosurgical patients. Specifically, Fosphenytoin
15 is indicated for a short-term limited five days, used
16 when IV Phenytoin is unavailable, inappropriate, or
17 less advantageous. It can substitute for oral
18 Phenytoin in SE patients.

19 Dosing for age in Fosphenytoin is in mg PE
20 or Phenytoin equivalents, which has resulted in
21 medication errors that will be discussed in later
22 presentations.

1 Both drugs have contraindications for
2 hypersensitivity to Phenytoin and hydantoin. Both
3 have contraindications in patients with compromised
4 ventricular automaticity, such as second and third
5 heart block. Warnings in Fosphenytoin include, not to
6 adjust to recommended doses when Phenytoin equivalent
7 units are used. Other warnings for Fosphenytoin
8 include cardiovascular depression, hepatic injury, and
9 for both, the designate maximum doses of IV Phenytoin
10 for neonates in adults are stated. Precautions exist
11 for elderly, hepatic, renal impairment populations for
12 both drugs.

13 I will now discuss adverse events linked to
14 cardiovascular events. This slide emphasizes the
15 importance of cardiovascular events found in the text
16 from the Fosphenytoin labeling. Similar text appears
17 in the Phenytoin labeling. A warning states that the
18 more important adverse clinical events by either drug
19 is cardiovascular collapse and/or CNS depression,
20 hypotension may occur with rapid IV administration.

21 What does the label say about hypotension?
22 Even in pre-marketing clinical trials for

1 Fosphenytoin, patients were discontinued from the
2 study at the rate of 0.3 percent for hypotension and
3 0.2 percent for Bradycardia. Comparing treatment
4 emergent hypotension for both drugs, with
5 Fosphenytoin, 7.7 percent developed hypotension,
6 whereas in those with IV Phenytoin, 9.1 percent
7 developed hypotension.

8 Now to other adverse events. This slide
9 compares mostly CNS adverse events from labeling.
10 Clearly, both products have other AEs that are well
11 recognized. Nystagmus, dizziness, somnolence, ataxia,
12 and nausea seem to be dose-related. Some other AEs
13 may have notable differences, such as more
14 parasthesias with Fosphenytoin and more nausea with IV
15 Phenytoin.

16 Now we move away from the labeling and
17 clinical studies and turn to the spontaneous adverse
18 events report in MedWatch System.

19 This slide is a quick overview about
20 spontaneous adverse events reports. You will hear
21 more about this in later OSE presentations. FDA
22 encourages submission from health professionals and

1 consumers of adverse events reports possibly due to
2 medications. This is called spontaneous adverse event
3 reporting.

4 The MedWatch Program was designed to help
5 with these submissions, and the reports themselves are
6 sometimes called MedWatch Reports. Drug sponsors that
7 become aware of serious AEs are required to submit AE
8 reports. This is also called spontaneous reporting.
9 These reports are placed in the Adverse Event
10 Reporting System, or AERS Database, or termed AERS
11 Reports. It's important to note that spontaneous AERS
12 Reports are designed to detect events that are rare,
13 serious, unexpected, or unlabeled. We still get
14 reports of clinically mild and labeled events. The
15 quality of information is highly variable. Some
16 reports include substantial information, some just one
17 line. Another limitation of spontaneous reporting is
18 that AERS Reports are subject to secular reporting
19 trends.

20 From secular to reporting trends, one
21 expects a higher number of reports for a newer drug
22 like Fosphenytoin compared to an older drug like

1 Phenytoin. One also expects a trend that an older
2 drug tends to have diminished reporting as it stays on
3 the market longer.

4 OSE has conducted numerous reviews of
5 Fosphenytoin and IV Phenytoin over the years based on
6 AERS Reports. This slide ranks the top 10 adverse
7 events based on the number of reports of serious
8 outcome for both agents from initiation of time of
9 market approval through July 2010. As of July 2010,
10 we note that there were 466 serious reports for
11 Fosphenytoin and 1,285 serious reports for IV
12 Phenytoin.

13 We can note that cardiovascular events,
14 including hypotension, are among the most frequent
15 events cited for each drug. I'll provide more detail
16 in the next few slides on that. For Fosphenytoin,
17 medication error and overdose, which suggest
18 medication error, were also cited. For IV Phenytoin,
19 injection site and reaction in serious skin
20 derangements are in the top 10 events.

21 Now we will focus on CD events from the time
22 at market approval to 2010 that represent unduplicated

1 reports. Again, bear in mind that limitations in
2 comparing Fosphenytoin that was initially marketed in
3 1996 and been on the market for 14 years, comparing
4 that to Phenytoin, which was marketed in 1956 and been
5 on the market for 50 years. The AERS, CV, and
6 hypotensive cases are shown in the table. There were
7 equal fatalities in both, 35 and 36 Fosphenytoin to IV
8 Phenytoin respectively. There were more cases of
9 hypotension in Fosphenytoin and more cases CV events
10 in IV Phenytoin. CV events are discussed in slide 21.
11 In cases of overdosing ages less than three will be
12 discussed in the drug error presentation.

13 Note the number for the age groups do not
14 add up because there were unknown ages in 7 cases for
15 Fosphenytoin and 16 for Phenytoin.

16 Now I'm going to discuss a sub-analysis of
17 the total dataset of all adverse events restricted to
18 2002 to 2010. The AERS Database was searched for
19 reports focused on CV events, which included cardiac
20 arrhythmias, decreased and non-specific blood pressure
21 disorders and shock, cardiac and vascular
22 investigations. From this sub-analysis, we reviewed

1 reports to assemble a case series, and we applied a
2 case definition which was what we used to help define
3 what was considered an associated case based on
4 temporal relationship of time of the adverse event to
5 the time of drug administration, objective evidence
6 such as blood pressure ECG, diagnosis of CV event or
7 hypotension, or if no alternative explanation was
8 found.

9 From the sub-analysis, we found the AERS
10 adverse events of cardiac arrhythmias and hypotension
11 were reported almost equally in both groups. With
12 Fosphenytoin, there were 23 cases of hypotension and
13 26 cases of cardiac arrhythmia. With IV Phenytoin,
14 there were 21 cases of hypotension and 23 cases of
15 arrhythmias. The outcome of death in this review
16 included 13 for Fosphenytoin and 9 cases for IV
17 Phenytoin.

18 Interestingly, in all these cases in an
19 outcome of death, 13 for Fosphenytoin and 9 for
20 Phenytoin, the majority of deaths occurred in adults
21 at recommended doses. In Fosphenytoin, 9 out of 13
22 deaths were in adults at recommended dose, and

1 Phenytoin, 7 out of 9 deaths were in this group.
2 Exceptions in the pediatrics or overdose cases include
3 four cases in the Fosphenytoin group and two cases in
4 the Phenytoin group. The causality of these cases is
5 variable with some having stronger associations than
6 others.

7 In summary, OSE analysis of the AERS
8 database concluded that cardiovascular AEs for both
9 drugs have been reported in all age groups. The
10 majority of these reports note pre-existing
11 cardiovascular disease, where known, a majority of
12 cases occurred when using the recommended doses or at
13 the recommended infusion rates for both drugs. Also,
14 a similar number of reactions occurred during the
15 infusion compared to after the infusion.

16 I will now discuss the literature.

17 Published literature was searched for
18 Fosphenytoin adverse events excluding Purple Glove
19 Syndrome. For all years, literature was retrieved
20 from either the NIH Pub Med on September 10, 2010, or
21 in searches of Pub Med Web of Science or Embase on
22 August 12, 2010. The terms Fosphenytoin and other

1 selected AEs, such as nausea, cardiac, cardiac arrest,
2 Bradycardia, arrhythmia, and hypotension, or adverse
3 effects or events in general were searched.

4 Even though the search was performed on
5 Fosphenytoin, I found that similar AEs occurred for
6 both drugs. Therefore, they were cited as if adverse
7 events occurred for both. In the current labeling of
8 both drugs, all major significant AEs from literature
9 were included. They were cardiovascular and
10 hypotension, CNS events, such as Nystagmus, dizziness,
11 sedation, somnolence, ataxia and stupor, systemic and
12 local dermatologic AEs, and drug errors.

13 Due the seriousness of the cardiovascular
14 outcome from among these prevalent AEs and published
15 literature, we asked what were the predisposing risk
16 factors. According to IV Phenytoin labeling, the
17 author Fischer and the Committee on Safety of
18 Medicines, and others, the following factors
19 predispose to complications. They include advanced
20 age, rapid infusion rate, and known cardiac disease.

21 Due to the interest in PGS, we searched in
22 published literature for cases of it from among these

1 prevalent adverse events. We asked if the frequency
2 in literature of PGS with Fosphenytoin was as high as
3 compared with IV Phenytoin and if PGS was a rare event
4 compared to the frequently reported adverse events of
5 burning, itching, and parasthesias. These questions
6 will be addressed in detail in the PGS presentations.
7 Overall, from the search in literature, no cases of
8 PGS were found for Fosphenytoin in contrast to reports
9 found for IV Phenytoin.

10 The search found dermatologic events of
11 venous irritation and phlebitis were less frequently
12 in Fosphenytoin. But in searching for burning,
13 itching, and parasthesias, they were more frequent.

14 Now, clinical considerations. From
15 published literature, it is important to note that
16 both Fosphenytoin and IV Phenytoin are often used
17 interchangeably in many clinical settings and
18 populations such as in pediatrics and adults.
19 Multiple authors suggest this interchangeability and
20 use both in clinical treatment algorithms, especially
21 for SE. For instance, in Rosen's Emergency Medicine
22 textbook, it discusses it in the context of neonatal

1 ICU as IA discusses it in the context of adult ICU.

2 Other references include the Merck Manual.

3 As sodium channel blockers, both drugs have
4 cardiovascular irritability that can induce CV events.
5 More importantly, these events can occur without
6 underlying comorbidities at recommended doses and
7 infusion rates.

8 Because of this, both need monitoring of
9 ECG, blood pressure, and neuro status. Both of these
10 drugs have been associated with medication errors
11 which will be discussed in the next presentation.

12 Use of Fosphenytoin was favored by some
13 authors in the published literature. For instance,
14 the Cleveland Clinic Foundation regulated its use for
15 certain adult and pediatric populations. Knake
16 recommended its use in neurological ICU, Brochet (ph.)
17 and neurosurgery patients. In the 33rd edition of the
18 Washington Manual at Therapeutics, recommended
19 Fosphenytoin in its algorithm for SE.

20 Furthermore, the considerations revolving
21 around the use of Fosphenytoin include that it can be
22 given by IM route if the IV route is limited and can

1 reach therapeutic Phenytoin concentrations more
2 rapidly. That it may be advantageous with limited
3 venous access, it may be compatible with other IV
4 fluids, but needs refrigeration.

5 Two other considerations in the use of
6 Fosphenytoin involve drug error and cost. Labeling
7 currently describes reports of medication errors
8 related to the total drug content in confusion with
9 the mg PE or Phenytoin Equivalent Unit, which may
10 still exist. Details will be forthcoming.

11 As previously illustrated, the calls for
12 Phenytoin has diminished greatly over the recent past
13 and its cost is closer to the cost of Phenytoin.

14 Let's move on to the use of IV Phenytoin.
15 Considerations revolving around the use of it include
16 injection site reactions that may diminish with slower
17 infusion rates. That's labeled in the precautions.
18 The use of a larger bore catheter in a large vein is
19 also described in precautions. The use of a saline
20 flush is also described in labeling, and the use of
21 filter is adjusted and no need for refrigeration is
22 also in labeling.

1 One other attribute of IV Phenytoin is its
2 unlabeled use for arrhythmias. According to the 33rd
3 edition of the Washington Manual published in April of
4 this year, although Phenytoin is not generally used
5 for arrhythmias, it can be used as an alternative for
6 digitalis-induced arrhythmia, especially with QT
7 prolongation.

8 In the past, in the 32nd edition of the
9 Washington Manual, it was also mentioned for use in
10 cases of overdose of tricyclics, ecstasy, and in a
11 neuroleptic syndrome. This has been removed in a
12 recent edition.

13 Conclusions. In this comparison of
14 Fosphenytoin to IV Phenytoin, it is important to
15 remember three conclusions regarding the safety of
16 both drugs. They include that firstly, published
17 literature and spontaneous post-marketing reports
18 highlight serious and fatal outcomes in cardiovascular
19 and hypotension events, CNS, and systemic and local
20 dermatologic AEs.

21 Secondly, although both drugs are widely
22 used and often used interchangeably in clinical

1 practice, there is no label to pediatric age to dose
2 stratification. Different sources report dosing in
3 pediatric groups, but do not state a specific age that
4 should receive a specific dose range. The reviewing
5 division is in the process of modifying label, and may
6 include further details of this.

7 Thirdly, it's important to remember that
8 cardiovascular events have been reported in healthy
9 adults and children without underlying comorbidities
10 at recommended doses and infusion rates.

11 Many thanks to Dr. Fine, Dr. Brinker, Dr.
12 Kortepeter, and Dr. Aviagan.

13 DR. ANDERSON: Thank you very much, and the
14 next presentation comes from Dr. Tobenkin.

15 **Medication Errors Associated with Phenytoin and**
16 **Fosphenytoin Use**

17 DR. TOBENKIN: Good morning. My name is
18 Anne Tobenkin, and I'm a safety evaluator in the
19 Division of Medication Error Prevention and Analysis,
20 which is in the Office of Surveillance and
21 Epidemiology.

22 Today, I'll present data on medication

1 errors associated with the use of Fosphenytoin and
2 Phenytoin. We were requested to provide a comparative
3 medication error safety profile of Phenytoin and
4 Fosphenytoin in order to understand the use of these
5 two products in the clinical setting.

6 This presentation will consist of a brief
7 discrimination of the databases and the search
8 criteria used to identify medication error cases
9 involving Fosphenytoin and Phenytoin. I'll present
10 the type of errors identified and the contributing
11 factors associated with these errors. Finally, I'll
12 provide conclusions and some general recommendations
13 that may help mitigate future medication errors.

14 I used two different data sources for my
15 medication error search. The first is the Adverse
16 Event Reporting System otherwise known as AERS. This
17 database contains voluntary or spontaneous reports
18 from consumers and health care professionals as
19 discussed by Dr. Gatti in the previous presentation.

20 The second source of medication error data
21 came from the Institute of Safe Medication Practices,
22 also known as ISMP, which is a non-profit organization

1 that receives medication error data from a number of
2 sources. These two databases that we received
3 Fosphenytoin and Phenytoin data from are inpatient-
4 based Quantros MedMarx and the Pennsylvania Patient
5 Reporting System.

6 Two separate searches were conducted within
7 the databases, one for Phenytoin and one for
8 Fosphenytoin. Search terms were used which focused on
9 medication errors and label issues. Duplicate cases
10 were removed, as well as cases that did not describe a
11 medication error involving Fosphenytoin or Phenytoin,
12 medication errors that involved oral administration of
13 Phenytoin and adverse events unrelated to a medication
14 error. Additionally, we removed system-related
15 errors, such as physician not ordering the drug,
16 pharmacy sent late, or nurse did not administer the
17 medication.

18 Our researches retrieved a total of 494
19 relevant medication errors. Two hundred ninety of the
20 medication error cases involved Fosphenytoin
21 exclusively. Sixty of the medication errors involved
22 Phenytoin exclusively. Sixty-two of the cases

1 involved concurrent administration of Fosphenytoin and
2 Phenytoin, and eighty-two of the cases involved
3 confusion between Fosphenytoin and Phenytoin.

4 This table is a summary of the type and
5 number of medication errors that we retrieved in our
6 searches. The major error types were wrong dose,
7 wrong drug, wrong technique, wrong route, wrong
8 frequency, wrong rate, and concurrent therapy, and
9 we'll be discussed in the upcoming slides.

10 Although we saw similar types of errors
11 associated with each product, the root causes of these
12 errors differed. Also, as you can see in the table,
13 two categories, wrong dose and wrong drug, had
14 considerably more medication errors associated with
15 Fosphenytoin. Some errors on this table will not be
16 discussed further in this presentation in order to
17 focus on the more deleterious or significant errors.
18 The next slides will analyze the most important errors
19 identified for each product and discuss the factors
20 that may have contributed to these errors.

21 We attempted to break down the errors by age
22 to identify if any patterns existed within a

1 particular age group. However, age was only reported
2 in 274 of the relevant medical error cases. This data
3 shows that most of the reported errors occurred in
4 adult patients. However, 49 cases reported
5 Fosphenytoin use in the pediatric population. It is
6 important to note that this is an age group that is
7 not approved for Fosphenytoin use.

8 The medication errors that resulted in death
9 occurred in the following categories: wrong dose,
10 wrong route, and wrong rate. There were 10 wrong dose
11 errors that resulted in death with Fosphenytoin.
12 Seven out of ten of these deaths occurred in the
13 pediatric patients aged 3 years or younger.

14 Overdoses occurred when practitioners
15 confused the product concentration with the amount of
16 drug in the vial. Wrong route errors that resulted in
17 death occurred only with Phenytoin. All five of these
18 cases occurred when the oral formulation was injected
19 intravenously. All cases which included patient age
20 were over the age of 16. Although not always stated
21 in the narrative, it was believed that most, if not
22 all, of these cases could be attributed to Phenytoin

1 oral solution being dispensed in an intravenous
2 syringe.

3 The one wrong rate error resulting in death
4 occurred with Phenytoin. The actual rate of
5 administration was not provided in the narrative, just
6 that the product was administered too fast. The
7 patient age in this case was over 16. Although in
8 this particular case the contributing factor that led
9 to the error could not be determined from the
10 narrative, other cases identified in our search
11 explicitly stated the container label led to
12 confusion.

13 So first, let's look at the wrong dose
14 errors associated with Fosphenytoin. The majority of
15 the wrong dose errors were practice-related, such as
16 incorrect transcription of dose or dosing based on
17 pounds instead of kilograms. However, a number of
18 overdose errors were related to the presentation of
19 information on the container label.

20 To understand how these overdoses occurred,
21 please first look at the Cerebyx vials on the left.
22 As you can see, the most prominent number on the vial

1 is 50. Practitioners assumed based on this
2 presentation that the vial contained only 50 mg rather
3 than 500 mg in the case of the 10 mL vial and 100 mg
4 in the case of the 2 mL vial. Because of this
5 confusion, overdoses occurred because patients were
6 administered more Cerebyx than prescribed.

7 On the right is the revised label, which now
8 prominently displays the total of drug content
9 contained in each vial, which, in this case, is 500
10 mg. All marketed Fosphenytoin products have revised
11 the labels to reflect this presentation. Errors of
12 this type have decreased, which is likely due to the
13 revised labels.

14 This chart demonstrates the decline in
15 reported errors of this type. The X axis has the
16 years and the Y axis is the number of errors. The
17 agency requested the vial labels be revised in 1999.
18 As you can see, after 2000, there was a decline in
19 this type of error. However, there are two deviations
20 in this trend. 2002, which is likely due to a delay
21 in reported errors and possible older vials still on
22 the shelves, and again, in 2007, which was related to

1 the automated display cabinets in a manner in which
2 the screens presented the strength. This was similar
3 in manner to the old Cerebyx labels with 50 mg per mL.
4 The display of these cabinets has since been revised.

5 Wrong dose errors occurred also due to the
6 use of mg PE or Phenytoin equivalence in describing
7 the Fosphenytoin strength. This is unique to
8 Fosphenytoin, as most drugs are dosed based on the
9 active ingredient. Since Fosphenytoin is a prodrug of
10 Phenytoin and the products are used interchangeably,
11 mg PE was designated for Fosphenytoin to avoid the
12 need for conversion calculations when switching
13 between these two products.

14 There was considerable confusion about what
15 mg PE was attempting to convey in addition to the lack
16 of consistency of its use by practitioners. This type
17 of wrong dose error occurred throughout prescribing,
18 dispensing, and administering, so, no particular type
19 of practitioner was more prone to confusion with mg
20 PE.

21 Although the reports have decreased over
22 time, there was at least one report received per year

1 regarding Phenytoin equivalency and its meaning.
2 Again, on the X axis is years and the Y axis, the
3 number of error cases. As you can see, the numbers
4 peaked in 2000 and have since declined. Cerebyx was
5 first marketed in 1997, so a confusion occurred more
6 in the first few years of marketing. However,
7 compared with the previous table, that showed almost
8 no reported errors after the label revision, this
9 continued reporting leads us to believe there still
10 may be confusion. The extent of which is unknown and
11 without further study, we may never get a true sense
12 of continued confusion.

13 In addition to the previously-identified
14 wrong dose Fosphenytoin errors, we also identified a
15 number of wrong dose errors that occurred in the
16 pediatric population. This may be due to a lack of
17 pediatric dosing recommendations in the prescriber
18 information, which may have led to varying dose
19 recommendation provided in the literature for
20 Fosphenytoin.

21 Additionally, we identified errors that
22 resulted from confusion with monitoring Phenytoin lab

1 values while the patient was prescribed Fosphenytoin.
2 Practitioners would see an elevated Phenytoin lab
3 value and write an order to discontinue Phenytoin or
4 Dilantin. However, the patient was on Fosphenytoin,
5 and based on the nurse or pharmacist's knowledge, the
6 Fosphenytoin may or may not have been discontinued.

7 There was also a number of wrong drug errors
8 associated with Fosphenytoin, predominantly due to
9 confusion between the proprietary name Cerebyx and
10 Celebrex. Confusion between Cerebyx and Celebrex
11 occurred because of the look-alike and sound-alike
12 similarities between these two drugs and some
13 overlapping characteristics, like frequency of
14 administration, which both can be twice daily and
15 available strength, which in this case is 100 mg.
16 this is an example of where the order Celebrex was
17 misinterpreted for Cerebyx. Multiple factors played a
18 role in this error, the look-alike nature of the name,
19 Cerebyx and Celebrex, the misspelling of the name
20 here, Celebrex is Cerebrex, and the presence of the
21 drug Neurontin, which may have prompted the
22 practitioner to consider epilepsy as the disease state

1 for this patient, and therefore, misinterpreted the
2 drug as Cerebyx.

3 The Division of Medication Error Prevention
4 and Analysis, otherwise known as DMEPA, requested a
5 name change with the most recently approved name
6 Celebrex, on a number of occasions. However, the name
7 was not changed. Errors of this nature continue, but
8 have lessened in frequency.

9 So, now we'll move onto the Phenytoin
10 errors. The reported errors stated Phenytoin
11 injection was delivered at a rate that exceeded the
12 labeled recommendation. The Phenytoin injection
13 package insert contains a boxed warning that
14 communicates the rate of administration for adults,
15 which should not exceed 50 mg per minute or a neonate
16 should not exceed 1 to 3 mg per kg per minute.

17 The package insert often does not accompany
18 the vial to the floors where the medication is
19 administered. Therefore, it may not be the most
20 appropriate means of communicating a recommendation
21 that is implemented at point of administration. Also,
22 as you can see, the container label below the strength

1 also has an ambiguous statement "no infusion," which
2 resulted in a medication error because it was assumed
3 "no infusion" meant rapid injection or push. Again,
4 as is the case is Fosphenytoin, this medication can be
5 used in emergent situations, where practitioners need
6 clear and concise information about the product on the
7 container label.

8 Most wrong route medication errors occurred
9 where oral Phenytoin solution was administered
10 intravenously. Some reports stated that the patient
11 was not taking oral medications or that the patient
12 had a G-tube, which leads us to believe that oral
13 Phenytoin solution was dispensed in a syringe.
14 Additionally, because it was given intravenously, we
15 suspect the product was dispensed in an intravenous
16 syringe rather than an oral syringe.

17 To the casual observer and perhaps to a
18 pharmacy technician who does not administer
19 medications, the syringe on the left and the syringe
20 on the right look very similar. However, to someone
21 who administers medications, the syringe on the left
22 indicates an oral route and the syringe on the right

1 indicates an intravenous route. If a medication is
2 sent up in an intravenous syringe and there are no
3 labels that state for oral use, it is likely that it
4 will be administered intravenously. This type of
5 error is not unique to Phenytoin and has occurred with
6 other medications that are available and in
7 intravenous and oral formulation. However, what was
8 notable is that most of these errors resulted in
9 death.

10 The other significant medication error
11 identified with Phenytoin was wrong dilution
12 technique. Unlike Fosphenytoin, which can be diluted
13 with either normal saline or dextrose, wrong technique
14 Phenytoin errors involve diluting or running Phenytoin
15 injection with solutions which contained dextrose.
16 These errors resulted in rapid precipitation, and if
17 administered, resulted in pain.

18 Although it is widely known that Phenytoin
19 rapidly precipitates when mixed with dextrose, we
20 noted that the insert does not specifically warn
21 against use with dextrose-containing products.
22 Rather, it ambiguously warns to not use with

1 intravenous infusions. Because this statement lacks
2 clarity, it can lead to this type of confusion when
3 preparing the product for administration.

4 We noted similar medication errors that
5 occurred between both Fosphenytoin and Phenytoin,
6 which had similar contributing factors. The wrong
7 frequency of administration was reported by
8 practitioners when Phenytoin or Fosphenytoin was dosed
9 once daily. The Fosphenytoin package insert does not
10 actually state the frequency which Fosphenytoin should
11 be administered.

12 Also, the manner in which the dose
13 recommendations is stated in the package insert, which
14 is 4 to 6 mg per kg per day was mimicked in the
15 ordering process by many physicians which ordered the
16 medication as a total daily dose once rather than
17 divided equally per dose throughout the day. Although
18 the insert states the frequency of administration in
19 the Phenytoin insert once daily administration of
20 Phenytoin could be because of the confusion between
21 these products. We noted a number of cases where both
22 Fosphenytoin and Phenytoin were administered

1 concomitantly.

2 Many of these errors occurred when
3 contingency orders were written, such as Dilantin PO
4 or if NPO, Cerebyx IV. Some contingency orders which
5 used the proprietary names resulted in confusion
6 because health care practitioners were unable to tell
7 that the medications were similar, and both were
8 administered to the patient.

9 Wrong dose errors also occur between
10 Fosphenytoin and Phenytoin. Some of these errors
11 occurred because of the look-alike and sound-alike
12 similarity between the product names Fosphenytoin and
13 Phenytoin. Additionally, both products share the same
14 product characteristics. They are both administered
15 intravenously, have the same indication, similar
16 dosing, and identical settings of use, which can
17 increase confusion between the products. These errors
18 occurred bidirectionally, meaning Fosphenytoin was
19 confused for Phenytoin and Phenytoin was confused for
20 Fosphenytoin. However, more occurs occurred when
21 Fosphenytoin was intended, but Phenytoin was ordered
22 or dispensed.

1 In summary, there is no value in comparing
2 rates of medication error to determine incidences in
3 comparative safety among these drug products. Using
4 this data because it's based on voluntary, spontaneous
5 reports, which are often influenced by a number of
6 different factors. Our analysis noted both products
7 have similar types of medication errors. However, the
8 root cause of these errors differ depending on the
9 product.

10 We concluded that many of the errors
11 associated with each product could be mitigated by
12 improving the vial labels and labeling. Some of these
13 issues have already been addressed through labeling
14 revisions and others are undergoing revisions with the
15 intention of mitigating errors and future confusion.

16 Areas that require future investigation
17 include confusion with Phenytoin equivalence or mg PE.
18 We need to determine how much confusion is still
19 incurring and what unintended consequences might rise
20 from revising labels at this stage of product
21 marketing.

22 Additionally, we need to gain a better

1 understanding of the root cause of concomitant
2 administration of Fosphenytoin and Phenytoin and
3 determine whether it's mostly proprietary name-driven
4 or if other factors play a role.

5 DR. ANDERSON: Thank you very much. Our
6 next presentation is by Dr. Fine.

7 **Purple Glove Syndrome**

8 DR. FINE: Good morning. My name is Andrew
9 Fine, and I'm a safety evaluator within the Division
10 of Pharmacovigilance with the Office of Surveillance
11 and Epidemiology. This morning, I'm going to discuss
12 the safety concern known as Purple Glove Syndrome and
13 its association with IV Phenytoin and Fosphenytoin.

14 The outline of this presentation is as
15 follows: First, I will discuss background information
16 on Purple Glove Syndrome as well as current product
17 labeling pertaining to Purple Glove Syndrome. Next, I
18 will discuss in detail the Office of Surveillance and
19 Epidemiology analysis of Purple Glove Syndrome with IV
20 Phenytoin and Fosphenytoin, which includes a
21 literature analysis and a review of spontaneous
22 reports from the Adverse Event Reporting System and

1 sponsor-submitted data. I will then finish with
2 summary conclusions. Note that throughout this
3 presentation, I will refer to Purple Glove Syndrome as
4 PGS.

5 Purple Glove Syndrome is a delayed soft
6 tissue injury, usually affecting the hand and forearm.
7 It is defined as a development of progressive distal
8 limb edema, discoloration, and pain following
9 peripheral IV administration of Phenytoin. It occurs
10 in three stages. First, dark, purple discoloration
11 around the IV site occurs 2 to 12 hours after the
12 infusion. Next, increase in edema and discoloration
13 spreading distally usually occurs 12 to 24 hours post
14 infusion. The final stage is gradual resolution over
15 days to weeks. Importantly, PGS may or may not be
16 associated with extravasation.

17 These clinical features are in contrast with
18 the more immediate injection site burning, usually
19 following IV Phenytoin administration. Of note, PGS
20 has also been referred to as Purple Hand Syndrome and
21 Phenytoin Hand Syndrome.

22 Several risk factors of PGS have been

1 reported and are listed on this table. These risk
2 factors are from two published studies, a case control
3 study by Spengler and colleagues in 1988, which was
4 the first case series to describe the features of PGS,
5 and a retrospective observational study in 1998 by
6 O'Brien and colleagues, which will be discussed in
7 more detail later.

8 One study by Spengler found that elderly
9 women were at risk for PGS, while the O'Brien paper
10 found that only elderly with no regard for gender were
11 at increased risk. Large doses and multiple injection
12 sites or acute seizure indications, which typically
13 require large, repeated doses are also reported risk
14 factors.

15 Needle bore size is contradictory, as one
16 study found that small borne needles increased the
17 risk, while another study found that large bore
18 needles increased the risk.

19 Infusion rates greater than 25 mg/min, as
20 well as patients with pre-existing cardiovascular
21 disease can increase this risk.

22 Finally, increased Phenytoin concentrations

1 which also contributed to the immediate local site
2 burning also predisposed patients to Purple Glove
3 Syndrome.

4 It is unclear which of these risk factors
5 predominate the risk and which are more likely to
6 contribute to the development of Purple Glove
7 Syndrome.

8 Many PGS outcomes have reported, and if
9 symptoms are identified early and the drug is
10 discontinued, minimal effects are expected and only
11 supportive care may be necessary. However, reports of
12 cases that do require intervention exist, and although
13 rare, serious outcomes like skin necrosis, ischemia,
14 and amputations have occurred.

15 The next few slides depict varying severity
16 of Purple Glove Syndrome. On the left side, is a
17 minor phenotype with moderate edema and reddish
18 discoloration. This case developed following non-
19 extravasated infusion of 1,500 mg of IV Phenytoin
20 through a vein in the dorsum of the right hand. As
21 depicted on the right side, after two weeks, the
22 condition begun to resolve spontaneously with some

1 areas of healing ulcerations in the fingertips.

2 In contrast, in this image, there is
3 evidence of more extensive edema and purple
4 discoloration. It is unknown what the outcome of this
5 case was, but as mentioned previously, severe outcomes
6 requiring interventions are uncommon.

7 To date, only Phenytoin has labeling for
8 PGS, which is in a general precaution section. It
9 describes the triad of edema, discoloration, and pain,
10 and that it may or may or not be associated with
11 extravasation. It also describes the typical outcomes
12 previously mentioned.

13 Though it's a prodrug with many labeled
14 commonalities, there is no mention of PGS in the
15 Fosphenytoin label because no well-accepted
16 association currently exists.

17 Although PGS is in the current labeling for
18 IV Phenytoin, it is not highlighted or differentiated
19 in any way, it could be potentially difficult to
20 locate if the prescribing information were consulted.
21 As you can see, this PGS description seems lost in the
22 label.

1 Moving on to the main focus of this
2 presentation, in the Office of Surveillance and
3 Epidemiology, or OSE, evaluation of Purple Glove
4 Syndrome, the two main objectives for this analysis
5 are to, one, determine if PGS occurs with
6 Fosphenytoin, and, two, describe the characteristics
7 of Phenytoin PGS cases. Several data streams were
8 utilized in this to fulfill these objectives. The
9 published literature, including case reports and
10 published studies, were evaluated for both agents.
11 Additionally, spontaneous adverse event reports from
12 the Adverse Event Reporting System, or AERS, were
13 reviewed for both agents, while data from the sponsor
14 of Fosphenytoin, which is Pfizer, was reviewed only
15 for Fosphenytoin.

16 First, I will discuss published case reports
17 of PGS.

18 As previously discussed, the first case
19 series of the clinical features of PGS was in the
20 1980s. In this case series, one of the nine cases was
21 attributed to extravasation. Following this first
22 published case series, additional case reports in the

1 1980s followed and attributed these similar features
2 of edema, discoloration, and pain to extravasation.
3 Purple Glove Syndrome was adopted to define these
4 clinical features around 1990. In the OSC analysis,
5 included reports after 1990 when PGS was used to
6 describe the events.

7 These more recent case reports, which as I
8 will depict in more detail in the next slide,
9 routinely lack essential information such as
10 administration rate, how the drug was diluted, and
11 even dose is missing in one case. This case series
12 did identify unique reports of Purple Glove Syndrome,
13 such as one case following an oral Phenytoin overdose
14 in a child and one case of purple discoloration in the
15 foot following IV Phenytoin administration via the
16 left saphenous vein.

17 These are the only reports of atypical PGS
18 identified with all remaining cases involving IV
19 administration of Phenytoin in the upper extremity.
20 Also, histopathology was reported in two cases with
21 one of these noting extravasation. As the focus of
22 this analysis was to identify PGS cases attributed to

1 Fosphenytoin, no relevant cases were found, and in the
2 literature, only case reports of PGS with IV Phenytoin
3 exist to date.

4 The characteristics of cases that
5 specifically mention Purple Glove Syndrome are shown
6 in this slide. Based on the range of publication
7 years, these cases continue to be reported. Age and
8 dosing is quite variable, although, as discussed
9 earlier, advanced age and larger doses are perceived
10 risk factors, reiterating infusion details are often
11 unknown.

12 Outcomes were typically minor with minimal
13 treatment and intervention which typically required
14 supportive care, such as limb elevation and
15 discontinuation of the drug. However, one case in
16 1993 of an amputation is reported in a 49-year-old
17 female. Unfortunately, this case lacks essential
18 dosing and administration information.

19 It's difficult to make robust conclusions
20 from the only 11 case reports over a 20-year period.
21 This series is better served to identifying important
22 outliers, such as the oral Phenytoin case, the

1 amputation case, features of Purple Glove Syndrome
2 affecting the lower extremity, and reports in younger
3 patients.

4 Next, I will discuss published observational
5 and clinical studies characterizing and evaluating
6 Purple Glove Syndrome.

7 Three studies are highlighted with varying
8 study designs. The first is a retrospective
9 observational study from O'Brien and colleagues and
10 aimed to determine the incidents of PGS in patients
11 receiving IV Phenytoin, as well as identified risk
12 factors and clinical features. Three years later, in
13 2001, Burneo and colleagues in a prospective,
14 observational study intended to be the first to study
15 Purple Glove Syndrome prospectively and report the
16 incidents in clinical features.

17 Lastly, Coplin and colleagues in an open-
18 label, randomized, prospective study wanted to provide
19 objective comparative data to be utilized in the
20 decision-making process of whether to add Fosphenytoin
21 to a hospital formulary. They compared adverse
22 events, which included Purple Glove Syndrome, as well

1 as emergency department length of stay.

2 I will now discuss each of these studies in
3 more detail.

4 First, in the O'Brien retrospective study,
5 investigators abstracted information from 152
6 consecutive patients receiving IV Phenytoin over a 3-
7 month period in 1991, which was 7 years prior to
8 publication. This study noted a 5.9 percent incidence
9 of Purple Glove Syndrome with predominately mild
10 phenotypes, although one patient required skin
11 grafting and an extended hospitalization. As
12 previously discussed, risk factors of an advanced age,
13 large doses, and large needle bore size were
14 identified in this study.

15 Aside from the retrospective and
16 observational design, several limitations do exist.
17 First, of the four cases identified only affected at
18 the forearm and did not progress distally to the hand.
19 Also a Purple Glove Syndrome diagnosis was not
20 recognized by the treating physician in approximately
21 50 percent of these cases.

22 There was also no mention of administration

1 rate, which was originally noted as a risk factor 10
2 years earlier by Spengler and colleagues. Also, it's
3 important to note that 33 percent of these cases did
4 describe extravasation occurring.

5 As the previous study was a retrospective,
6 observational design, this slide details a prospective
7 study by Burneo and colleagues. In this paper, 157
8 patients receiving IV Phenytoin had their upper
9 extremities photographed and evaluated by a blinded
10 investigator. In this sample, 2 minor cases of Purple
11 Glove Syndrome both resolving within 4 weeks in a 65
12 and 33-year-old were noted, resulting in incidence of
13 1.7 percent. Both of these patients were females
14 receiving large doses via a 22-gauge needle.

15 Limitations in this data are that pain, one
16 of the triad of the clinical features, was not
17 recorded, and patients receiving the drug in the lower
18 extremity were excluded.

19 As the previous two studies were
20 observational designs, on this slide, a randomized and
21 prospective study by Coplin and colleagues is
22 discussed. In this prospective, clinical study, 77

1 patients were randomized to Phenytoin and 202 patients
2 were randomized to Fosphenytoin in an emergency
3 department. Administration of drug was based on
4 whether an IV anti-epileptic drug was indicated.

5 For those receiving IV Phenytoin, a strict
6 administration protocol was implemented. The IV
7 Phenytoin was mixed in 50 mLs of normal saline. The
8 IV site was tested with a saline flush. The Phenytoin
9 was infused with an inline filter at a rate of 20
10 mg/min, and the IV site was flushed afterwards. No
11 cases of Purple Glove Syndrome were found in either
12 group.

13 To accurate for any delayed reaction, such
14 as Purple Glove Syndrome, for those who may have been
15 quickly discharged from the ED, emergency department
16 records were reviewed to identify patients that may
17 have returned. Of the adverse events compared,
18 Phenytoin patients were more likely to have vein
19 burning, while Fosphenytoin patients were more likely
20 to have pruritus, which are labeled events.

21 This slide summarizes the published case
22 reports and studies describing Purple Glove Syndrome.

1 Published case reports of PGS exist for IV Phenytoin
2 therapy only and continue to be reported in the
3 literature. The outcomes are predominately minor,
4 except for the one amputation with many reports
5 lacking essential details. Incidence estimates of PGS
6 in the literature range from zero to 6 percent with
7 varying study designs. Although each study had
8 strengths and weaknesses, events are predominately
9 non-serious outcomes.

10 The observational studies lack important
11 administration details, such as if the drug was given
12 diluted and at what infusion rate. However, in the
13 randomized and prospective study, detailed IV
14 Phenytoin administration was closely followed,
15 yielding zero cases of PGS.

16 Next, I will discuss data from the Adverse
17 Event Reporting System, or AERS, and sponsor-submitted
18 data.

19 As discussed in previous presentations, the
20 Adverse Event Reporting System, or AERS, is a
21 computerized database which contains spontaneous
22 adverse event reports from an individual, such as a

1 consumer or health care professional. These reports
2 are submitted to the company or directly to the FDA
3 that describe a suspected adverse event.

4 Additionally, as discussed previously in
5 other talks, when interpreting the AERS data,
6 especially for two drugs, it's important to understand
7 the limitations, many of which are listed on this
8 slide. Notably, AERS is not useful for comparative
9 incidence rates or comparing drugs in the same class.

10 In order to identify cases of spontaneous
11 reports of PGS with IV Phenytoin or Fosphenytoin, the
12 following case definition was applied: Relevant cases
13 were required to have a diagnosis of Purple Glove
14 Syndrome or a temporal relationship between drug
15 administration and onslaught of symptoms plus bluish
16 or purplish discoloration and edema or pain at limb
17 distal to the injection, plus no alternative
18 explanations for the reported events. Note that this
19 definition was applied to all spontaneous reports,
20 those from AERS, as well as those from the sponsor.

21 In order to identify relevant cases of PGS
22 in the AERS Database, the following search strategy

1 was used: AERS was searched for both agents using the
2 preferred term "Purple Glove Syndrome."

3 Additionally, all cases were text-searched
4 in an effort to identify additional cases suggested of
5 Purple Glove Syndrome, as well as differentiate these
6 cases from other non-Purple Glove Syndrome infusion
7 reactions. Examples of text-searched terms used were:
8 purple, hand, foot, discoloration, amputation,
9 swollen, edema, or other terms and phrases describing
10 features of PGS. Each product was searched from the
11 individual approval data through June 8, 2010, and
12 resulted in 43 cases of Phenytoin and 4 cases of
13 Fosphenytoin, meeting its predefined case definition.

14 As previously mentioned, in addition to AERS
15 data, sponsor data was included in the OSE analysis.
16 In 2008, at the request of the Division of Neurology
17 Products, Fosphenytoin sponsor, Pfizer, queried their
18 internal database for spontaneous adverse event
19 reports of PGS and provided analyses for IV Phenytoin
20 and Fosphenytoin. For the OSC analysis of this data,
21 only Fosphenytoin reports were evaluated, an effort to
22 obtain a comprehensive total of Fosphenytoin PGS

1 reports. The sponsor identified five cases as
2 probable/possible Purple Glove Syndrome attributed to
3 Fosphenytoin.

4 This slide highlights the efforts to
5 combined the Fosphenytoin data from the AERS search
6 with the data submitted from the sponsor and obtain a
7 comprehensive total. As you recall, four cases of PGS
8 were identified in AERS and five cases were identified
9 by the sponsor. However, the four cases found in AERS
10 were also identified and included in the sponsor's
11 case series of five cases. The additional case
12 identified by the sponsor, but not found in AERS, also
13 fit the predefined case definition for this analysis.
14 And as a result of combining the sponsor data with the
15 AERS data, five cases of Fosphenytoin-related PGS are
16 included.

17 The next series of slides describe the
18 results of the Phenytoin and Fosphenytoin cases, and I
19 will begin with the Fosphenytoin data.

20 This table summarizes these five cases of
21 PGS with Fosphenytoin. Not all cases included
22 detailed characteristics, and the results here are

1 based on those reports that provided the specified
2 characteristic. When reported, these cases reported
3 between 1998 and 2007 affected males and females, and
4 one reported two of the three cases occurred in the
5 elderly. One patient had a reported cardiovascular
6 history based on the medication list reported and
7 included in this table. Finally, reported doses were
8 all greater than 600 mg of Phenytoin equivalence and
9 within the therapeutic range.

10 The next slide provides details for the
11 reported adverse event in each case.

12 The first case described hand dark purple,
13 erythema, edema, pain, PGS. The next case describes
14 skin discoloration "Black Glove Syndrome
15 extravasation." The third case describes purple
16 discoloration, bleed, blisters, skin sloughing on hand
17 and forearm, but not fingers, PGS.

18 The next case elbow to fingertips red, hard,
19 swollen, painful, extravasation. And the final case
20 described Purple Glove Syndrome, which was
21 characterized by bruising up the hand, similar to what
22 occurs with intravenous Dilantin or Phenytoin.

1 Benign outcomes and minimal treatment
2 resulted from these reports with the exception of one
3 report where a patient required debridement and
4 hyperbaric treatment. Additionally, extravasation was
5 reported in two of these cases.

6 In order to responsibly evaluate
7 Fosphenytoin in spontaneous reports, it's important to
8 understand recently-identified possible deficiencies
9 in adverse drug event reporting for Fosphenytoin by
10 its sponsor, Pfizer.

11 The next two slides discuss recent FDA
12 observations, Office of Compliance actions, and
13 challenges of case ascertainments.

14 OSC noted that between 1997 and 2008, 58
15 percent of Fosphenytoin reports were directly reported
16 to FDA in contrast to the roughly 6 percent of reports
17 in AERS sent directly to FDA. As a result, Pfizer was
18 instructed to implement a specialty reporting
19 procedure for Fosphenytoin and cases of Purple Glove
20 Syndrome. Its intention was to aide in identifying
21 and following-up on cases that were suggested of
22 Purple Glove Syndrome, an effort to enhance

1 surveillance of PGS related to Fosphenytoin use.

2 However, in an enforcement letter from May
3 2010, FDA stated that Pfizer had failed to adequately
4 implement such a specialty reporting requirement.
5 Pfizer then submitted a formal response in June 2010,
6 expressing 100 percent compliance with specialty
7 reporting requirements between February and May 2010.
8 Pfizer also stated that no reports suggested of Purple
9 Glove Syndrome were identified since October 2009.
10 the bottom line is that due to the complexity of case
11 ascertainment, FDA is uncertain whether additional
12 cases exist and have not been captured or whether in
13 fact no additional cases exist.

14 Switching to the Phenytoin results, the next
15 few slides describe the results of the 43 cases of
16 Purple Glove Syndrome. These reports were received
17 between 1998 and 2010. Interestingly, 16 reports were
18 received between 1998 and 2000, and 10 reports in 2008
19 to 2009.

20 This influx could be attributed to the 1998
21 Purple Glove Syndrome study by O'Brien and a 2008 FDA
22 Web posting pertaining to Purple Glove Syndrome with

1 Phenytoin. These cases affected a broad age range
2 with a mean of 59, and several patients had a history
3 of cardiovascular disease or peripheral vascular
4 disease.

5 When treatments were reported, they were
6 mainly supportive in nature, which included drug
7 therapy, like prophylactic antibiotics and even
8 brachial plexus block, but a few reports did require
9 surgical intervention and one case required
10 debridement and a skin graft.

11 Additionally, one reported most patients
12 recovered without any impairments, but there were
13 single reports of compartment syndrome and an
14 amputation. The reported resolution, which was
15 included in only nine cases, ranged from 12 hours to 3
16 months.

17 A focus of PGS has been on administration
18 details of the drug. Based on the Phenytoin AERS case
19 series and this slide, of the 28 cases that reported
20 the administered dose, a wide range of Phenytoin-based
21 doses within the therapeutic range were identified.
22 Specifically, the mean dose was 635 mg with a median

1 of 800 mg. Additionally, PGS events occurred after
2 single doses or multiple doses. Infusion rate details
3 were only reported in 7 of the 43 cases, and included
4 rates that were less than 25 mg/min.

5 This slide comments on the results of the
6 AERS and sponsor data for Purple Glove Syndrome
7 involving IV Phenytoin and Fosphenytoin. From this
8 data, the first case series of PGS attributed to
9 Fosphenytoin administration was identified. This data
10 also reinforces several risk factors identified in the
11 published literature for PGS, like pre-existing
12 cardiovascular disease and multiple doses. Though
13 other risk factors were not necessarily identified,
14 this largely could be a result of many cases lacking
15 essential dosing and administration details. The
16 spontaneous data is not meant for comparisons and
17 incidences or reporting rates between these two
18 agents, especially when the spontaneous reports are
19 from drugs marketed decades apart and when considering
20 possible discrepancies and adverse drug event
21 reporting practices for Fosphenytoin.

22 Based on all of the data reviewed, which

1 includes the published literature, AERS data, sponsor-
2 submitted data, several conclusions can be made.
3 First, the understanding of IV Phenytoin risks like
4 Purple Glove Syndrome, risk factors, and
5 administration techniques have evolved over time, as
6 20 to 25 years ago, Phenytoin was given undiluted
7 without close regard to administration rates.

8 Next, cases of PGS with Phenytoin continue
9 to be reported in the literature and in the AERS
10 database. Based on the data reviewed, clinical
11 features of PGS have been reported following
12 Fosphenytoin therapy, however, based on differential
13 reporting in the literature, PGS appears to occur more
14 frequently with IV Phenytoin.

15 Next, the administration rate, a perceived
16 PGS risk factor, is routinely not reported, and even
17 published studies fail to specify all infusion
18 details.

19 And finally, the phenotype of PGS is
20 typically minor in nature, though serious outcomes
21 have been reported.

22 And I would like to acknowledge some of my

1 OSC colleagues who have assisted in my presentation.

2 Thank you.

3 DR. ANDERSON: Thank you very much. We now
4 have our last of the initial FDA presentations from
5 Dr. Pinheiro.

6 **Purple Glove Syndrome Associated with Phenytoin or**
7 **Fosphenytoin: Preliminary Report**

8 DR. PINHEIRO: Good morning. My name is
9 Simone Pinheiro, and I'm an epidemiologist in the
10 Division of Epidemiology in the Office of Surveillance
11 and Epidemiology. In today's presentation, I'll
12 introduce you to efforts we are currently undertaking
13 along with researchers at the Department of Veterans'
14 Affairs, referred to as the VA, to examine the risk of
15 Purple Glove Syndrome among patients who received
16 parenteral Phenytoin or Fosphenytoin during a
17 hospitalization. The purpose of this presentation is
18 to share with you our ongoing efforts and the
19 challenges we have encountered during this evaluation.

20 This is an outline of my presentation today.
21 First, I'll describe to you and review the relevant
22 background on Purple Glove Syndrome. I'll then move

1 on to describe the methods used in this retrospective
2 evaluation and discuss the main challenges we have
3 encountered. I will then close this presentation with
4 a few concluding remarks and questions concerning next
5 steps on how to move forward. I'd like to mention
6 that I welcome input from the members of this
7 committee on how to best proceed with this evaluation.

8 As previously presented in greater detail,
9 Phenytoin-associated Purple Glove Syndrome is well-
10 documented. There have been several spontaneous post-
11 marketing MedWatch reports of Phenytoin-associated
12 Purple Glove Syndrome. Additionally, these reports
13 and a few observational studies documenting occurrence
14 of Phenytoin-associated Purple Glove Syndrome are
15 available in the published literature. Across the
16 epidemiologic and clinical studies that evaluated
17 Purple Glove Syndrome, the incidents of Purple Glove
18 Syndrome of any severity ranged from zero to 5.9
19 percent. The incidents of severe Purple Glove
20 Syndrome from these studies ranged from zero to 0.7
21 percent.

22 There is Purple Glove Syndrome associated

1 with Fosphenytoin. It's less well-documented. A few
2 spontaneous post-marketing MedWatch reports have been
3 received as described in the previous presentations.
4 A relatively small clinical study conducted in an
5 emergency department reported no cases of Purple Glove
6 Syndrome in patients receiving Fosphenytoin, as well
7 as among those receiving Phenytoin, as just
8 described. No case reports or observational studies
9 of Fosphenytoin-associated Purple Glove Syndrome are
10 available in the published literature.

11 To date, no large studies evaluating the
12 differential risk of Purple Glove Syndrome between
13 Phenytoin and Fosphenytoin have been conducted. In an
14 attempt to obtain data that could help informed
15 decisions of this advisory committee meeting, on July
16 of 2010, we, in collaboration with investigators at
17 the VA, initiated an evaluation of the VA database to
18 characterize the risk of Purple Glove Syndrome among
19 patients who received Phenytoin or Fosphenytoin during
20 a hospital stay. Due to the time constraints, these
21 efforts were initiated as a rapid cycle analysis.
22 Rapid cycle analysis fall under the auspices of Drug

1 Safety and Pharmacovigilance Projects at the VA, which
2 allow for the conduct of analysis over a short period
3 of time to inform drug safety issues of high public
4 health concern. IRB approval is typically waived for
5 rapid cycle analyses.

6 This effort was conducted using a stepwise
7 approach. I present the methods and preliminary
8 results of the first step of this approach.

9 The VA database was selected for these
10 analyses for several reasons. It is a large claims
11 and electronic health record database containing data
12 on over 5 million veterans annually nationwide.
13 Importantly, the VA captures inpatient prescription
14 data, which is the setting in which parenteral
15 Phenytoin and Fosphenytoin are typically used.

16 Additionally, the VA System allows for
17 electronic retrieval and abstraction of medical
18 records, allowing for fast validation of outcomes.
19 Ability to validate the outcome is particularly
20 important in this evaluation due to the nature of
21 Purple Glove Syndrome, a poorly defined outcome for
22 which there are no ICD-9 codes available. It is

1 important to note that the VA patient population is
2 largely composed of older males, many of whom have
3 several comorbidities.

4 This analysis is being conducted to address
5 the following objectives: to characterize the risk of
6 Purple Glove Syndrome among patients receiving
7 parenteral Phenytoin or Fosphenytoin during a hospital
8 stay and to compare the risk of Purple Glove Syndrome
9 among patients receiving parenteral Phenytoin or
10 Fosphenytoin during a hospital stay.

11 This evaluation was constructed as a
12 stepwise approach, as I just mentioned. In the first
13 step, we initiated a retrospective cohort evaluation,
14 including all patients who received parenteral
15 Phenytoin or Fosphenytoin between 2002 and 2010 during
16 a hospital stay at a VA medical facility. The main
17 analyses were restricted to patients without
18 prescriptions for parenteral Phenytoin or Fosphenytoin
19 in the previous six months from first prescription.

20 These patients were identified in the
21 Pharmacy Benefits Management Prescription Database. I
22 will now describe the key definition used in this

1 evaluation. The code algorithm was developed by
2 researchers and the VA and was based on the literature
3 spontaneous post-marketing reports and on the opinion
4 of experts, including neurologists, a dermatologist,
5 and a plastic surgeon.

6 First, we identified ICD-9 codes and CPT
7 codes potentially related to severe Purple Glove
8 Syndrome phenotype. ICD-9 codes included codes for
9 amputation, skin grafting, fasciotomy, gangrene, and
10 compartment syndrome. CPT codes included codes for
11 skin debridement, fasciotomy, skin grafting/flaps, and
12 amputation.

13 Next, we searched the electronic medical
14 records of patients identified via these codes for a
15 diagnosis of Purple Glove Syndrome or variations of
16 it. For example, Purple Hand Syndrome. We then
17 imitated an additional search to the electronic
18 medical records of patients identified via ICD or CPT
19 codes, searching for the following symptoms: a triad
20 of symptoms including pain, edema, and discoloration
21 or symptoms described in necrosis of extremities.

22 Again, variations of these terms, such as

1 swelling in addition to edema were used. Due to the
2 time constraints, the performance of this algorithm
3 was not formally evaluated during the first step of
4 these analyses.

5 In this slide, I present preliminary results
6 of the analysis using the algorithm I just described.
7 Between 2002 and 2010, we identified approximately
8 20,000 patients; 9,356 and 10,724 patients who
9 received parenteral Phenytoin or Fosphenytoin
10 respectively. Using the selected ICD and CPT codes,
11 as just described, a total of 57 and 65 potential
12 cases of Purple Glove Syndrome were identified among
13 Phenytoin and Fosphenytoin cohorts respectively.

14 Upon review of the medical records of these
15 potential cases, the diagnosis of Purple Glove
16 Syndrome was identified in none of the patients. We
17 then reviewed the medical records in search of
18 symptoms as I just mentioned, the triad, including
19 pain, edema, and discoloration or symptoms describing
20 necrosis of extremities.

21 These symptoms were identified in a few
22 number of cases across both cohorts, however, none of

1 these patients could be validated as Purple Glove
2 Syndrome cases due to the presence of other
3 comorbidities in attributing factors. What I mean by
4 that is, that upon close review of the medical records
5 by clinicians in our team, the symptoms described in
6 the records could not be definitively attributed to
7 the administration of Phenytoin or Fosphenytoin due to
8 the presence of other potential attributing factors,
9 including sepsis and use of aggressive vasopressor
10 therapy, presence of limb fracture, and thrombosis.

11 In conclusion, we have encountered several
12 challenges in these analysis most related to the
13 difficulty in ascertaining Purple Glove Syndrome
14 retrospectively in a claims and electronic record
15 database.

16 First, there is no specific ICD-9 code to
17 define Purple Glove Syndrome. Therefore, our strategy
18 involved selection of codes as proxy measures of
19 conditions or of procedures that could be related to
20 the severe phenotype of Purple Glove Syndrome.
21 Additionally, we were unable to capture Purple Glove
22 Syndrome in this study. Upon review of the electronic

1 medical records, a selected ICD and CPT codes did not
2 capture the diagnosis of Purple Glove Syndrome. It
3 is, therefore, likely that the selected algorithm was
4 not sensitive for Purple Glove Syndrome and may have
5 resulted in a number of false negatives.

6 Additionally, although a few patients had
7 symptoms of Purple Glove Syndrome, including pain,
8 edema, discoloration, or symptoms described in
9 necrosis of extremities, a close review of these
10 patients' medical records did not allow for validation
11 of Purple Glove Syndrome diagnosis due to presence of
12 a number of other likely attributing factors,
13 including sepsis and receipt of aggressive vasopressor
14 therapy, presence of the limb fractures in thrombosis,
15 all of which were found to be probable causes of the
16 described symptoms.

17 Finally, lack of familiarity of clinicians
18 with the condition of Purple Glove Syndrome may also
19 add to the difficulty in identifying Purple Glove
20 Syndrome retrospectively using an electronic record
21 medical database.

22 At this time, no definitive conclusions can

1 be drawn from the preliminary results of this crude
2 retrospective analysis of Purple Glove Syndrome in the
3 VA database. As previously mentioned, due to the time
4 constraints, this rapid cycle analysis did not allow
5 for formal evaluation of the algorithm used to
6 identify severe cases of Purple Glove. Further,
7 evaluation of the algorithm is warranted as it is
8 likely the algorithm was not sensitive enough for
9 Purple Glove Syndrome.

10 Additionally, the algorithm may not have
11 been specific enough to identify Purple Glove Syndrome
12 in the sick VA population.

13 Due to the nature of Purple Glove,
14 adequately-powered perspective studies may be needed
15 to evaluate the risk of Purple Glove Syndrome
16 associated with parenteral Phenytoin or Fosphenytoin
17 exposure.

18 In light of the challenges encountered in
19 this evaluation, we are considering the following
20 future steps. The conduct of pilot studies to refine
21 the algorithm developed to identify Purple Glove
22 Syndrome in the VA database. The national VA database

1 used in the current evaluation does not allow for the
2 automated text string searches across all records.
3 Instead, its record was downloaded and text string
4 searches were performed individually on each record.
5 We're now considering conducting a pilot study in one
6 or more of the VA system networks with high use of
7 parenteral Phenytoin or Fosphenytoin to refine the
8 text string search algorithm. The refined algorithm
9 could then be applied to a sample of an enriched
10 population of patients with at-risk factors for Purple
11 Glove Syndrome, including those with cardiovascular
12 disease and older age.

13 Alternatively, it may be more informative to
14 initiate or request the conduct of a study which
15 allows for the prospective definition of the outcome.
16 However, based on the reported low instance of severe
17 cases of Purple Glove Syndrome, this study would
18 likely require a large sample size, particularly if
19 the goal was to detect cases of Purple Glove Syndrome
20 of severe phenotype.

21 This concludes my presentation, but I'd like
22 to thank and recognize the work done by the VA team

1 and to mention the director of the Center for
2 Medication Safety in the Department of Veterans'
3 Affairs, Dr. Cunningham is also here today and may
4 also help with any questions that you have about this
5 evaluation.

6 Thank you.

7 **Clarifying Questions**

8 DR. ANDERSON: Well, I would like to thank
9 all the presenters today for the information they've
10 shared and we will have time this afternoon to sort of
11 debate the issues more generally. What we have now is
12 an opportunity until our scheduled break at 10:15 is
13 to ask questions of the FDA presenters that would
14 clarify any aspects of their presentations today or
15 the data that they shared with us that the committee
16 feels would be helpful or useful.

17 Is there anybody who--okay, so, we'll start
18 with Dr. Wolfe, please.

19 DR. WOLFE: Just a couple of clarifying
20 quick questions for some very nice presentations. On
21 Dr. Chai's presentation on slide 10, she shows quite
22 clearly that there has been a big increase in the use

1 of alternatives really to Fosphenytoin or Phenytoin in
2 the form of Lorazepam and Midazolam. It looks like
3 there are about twice as many by 2009, twice as many
4 discharged diagnoses for those two as there are for
5 Fosphenytoin, and then on slide 10, she shows the time
6 curve which shows probably it looks like about 3,000 a
7 year discharges for the combination of Fosphenytoin
8 and Phenytoin in the younger age group.

9 So, the question is, given that it looks
10 like these have been somewhat supplanted by other
11 drugs, do we have data comparable to what is in slide
12 12 for the usage patterns in that age group for
13 Midazolam and Lorazepam? It'd be extremely helpful
14 because, as we go farther into the day, it is not
15 simply the alternative between Fosphenytoin and
16 Phenytoin, it's also other alternative, particularly
17 if there are people who think that those other
18 alternatives may be a better choice. So, it'd be very
19 helpful, if possible, to get those age-related
20 discharge data, particularly currently in the last
21 couple of years for most people.

22 And I have just another question not for Dr.

1 Chai--

2 DR. ANDERSON: Well, maybe we'll let Dr.
3 Chai address that one.

4 DR. WOLFE: Okay, that's fine.

5 DR. ANDERSON: So we don't lose the thread
6 here and then we'll come back to you.

7 So, Dr. Chai, the question is for slide 12,
8 do you have date for the other medications that you
9 showed earlier sort of presented in this way, as well?

10 DR. WOLFE: Particularly, for the younger
11 age group.

12 DR. ANDERSON: Especially for the younger
13 age groups.

14 DR. WOLFE: Right.

15 DR. CHAI: The following analysis that
16 you're requesting was not conducted for the review or
17 for the AC presentation. Also, it would be difficult
18 to attribute that it's definitely used for status
19 epilepticus, but the primary diagnosis of status
20 epilepticus was indicated on the discharge for those
21 medications. So, the analysis that you're asking for
22 could be done, but it does have caveats just like the

1 Fosphenytoin and IV Phenytoin data has.

2 DR. WOLFE: But wouldn't the discharged
3 diagnoses for status epilepticus for Lorazepam and
4 Midazolam be similarly indicated as they were for the
5 two--

6 DR. CHAI: Well, in slide 12, this data was
7 irregardless of diagnosis.

8 DR. WOLFE: Right. Okay.

9 DR. CHAI: I just want to make that clear.

10 DR. WOLFE: Okay, but then it would still be
11 useful to see how much in these younger children these
12 other drugs are being used.

13 Thank you.

14 Then the question for Dr. Gatti, which is
15 now--

16 DR. ANDERSON: So, one second. Is it
17 particularly relevant--okay, so, Dr. Hershkowitz has a
18 point related to this same question.

19 DR. WOLFE: Okay.

20 DR. HERSHKOWITZ: I just want to make a
21 point that it's difficult to compare the
22 Benzodiazepine treatment in this situation because

1 whereas Lorazepam or Midazolam may be given acutely,
2 this may be followed by a dose of Fosphenytoin or
3 Phenytoin for maintenance. These drugs are generally
4 short-acting, and I use acutely because you'll still
5 have a use in that regard and status, but not the same
6 use. So, it's difficult to do a comparison.

7 Okay. Thank you.

8 DR. WOLFE: Slide 17, I think. Slide 17.

9 Yes, this was the slide where you were looking amongst
10 serious adverse events for Fosphenytoin and Phenytoin,
11 and medication error, and we've heard a lot of
12 discussion about that, comes up fairly high, and just
13 the question is: Of those 466 serious adverse events
14 with Fosphenytoin, how many you chose that ranks
15 third, but how many of these were medication errors or
16 overdoses that's down there, too?

17 And similarly, for the Phenytoin, which is
18 the bottom-ranking one on the right-hand column, how
19 many of the 1,285 were drug level above therapeutic?
20 I mean, just to get some idea not only in terms of
21 ranking, but in terms of the number of cases that
22 showed up of those two categories. Is that possible

1 to do it? I mean, you must have done the counts or
2 you couldn't have ranked them. So, it'd just be
3 helpful if you could possibly provide the counts on
4 both of those.

5 DR. FINE: I can answer--

6 DR. GATTI: (Off microphone.)

7 DR. FINE: Just to provide a quick
8 disclaimer about the data that is projected there is
9 that these are what we'd call crude counts. These are
10 unevaluated cases. We're only taking the coding by
11 preferred term of the adverse events in all cases for
12 IV Phenytoin and IV Fosphenytoin, and when you're
13 looking at crude counts, especially if you're
14 comparing the two, actual numbers can be extremely
15 misleading because it's not accurate to give
16 comparisons because of the different marketing
17 periods, as well as without knowing the exact
18 causality and the specific events, it's difficult

19 DR. WOLFE: Well, I fully understand the
20 comparison thing, but just looking at Fosphenytoin
21 alone, it would be helpful to see how many of those
22 466 were medication errors or overdose. You must have

1 those counts at least.

2 DR. FINE: I could consult to see the exact
3 numbers.

4 DR. WOLFE: Right.

5 DR. FINE: But I do know medication errors
6 are the highest.

7 DR. WOLFE: Okay. Again, out of 466, how
8 many are there? They were ranked third behind
9 hypotension and convulsion, I assume.

10 DR. GATTI: If you want to look at slide 39,
11 please. That'll explain a little bit of the
12 limitations we're dealing with.

13 DR. WOLFE: Thirty-nine. Your slides, 39.

14 DR. ANDERSON: So, but is the data that Dr.
15 Wolfe's requesting available or easily obtainable as
16 to sort of what those counts were or at least sort of
17 some, I guess, approximation. Hypotension is 459 and
18 then everything on the list is 1, or we know that they
19 are sort in the same ballpark, but may be minor.

20 DR. WOLFE: Right, right.

21 DR. ANDERSON: I mean, we're looking at
22 least from relative comparisons on the list.

1 DR. TOBENKIN: I think you need to consider
2 the medication errors as I had shown, were
3 predominantly related to when it first came out. So,
4 there was a lot of name confusion with Cerebyx and
5 Celebrex. It should also be pointed out I went back
6 to 2000.

7 So, mine were 10 years. They included from
8 1996 to 2010. So, that included all of the medication
9 errors when it first released into the market, which
10 accounts for a lot of errors because if it's the mg
11 PE, the total drug content issues and the Cerebyx and
12 Celebrex. So, out of those that I showed, only 10 had
13 significant harm and the death, and those were all
14 related to the total drug content, which was an
15 overdose.

16 DR. ANDERSON: So, we got what we can get on
17 that one here. So--

18 DR. WOLFE: Sort of.

19 DR. ANDERSON: Sounds like we tried.

20 So, Dr. Cooper, please.

21 DR. COOPER: My question is for Dr. Chai.

22 In Dr. Fine's presentation, he reported on some

1 regulatory concerns regarding underreporting by
2 Pfizer, but that since October 2009, there had not
3 been any events of Purple Glove Syndrome associated
4 with Fosphenytoin. On slide 7 of your presentation,
5 Dr. Chai, did I understand you correctly to say that
6 the Pfizer manufacturing only accounted for 1 percent
7 of the Fosphenytoin sales? And, if so, having no
8 events among that small proportion would seem to be of
9 limited information.

10 DR. CHAI: I'm sorry; I missed the last part
11 of your question.

12 DR. COOPER: So, first off, just is this
13 slide showing that Pfizer's only responsible for 1
14 percent of the sale during the period in which
15 Pfizer's database shows no Fosphenytoin-related
16 events.

17 DR. CHAI: It seems Dr. Fine's presentation
18 included adverse events from Pfizer for market
19 approval, and my pie chart only shows this current
20 year to date, January 2010 to August 2010. I think in
21 Pfizer's presentation, they're going to let you know
22 that they no longer market Cerebyx.

1 DR. ANDERSON: Dr. Fine's presentation--

2 DR. CHAI: I know.

3 DR. ANDERSON: --also specifically had a
4 line that said October 2009 to the present, and, so, I
5 think the question is that statement from Dr. Fine's
6 presentation and your chart here covering
7 approximately the same period of time?

8 DR. FINE: Let me clarify two points.
9 first, all the data from the AERS Database was from
10 market approval to 2010, and, yes, the comments on the
11 specialist reporting requirement and possible
12 discrepancies was more related to the 2008 to 2010,
13 where there was discussion of implementing a specialty
14 reporting requirement and aspects in any cases from
15 any specialty reporting requirement would be in this
16 based on the conclusions from the one slide would be
17 after October 2009, no cases of Purple Glove Syndrome
18 were identified, and that they were compliant with the
19 reporting requirements within that time period of
20 2010, which is reflected by this timeframe on this
21 slide.

22 DR. ANDERSON: Okay.

1 DR. FINE: Does that clarify?

2 DR. ANDERSON: I think that does clarify.

3 And, Dr. Avigan, you had something you
4 wanted to add to that last question?

5 DR. AVIGAN: Well, I was going to actually
6 make a point about the previous question that Dr.
7 Wolfe had asked about exact numbers and whether in
8 that hierarchy what the proportionalities were, and I
9 just wanted to point out that, generally speaking,
10 that kind of data is not numerically useful. It
11 really just gives a general landscape from which you
12 then--to the next step, which is to zoom in on
13 specific questions, which does very elegantly for us
14 by the medical errors people. So, the information
15 really is complementary.

16 The bottom line about medical errors is
17 actually the case review, which we've heard
18 extensively about. So, that first step really is just
19 a broad sense of the landscape of key safety events
20 that would be of concern to then turn the microscope
21 on. So, the numerical question then was answered at
22 the case review step.

1 DR. ANDERSON: So, we will have a chance for
2 further efforts to clarify from the FDA, but some
3 people will need the 10-15 break. So, I'm going to
4 give Dr. Green the last question of this session, and
5 then when he's done, we'll take our break, and we will
6 have another opportunity to come back for clarifying
7 questions later in the day.

8 So, Dr. Green?

9 DR. GREEN: Okay, thank you. I don't want
10 to oversell a single case report, but I read the oral
11 case in the past with great interest, and I think
12 there may be an enormous amount to learn from that
13 case of a little boy who received an error and a
14 significant overdose. Obviously, no injection.
15 Obviously, different constituents in an oral Phenytoin
16 tablet compared to an IV form.

17 So, my question is: Was anyone able to get
18 additional information other than what I saw in the
19 case report when I read it from the source? And then
20 the other's a real quick question.

21 DR. FINE: So the case, the single case
22 report of following oral administration was from Japan

1 and it was published in the medical literature. I'm
2 not aware of any efforts to follow-up on that case,
3 but to provide more details, if necessary, with the
4 case you're referring to, it was a 10-year-old male
5 who was 18 kg that was administered the drug via
6 nasogastric tube, and based on the mg/kg dose, it was
7 a 55 mg/kg, which is a tenfold overdose, and he did
8 have the discolorations in both extremities and both
9 feet. There was purple discoloration, just to
10 clarify.

11 DR. GREEN: And the other one is a
12 particularly dumb question, but I really don't deal
13 with these oral syringes, and there were photographs
14 of the oral syringes given where there are errors
15 where they were given intravenously.

16 Can an oral syringe accept a luer lock?

17 DR. TOBENKIN: You would have to jam it in.

18 DR. GREEN: I mean, you could sort of do it
19 if you work on it hard enough.

20 DR. TOBENKIN: Yes. Well, and it should be
21 noted that they have been since revised and the oral
22 syringes that contain Dilantin or Phenytoin are bright

1 orange, and they typically always have for oral use on
2 them. So, they have undergone revisions to ensure
3 that errors like that still don't occur.

4 DR. ANDERSON: So, at this point, we will
5 take a 15-minute break and return again to sharply
6 start at 10:30 again. And, please, panel members
7 don't discuss any aspects of these morning
8 presentations until we resume.

9 (Break.)

10 DR. ANDERSON: The next item on our agenda
11 is a presentation from a industry representative. So,
12 we're going to hear from Susan Welsh now, and she's
13 already at the podium. So, please begin when you're
14 ready.

15 **Industry Presentation:**

16 **Summary of Information about Purple Glove Syndrome in**
17 **Association with Intravenous Administration of**
18 **Phenytoin and Fosphenytoin**

19 DR. WELSH: Thank you very much. Good
20 morning and thank you for the opportunity to speak
21 today at this advisory committee meeting. My name is
22 Susan Welsh. I'm the vice president of Worldwide

1 Safety Strategy at Pfizer.

2 Here is an outline of what my presentation
3 will cover today. First of all, I will speak to the
4 purpose of the presentation, which is to provide a
5 summary of the safety information about Purple Glove
6 Syndrome noted here as PGS in association with the
7 intravenous administration of Phenytoin and
8 Fosphenytoin. I will provide a brief background on
9 the drugs with a brief description of the products. I
10 will review the indications for Cerebyx and for
11 Dilantin parenteral, and provide some information on
12 differences in safety information.

13 Then as regards Purple Glove Syndrome, I
14 will review data from clinical trials, from the
15 literature, and also from the Pfizer Safety Database
16 regarding this syndrome. Finally, I will discuss some
17 conclusions from the data and there will be later a
18 chance for questions.

19 Some brief background then on the product
20 Dilantin, generic name Phenytoin sodium injection,
21 this is a ready-mix solution of Phenytoin sodium,
22 which has a pH of 12, which is for parenteral

1 administration. The drug was approved in the U.S. in
2 the year 1956. Several manufacturers market generic,
3 injectable Phenytoin in the U.S. Pfizer has not
4 marketed this projected Dilantin injection in the U.S.
5 for several years, but does market the product in
6 other countries worldwide.

7 Some brief background on the product
8 Cerebyx, this is a water-soluble phosphate ester
9 Phenytoin prodrug, which is indicated for parenteral
10 administration. The pH is 8.6 to 9. It was approved
11 in the U.S. in August 1996. Several manufacturers
12 have marketed generic Fosphenytoin in the U.S. when it
13 went to generic in the year 2007. It has not been
14 marketed by Pfizer in the U.S. since January of this
15 year, but the company does market it in other
16 countries.

17 This is a review of the approved indications
18 for these products in the U.S. Firstly, Dilantin
19 injection is approved for the following indication:
20 the control of status epilepticus of the grand mal
21 type, and, also, for the prevention and treatment of
22 seizures occurring during neurosurgery. Cerebyx is

1 indicated for the short-term parenteral administration
2 when other means of Phenytoin administration are
3 unavailable, inappropriate, or deemed to less
4 advantageous. The safety and effectiveness in this use
5 has not been systematically evaluated for more than
6 five days.

7 The drug is also used in the control of
8 generalized convulsive status epilepticus and the
9 prevention and treatment of seizures occurring during
10 neurosurgery. It can be substituted short-term for
11 oral Phenytoin.

12 I'd like to define Purple Glove Syndrome.
13 This is a syndrome recognized in the literature, and
14 the definition per literature is as follows: It's an
15 adverse reaction characterized by the progressive
16 development of discoloration, edema, and pain distal
17 to the site of intravenously-administered Phenytoin.

18 Now, I'd like to review data from the
19 clinical development program of Cerebyx.

20 Clinical trial data was reviewed
21 retrospectively in year 2008 to determine whether
22 there were cases suggestive of Purple Glove Syndrome.

1 All adverse events were reviewed. The review of the
2 Fosphenytoin clinical trial data did not reveal cases
3 suggestive of Purple Glove Syndrome.

4 I'd like to turn to the literature review.
5 In the literature, evidence exists for an association
6 of Purple Glove Syndrome with intravenous Phenytoin.
7 There's a wide range of published incidence rates
8 possibly due to differences in syndrome, definition,
9 particularly in less-severe cases.

10 Most cases of Purple Glove Syndrome in the
11 literature appear to resolve without surgical
12 intervention. And although data is limited, studies
13 from the literature suggest the following risk
14 factors: being of increasing age, for example, more
15 common in the elderly, being of the female sex, the
16 number of treatments given, and the rate of infusion.
17 In the literature, there are no citations describing
18 an association of Purple Glove Syndrome with
19 Fosphenytoin.

20 I'd now like to turn to a review of the
21 Pfizer Global Safety Database, specifically for
22 Phenytoin and Fosphenytoin, both parenteral forms.

1 Pfizer's Safety Database contains cases of
2 adverse events in the following categories: First of
3 all, those reported spontaneously to Pfizer, those
4 reported from health authorities, adverse events that
5 are published in the medical literature, and also
6 serious adverse events that are reported from clinical
7 studies as well as from Pfizer-sponsored marketing
8 programs in which case the solicited cases, regardless
9 of causality.

10 This database is intended to capture reports
11 of adverse events for drug products that are
12 manufactured by Pfizer. Some reports involving
13 patients taking Fosphenytoin or Phenytoin manufactured
14 by generic or other companies may also be captured in
15 Pfizer's database. It is likely also that some
16 reports involving Pfizer manufactured products are
17 made to other product manufacturers and to the FDA,
18 but not to Pfizer.

19 When reviewing these cases, we use the
20 following categorization criteria for signs and
21 symptoms to categorize the cases as probable,
22 possible, unlikely, or excluded. I'll review those

1 categories.

2 The probable category would be a case where
3 the narrative mentions Purple Glove Syndrome, the case
4 is coded as Purple Glove Syndrome, the patient develop
5 significant sequelae, for example, fasciotomy,
6 necrosis in the absence of any other causative
7 explanation, or the clinical case course was
8 consistent with the definition of Purple Glove
9 Syndrome.

10 For the possible category, the majority of
11 signs and symptoms and the clinical course appear
12 consistent with Purple Glove Syndrome, but there's not
13 enough specific information to categorize it as
14 probable or there are minor inconsistencies. This
15 includes cases where the reaction moved away from the
16 site of administration.

17 In the unlikely category, the majority of
18 signs and symptoms and clinical costs were
19 inconsistent with Purple Glove Syndrome, but that case
20 could not be ruled out definitely.

21 And then, finally, for the excluded
22 category, were reports of clearly localized reactions

1 thrombosis-only, extravasation-only, cellulitis, or
2 infection, and cases reporting intra-arterial use,
3 which is a medication error, without any other signs
4 and symptoms suggestive of Purple Glove Syndrome.

5 It should be noted that all probable,
6 possible, and unlikely cases have been reported to the
7 FDA.

8 This is the results of that Safety Database
9 review, using the categorization described. The cases
10 reported through to September 23, 2010, for
11 Fosphenytoin, there were four probable cases, one
12 possible case, and three unlikely cases. For
13 Phenytoin, there were 59 probable cases, 60 possible
14 cases, and 39 unlikely cases.

15 To further review the Phenytoin cases, here
16 is provided some more detail. So, of the 119 cases of
17 probable, possible Purple Glove Syndrome, 35 actually
18 reported the event Purple Glove Syndrome. Other
19 commonly-reported events at 5 percent or greater of
20 cases were as follows: injection site reaction,
21 oedema peripheral, extravasation, skin discoloration,
22 oedema gangrene, injection site necrosis, soft tissue

1 injury, and blister. Forty-seven of 119 cases
2 reported extravasation or infiltration. Forty-one of
3 119 cases reported recovered or recovering with or
4 without sequelae. Twenty-six of the 119 reported some
5 form of surgical treatment, including eleven
6 amputations.

7 Here is some more detail on the Fosphenytoin
8 cases from the Pfizer Safety Database. Of the five
9 cases of probable, possible Purple Glove Syndrome,
10 three of the cases reported the event of Purple Glove
11 Syndrome. One case described a Black Glove Syndrome,
12 and one case described events which were erythema,
13 extravasation, induration, peripheral edema, and
14 extremity pain that might indicate Purple Glove
15 Syndrome.

16 Follow-up was conducted. Two cases reported
17 an outcome of resolved. No outcome was reported in
18 three cases. No specific treatment was reported.

19 Following this review of the databases, a
20 further review was conducted using different criteria
21 according to a new reporting requirement provided to
22 Pfizer by the FDA.

1 In this requirement, all adverse events with
2 the term of extremity from the U.S. or any foreign
3 affiliate worldwide either serious or non-serious were
4 to be reported as expedited adverse events within the
5 15-day reporting period. This criteria was therefore
6 used for a second review of the Pfizer Global Safety
7 Database.

8 The results of this review are as follows:
9 This review did not identify any additional cases that
10 might be indicative of Purple Glove Syndrome. All
11 Purple Glove Syndrome cases previously assessed as
12 probable, possible, or unlikely have been submitted to
13 the FDA.

14 To summarize, the published literature has
15 identified Purple Glove Syndrome in association with
16 the intravenous administration of Phenytoin. There is
17 a wide range of published incidences, possibly due to
18 differences in syndrome definition, particularly in
19 less-severe cases, and there are variations with
20 respect to risk factors.

21 Phenytoin cases in the Pfizer Safety Global
22 Database from both clinical trials and post-marketing

1 data appear to be consistent with those reported in
2 the literature. Five cases of possible or probable
3 Purple Glove Syndrome in association with Fosphenytoin
4 have been reported to Pfizer. No case reports were
5 found in the literature documenting Purple Glove
6 Syndrome among users of Fosphenytoin, nor in the
7 clinical studies of Fosphenytoin.

8 The conclusions are as follows: Cases of
9 Purple Glove Syndrome have been reported in
10 association with the intravenous administration of
11 both Phenytoin and Fosphenytoin. Purple Glove
12 Syndrome appears to be an event described more often
13 with Phenytoin. No firm conclusions are possible
14 after the relative incidence or reporting rates
15 between the two drugs, given the following: The lack
16 of comparative data in the literature, the lack of
17 comparative data in the clinical trials, the lack of
18 definitive exposure information, and the inherent
19 limitations of the spontaneous reported adverse
20 events. Thank you.

21 **Clarifying Questions**

22 DR. ANDERSON: Thank you very much. At this

1 point, what I'd like to do is I guess sort of start
2 with clarifying questions that we may have for this
3 speaker, and then depending on how long that takes, we
4 can return to our clarifying questions that are sort
5 of left over for the FDA sessions this morning. And
6 I'll see if anyone else has a question since you
7 started the last one. Otherwise, I'll give you the
8 first shot.

9 So, why don't we start with Dr. Fountain,
10 and we'll come back to you.

11 DR. FOUNTAIN: On slide 12, what is the
12 interval over which you examine the cases. It says
13 323, September 2010, but is that from 1956 for
14 Phenytoin and 1996 for Fosphenytoin, or is it some
15 other interval?

16 DR. WELSH: The cases of Fosphenytoin go
17 from the time that Fosphenytoin was first developed
18 through to that date, and the cases for Phenytoin I
19 will have to confirm that to you later after the
20 break, but my belief is that that is from the time
21 that we acquired the product; we assumed the clinical
22 database at that time. So, I'd have to give you a

1 precise date later on, but it goes through to
2 September 23, 2010.

3 DR. FOUNTAIN: Okay, and the follow-up to
4 that on slide 13 then is do I understand that of the
5 119 cases, there were 11 amputations?

6 DR. WELSH: Could you repeat the question,
7 please?

8 DR. FOUNTAIN: On slide 13, of the 119 cases
9 of PGS associated with Phenytoin, there were 11
10 amputations or about 10 percent?

11 DR. WELSH: Yes.

12 DR. FOUNTAIN: And, presumably, all of those
13 were reported to the FDA?

14 DR. WELSH: Yes, all of these cases were
15 reported with the outcomes.

16 DR. FOUNTAIN: Okay.

17 DR. ANDERSON: We'll come back to Dr. Wolfe.

18 DR. WOLFE: This is not on Purple Glove, but
19 since you are the representative of Pfizer, in his
20 opening remarks, Dr. Cass said I think something to
21 the effect that you cannot write a valid dosing
22 recommendation for Fosphenytoin in children, and there

1 seems to have been a tug going on for a long time over
2 whether or not there are adequate pharmacokinetic
3 data.

4 I mean, if you had adequate pharmacokinetic
5 data, you obviously could write this, and at least one
6 plausible reason for some of these misdoses, overdoses
7 in children is the drug is not approved in children.
8 It's clearly used including before the generic ones
9 were available. So, from your perspective, what is
10 the problem? I mean, one of these studies has an n of
11 8, and it says "wide variability of Cmax." It's not
12 surprisingly.

13 From your perspective, just what has been
14 the problem, again, let's go back to prior the generic
15 because you really don't have very much on the market.
16 What has been the problem in producing adequate
17 pharmacokinetic data so that one could, contrary to
18 what Dr. Katz said, make some valid dosing
19 recommendations?

20 DR. WELSH: Thank you for the question.
21 I'll provide some history on the development of
22 pediatric dosing that may be helpful here. The

1 product, as stated earlier by yourself, is not
2 approved for use in children. Park Davis did conduct
3 studies in children, but the data was not found by FDA
4 to be sufficient to support its use.

5 We have looked at conducting additional
6 studies, but later proposed labeling in 2003 to make
7 clear that the drug was not approved for use in
8 children. We had discussions with the FDA in July of
9 this year in which the FDA did propose to Pfizer that
10 a bridging study to some earlier pharmacokinetic data
11 be collected for Fosphenytoin using intravenous
12 Phenytoin to develop some labeling language for use in
13 children. Internal counsels of pediatric experts
14 within Pfizer reviewed this and saw that there was
15 some issues with the feasibility of the study, and
16 instead, have proposed a stepwise approach to get the
17 necessary information.

18 It's understood that Pfizer notified FDA in
19 August at the high-level proposal and requested a
20 meeting to discuss this further. Pfizer is, in fact,
21 analyzing existing data on which to base dosing
22 recommendations, and, in fact, did submit a meeting

1 request just recently to discuss further with FDA.

2 DR. WOLFE: Thank you. That answers my
3 question.

4 DR. ANDERSON: We have Dr. Cavazos next.

5 DR. CAVAZOS: Just to clarify, you are
6 indicating here Phenytoin IV, correct?

7 DR. WELSH: Yes, we have both, not in the
8 U.S. The products are not marketed in the U.S. by
9 Pfizer, Phenytoin.

10 DR. CAVAZOS: Okay.

11 DR. WELSH: Either dose types, intravenous
12 or intramuscular. However, it is marketed in other
13 parts of the world, and there exists both intravenous
14 and intramuscular indications.

15 DR. CAVAZOS: Okay, so, the question in
16 follow-up to the case that Dr. Green indicated earlier
17 is: Is there information that you have on Phenytoin
18 overdose orally that induces a Purple Glove Syndrome
19 and where you carry out a review of those cases?

20 DR. WELSH: Yes. I cannot speak immediately
21 to overdoses with Phenytoin. I can get back to you
22 later after the break on information with respect to

1 Phenytoin overdoses. I believe your question is
2 related to Phenytoin overdoses, is that correct?

3 DR. CAVAZOS: Yes, it is.

4 DR. WELSH: Yes.

5 DR. ANDERSON: Okay, so, next Dr. Marder.

6 DR. MARDER: Yes, I'd like to go back to
7 slide no. 13. I don't think I understand that. there
8 were 119 cases that you found that fit some of the
9 criteria, and if only 35 of them were Purple Glove
10 Syndrome, then 84 were skin reactions that were not
11 classified as Purple Glove Syndrome, and there were 11
12 amputations. So, does this say that there are very
13 serious skin reactions that aren't Purple Glove
14 Syndrome and they seem to be more common and more
15 severe?

16 DR. WELSH: Yes. Let me know if this
17 doesn't answer the question, but what we did was we
18 used the categorization criteria described of
19 probable, possible, unlikely, and the 119 cases here
20 represent the probable and possible cases. And, for
21 some of those, the actual case, when reported,
22 actually had Purple Glove Syndrome written into the

1 case when reported. But there were others that did
2 not have that specific syndrome specified, but did
3 describe features of Purple Glove Syndrome and was
4 coded as such, or indeed, may not have coded as such,
5 but on reviewing the specifics of the case, had signs
6 and symptoms reported that were indicative of Purple
7 Glove Syndrome.

8 So, in fact, this includes cases where
9 practitioners, pharmacists, others, et cetera,
10 actually specified Purple Glove Syndrome on the report
11 when reporting in the adverse event or other cases
12 where it was not reported in, but it was actually
13 classed as probable or possible based on the criteria
14 that I described earlier.

15 Does that answer the question?

16 DR. MARDER: I think so. So, that means
17 that there are actually 119 and not 43 cases?

18 DR. WELSH: The 119 does not include the
19 unlikely cases.

20 DR. MARDER: Okay.

21 DR. WELSH: There were unlikely cases where
22 the majority of signs and symptoms were not consistent

1 with Purple Glove Syndrome, but it cannot be ruled
2 out.

3 DR. MARDER: Thank you.

4 DR. ANDERSON: Okay, and Dr. Temple had
5 something related to this.

6 DR. TEMPLE: Actually, what I wanted to do
7 is ask whether there's an animal model for this
8 syndrome. If there were, that seems a good place to
9 see whether the two drugs are similar in their
10 behavior.

11 DR. WELSH: Yes. So, could you repeat the
12 question?

13 DR. TEMPLE: Is there an animal model? Can
14 you induce something like this in animals by injecting
15 these drugs somehow? Intra-arterially or in any way?

16 DR. WELSH: Yes, that is a question that I
17 would like to get back to you on. I'm not involved in
18 the toxicology area, and I'm not aware of such a
19 model, but certainly would like to get back to you on
20 that particular question. Thank you.

21 DR. TEMPLE: Okay, I mean, I'd also be
22 interested in whether anyone tried to find one. Not

1 just whether there is one.

2 DR. WELSH: Yes, okay. That will be
3 answered, too.

4 DR. ANDERSON: How about as a general
5 question of the panel, is anyone aware of an animal
6 model of Purple Glove Syndrome?

7 (No response.)

8 DR. ANDERSON: Okay. So, next is Dr.
9 Chapman.

10 DR. CHAPMAN: So, just going back to that
11 slide 13, is this is the Worldwide Safety Database, or
12 is just for the U.S.?

13 DR. WELSH: No, this worldwide. The way
14 that Pfizer manages safety reporting is we work on a
15 global basis, U.S. operation as well as our foreign
16 affiliates report adverse events into the central U.S.
17 unit for processing and onward management. So, all of
18 these cases represent the Global Safety Database at
19 Pfizer.

20 DR. CHAPMAN: Just a follow-up if I could,
21 do you have sort of an idea of how frequently
22 Fosphenytoin is used overseas, because one of the

1 interesting things is that all of the cases about
2 Purple Glove Syndrome with Fosphenytoin apparently are
3 in the United States. Does that mean we use 90
4 percent of the world's Fosphenytoin or is it sort of a
5 breakdown similar to what we do here?

6 DR. WELSH: Yes, I don't have specific
7 marketing data to present at this moment, but I could
8 get back to you, but I will point out that there are
9 generic manufacturers of Fosphenytoin, and it may well
10 be that they are also reporting cases to FDA in
11 addition to Pfizer.

12 So, Pfizer doesn't have a very big share of
13 the market now, given that there are a number of
14 generic manufacturers worldwide, so, one would expect
15 that it's not beyond the realms of possibility that
16 there will be cases reported in from other
17 manufacturers, as well from Pfizer.

18 DR. ANDERSON: Okay, next is Dr.
19 Silbergleit.

20 DR. SILBERGLEIT: Yes, I think mostly I
21 wanted to follow-up on--so, of the 119 cases, do we
22 know what proportion of those are U.S. cases versus

1 non-U.S. cases?

2 DR. WELSH: Yes, I can get back to you later
3 with that answer. I don't have that in front of me
4 right now, that specific information. They are coming
5 from our Global Database, but country of origin, I
6 would have to provide that to you after the break.

7 DR. SILBERGLEIT: Okay. And can you speak
8 as to whether the withdrawal from the U.S. market of
9 both these drugs was related to safety concerns or
10 safety reporting?

11 DR. WELSH: Yes, I can comment on that. The
12 cessation of marketing of Phenytoin was based on a
13 commercial decision by the company. It is no longer
14 marketed, Phenytoin that is, in the U.S. The
15 cessation of marketing of Fosphenytoin was based to
16 not being able to identify a suitable manufacturer.
17 Activities are underway right now to identify a
18 manufacturer that meets quality control requirements,
19 and it's intended that once that has been done that
20 Pfizer would resume marketing of the Fosphenytoin,
21 Cerebyx drug in the U.S. market.

22 DR. ANDERSON: So, does that mean that

1 Pfizer markets a medicine that it can't met U.S.
2 marketing standards, and so, the medicine that is
3 manufactured that doesn't meet standards is what
4 Pfizer markets worldwide?

5 DR. WELSH: No, it does not, because we have
6 other manufacturers worldwide. We have to oversee,
7 have a FDA-approved manufacturing site to sell within
8 the U.S.

9 DR. ANDERSON: So, the next one on the list
10 is Dr. Nelson.

11 DR. NELSON: Thank you. In the absence of
12 an adequate animal model and in an attempt to really
13 understand to me the mechanism by which this adverse
14 event happens, the Purple Glove Syndrome, have you
15 done any more intensive case investigation or any
16 other sorts of, not necessarily case-based, but other
17 investigation?

18 For instance, if the extravasation was the
19 cause of the problem, as simple as that, then you'd
20 think that the lesion would be right around the site
21 of the IV. Now, from my understanding, not all of
22 these cases happen that way. The IV could be in the

1 arm or in the saphenous vein, and the foot or the hand
2 can actually be affected, right? And that's inclusive
3 in your possible diagnosis category, right?

4 In other words, lesions distant from the
5 site of the intravenous infusion. So, and then you
6 throw the oral case in there, and obviously, it's a
7 case with a lot of data missing, but it does raise
8 this whole question about how this could happen. Now,
9 it's possible that the reason we've not seen it with
10 Fosphenytoin is just because of the limited number of
11 use.

12 Maybe it's related to all the good things
13 about the drug that we've considered, but I guess is
14 there, from your perspective, and I guess I could ask
15 Dr. Fine the same question, but how do we really
16 understand what it is that's happening that we could
17 intuit whether or not Fosphenytoin is going to, in
18 fact, be safer?

19 DR. WELSH: We haven't to date performed any
20 specific studies to look at the pathogenesis. There
21 is, obviously, literature information regarding what
22 the pathogenesis might be. However, following the

1 outcome of today's advisory committee meeting, we are
2 very much open to discussing any studies for the
3 future to further understand.

4 DR. NELSON: Yes, if I could just follow-up.
5 You didn't really discuss about other toxicity besides
6 Purple Glove, and maybe that wasn't what you were
7 asked to do. But I know when we talk about the
8 cardiovascular toxicity and the propylene glycol, I
9 mean, it's been shown to some extent that propylene
10 glycol is responsible for some of the cardiovascular
11 effects, but clearly not for all of them.

12 Do you have any desire to discuss any other
13 effects besides propylene glycol?

14 DR. WELSH: Apart from Purple Glove?

15 DR. NELSON: I'm sorry, besides Purple
16 Glove.

17 DR. WELSH: Was your question relating to
18 discussing other safety effects--

19 DR. NELSON: Right, the rest of the safety
20 effects.

21 DR. WELSH: Certainly. If we can take the
22 backup slides, please, and go to slide no. B5. So,

1 what I'll do is just to review for you some data from
2 a clinical trial database which represents the
3 clinical trial program for Fosphenytoin. This is
4 around 1,000 patients and represents a total of 873
5 patients who took Fosphenytoin. There are also
6 patients who received Dilantin and patients receiving
7 placebo. So, first of all, to look at adverse events,
8 compare them for the nervous system. As you can see
9 here, generally, the adverse events are a very similar
10 order of magnitude.

11 Moving to the next slide, please. Slide B6.
12 This slide here shows comparative rates for the body
13 as a whole and you will note that for injection-site
14 reaction and injection-site pain, these are elevated
15 comparatively in the Dilantin group compared to the
16 Fosphenytoin group.

17 Slide B7, please. This reviews the
18 cardiovascular events with the two different drugs and
19 placebo. As you will see, the events of hypotension,
20 vasodilatation, Tachycardia and Bradycardia and of
21 about the same order of magnitude.

22 Slide B8, please. This is the adverse

1 events relating to skin, and there is a higher
2 frequency of Pruritus in the group who received
3 Fosphenytoin.

4 Slide B9, please. This is events relating
5 to the digestive tract, and these are of a similar
6 order of magnitude.

7 Slide B10. Special senses adverse events,
8 these are of a similar order of magnitude.

9 Slide B11. And then for the hemic and
10 lymphatic system, ecchymosis. This is also, again, of
11 a similar order of magnitude. So, that provides an
12 overview from the clinical trial program of the Safety
13 Database and some understanding of the comparative
14 adverse event rate from the clinical studies.

15 DR. ANDERSON: Dr. Varelas?

16 DR. VARELAS: Yes. Just following the
17 previous question, it seems you had 11 cases of
18 amputation. Has anybody done any pathology in these
19 amputated limbs to find out what exactly is going on
20 with these limbs? I mean, was it just a vasculitis
21 that developed or was it just a massive clotting in
22 that area? Was it just spasm of the vessels? Were

1 these hands actually profused by a single artery, just
2 a radial, and it was not ulnar artery profusing these
3 fingers? Has anybody any details or any data about
4 what's really going on with this syndrome?

5 DR. WELSH: Was that a question--okay.

6 DR. ANDERSON: Yes, I think is: Does Pfizer
7 have any knowledge of the pathology of the amputated
8 limbs in the 11 identified cases of amputation?

9 DR. WELSH: No, at this time, we do not have
10 that information.

11 DR. ANDERSON: Was that it or did you have
12 another question?

13 Okay, so, Dr. Fountain?

14 DR. FOUNTAIN: Just a clarification on my
15 earlier question about the 11 amputations. I'm trying
16 to reconcile are there 11 amputations and 119 cases
17 from Pfizer and only 1 amputation and 43 reports from
18 the FDA that we heard about?

19 It says you look at the data about the
20 interval over which those cases were collected. If
21 you could not just know the total interval but over
22 approximately when the amputations were reported so we

1 can see if it reconciles with the FDA. I'm trying to
2 figure out why that's such as drastically different
3 number.

4 DR. WELSH: Yes, I do not have that
5 information available now. Certainly, we could look
6 to finding that information and providing it to the
7 FDA.

8 DR. ANDERSON: Does the FDA have a comment
9 about why they would have 11 on their slide and you
10 would have 1 in your presentation?

11 Dr. Fine?

12 DR. FINE: Yes, I can comment. So, although
13 both the FDA analysis as well as Pfizer's analysis
14 looking at spontaneous data, the methodology was
15 slightly different.

16 Just to comment on the FDA data, based on a
17 date range of the reported cases of Purple Glove
18 Syndrome for Phenytoin, our date ranges that was
19 identified was between 1998 and 2010. That could be
20 attributed to the methodology because we searched all
21 the Phenytoin cases oral and IV over the product life
22 sale, which included over 10,000 reports.

1 Instead of using the extensive metric PT
2 term list that Pfizer had implemented, we used text
3 string searches for terms suggested of Purple Glove
4 Syndrome, and based on how far back the cases go, that
5 some of the narrative information may be limited since
6 some of the more historic cases prior to 1998, for
7 example, may have been amputations, but based on a
8 narrative text string search, they may not have been
9 captured. So, the data presented is from 1998 to
10 2010, where we're confident with the narrative text
11 string search to capture these cases.

12 DR. ANDERSON: I guess it would relevant to
13 get these cases--

14 DR. FINE: I concur.

15 DR. SILBERGLEIT: (Off microphone.)

16 DR. ANDERSON: Sure, go ahead.

17 DR. SILBERGLEIT: I mean, isn't the most
18 obvious explanation that they're non-U.S. cases? I
19 mean, with a different threshold for reporting.

20 DR. ANDERSON: Well, he knows a lot about
21 where the FDA's cases came from. But it's not clear
22 that--

1 DR. FINE: You can't say--

2 DR. ANDERSON: --Dr. Welsh right at the
3 moment has all the data on--

4 DR. SILBERGLEIT: You can't say for sure,
5 but wouldn't that be an--I mean, that might be rather
6 than some of the things, the difference between the
7 measure of coding, I mean, that's sort of a more
8 obvious alternative source.

9 DR. ANDERSON: So, Dr. Silbergleit, I'm
10 supposed to make sure that I mention or you all
11 mention your names during the case because I guess
12 these are transcribed, and so, they want to be able to
13 identify the speakers. So, for Dr. Welsh here, at
14 this point, you're not exactly clear on the date range
15 and the geographic limitations of where those 119
16 cases came from, is that true?

17 DR. WELSH: Yes, I did indicate that we
18 could provide that information after the break.

19 DR. ANDERSON: Right, right. So, I think
20 there should be some time perhaps following the open
21 public hearing before the panel discussion where we
22 should have some time that if you have the opportunity

1 to acquire that information, we should be able to give
2 you a chance to share it, and also, the panel's
3 request whether you could learn whether Pfizer had
4 done any work with animal models for trying to produce
5 the Purple Glove, as well.

6 DR. WELSH: Sure.

7 DR. ANDERSON: We could come back to that at
8 that time.

9 DR. GATTI: Dr. Anderson, could I also ask
10 for--this is Dr. Gatti here. Sorry. Clarification as
11 to the date the other adverse events were collected
12 from the clinical trial data you presented. Dr.
13 Welsh. Could I ask when those were collected?

14 DR. WELSH: Could you repeat the question,
15 please?

16 DR. GATTI: In the last slides you showed,
17 those adverse events, the non-PGS adverse events that
18 you showed for those clinical trials, what year were
19 those collected?

20 DR. WELSH: Yes, these were collected from
21 the clinical trial development program of
22 Fosphenytoin. So, that data was collected during the

1 90s and reviewed in 2008. In total, it was 21
2 studies. This included 9 studies in patients, and
3 this included patients who had status epilepticus,
4 patients with epilepsy, and patients undergoing
5 neurosurgery. Totally, there were 873 patients taking
6 Fosphenytoin in those studies. This represented
7 actually the MAA, Marketing Authorization Application,
8 for the EU. It's the largest database we have of
9 clinical study data.

10 DR. GATTI: Okay. So, that data was
11 collected in the 1990s though, is that correct?

12 DR. WELSH: Yes, that's when the studies
13 were being done with a view to getting approval of the
14 product.

15 DR. GATTI: And I just wanted to also
16 clarify in your slide no. 13, of the 11 amputations,
17 we're assuming that those were all of the cases that
18 were defined as Purple Glove Syndrome, is that
19 correct? Or no?

20 DR. WELSH: No. One can't make that
21 assumption. That would need to be confirmed back
22 because, as mentioned in this group, there are cases

1 that are defined as possible Purple Glove Syndrome,
2 and they may not have specifically reported in the
3 term Purple Glove Syndrome. It may have been coded as
4 Purple Glove Syndrome, but also it may have just been
5 that the clinical cause and the signs and the symptoms
6 matched that of Purple Glove Syndrome and that
7 attribution was made in the categorization process.

8 DR. GATTI: Thank you.

9 DR. ANDERSON: All right. So, as you heard,
10 we should have some more time to come back. So, for
11 this session, we'll give Dr. Woods the last question
12 here.

13 MR. WOODS: You mentioned earlier that
14 you're in the process of looking for a partner to
15 manufacture Fosphenytoin. At present, the supply of
16 this product is unreliable, and we're experiencing
17 intermittent drug shortages. Were Phenytoin to be
18 removed from the market, would this create in your
19 view a situation where we would be unable to make up
20 that capacity with Fosphenytoin given our present
21 manufacturing situation?

22 DR. WELSH: Sure. Well, as to regards of

1 the manufacturing situation, I will mention that one
2 of the aspects considered in that is the attributes of
3 the drug, the chemical attributes, have led to some
4 impact in the glass vial, and this is the reason using
5 modern QA testing that we have not just yet identified
6 a manufacturer for the supply of Fosphenytoin in the
7 U.S.

8 Now, we obviously would like to bring the
9 product back to the market once having found a
10 suitable manufacturer that meets the requirements. At
11 the present time, it's not known when that will occur,
12 and it would appear that there is a role for Phenytoin
13 in these indications. I'm not a clinical expert and I
14 wouldn't want to volunteer the opinion of the experts
15 here today, but it would seem that in the absence of
16 having Fosphenytoin marketed in the U.S. by anyone
17 that the IV Phenytoin serves some clinical role in the
18 armamentarium available to the physician.

19 DR. ANDERSON: Okay, so, I jotted down a few
20 questions that people had hoped that you might help
21 find the answers to. So, before the lunch break, if
22 you and I can meet.

1 DR. WELSH: Okay.

2 DR. ANDERSON: I'll compare notes with you.

3 DR. WELSH: Yes.

4 DR. ANDERSON: And we can see if you have a
5 chance to find some of that for us.

6 Otherwise, we can still come back to
7 clarifying questions, but I'm trying to sort of keep
8 the speakers who have scheduled their time to be able
9 to start on time. So, the next component of the
10 session is our point-counterpoint presentations and
11 our first presenter will be Dr. Coplin.

12 **Guest Speaker Presentations:**

13 **Point-Counterpoint: Should Intravenous Phenytoin**

14 **Remain on the Market Point**

15 DR. COPLIN: Hi, my name is Bill Coplin, and
16 my credentials were presented before. I am a daily
17 user of these drugs, particularly Phenytoin. Not
18 myself personally, but a prescriber. So, that should
19 be known at least for experience case. And I was
20 asked to take the point that intravenous Phenytoin
21 should be left on the market. One thing I would ask
22 the committee at some point, if I can ask a question

1 to them for an answer, is how did this get to this
2 committee, this question?

3 DR. ANDERSON: We'll let Dr. Katz respond to
4 that again.

5 DR. KATZ: Yes, questions were raised to us
6 about why Phenytoin should stay on the market, given
7 the incidence of Purple Glove Syndrome and the
8 presumed absence of cases with Fosphenytoin. And
9 since Fosphenytoin is for all intents and purposes
10 from an effectiveness point of view, a direct
11 substitute for Phenytoin, the question was raised.
12 And we looked through our data, and you've seen it all
13 presented, and remained questions internally about
14 whether or not there really were good cases with
15 Fosphenytoin. So, if you think of it in terms of
16 well, maybe there's no cases with Fosphenytoin, there
17 are plenty of cases with Phenytoin. What's the
18 advantage of keeping Phenytoin on the market? That's
19 how it evolved.

20 DR. COPLIN: All right. So, initially, I
21 think this is essentially a question of safety to be
22 raised, and has been brought up the incidents and

1 issues regarding Purple Glove Syndrome as seen with
2 the use of Fosphenytoin. Now, remember, this is a
3 drug that is a phosphate ester prodrug of Phenytoin,
4 and local phosphates is available anywhere in the body
5 essentially can convert this drug with an effective
6 conversion halftime of about 15 minutes into the
7 active drug Phenytoin.

8 So, reasons for this to be in the AERS
9 Database and potentially not in the medical literature
10 would include that non-academicians have been the ones
11 reporting this, and, therefore, may not be ones to
12 report this in the literature, not that it doesn't
13 exist. And so, to think that this could occur locally
14 with extravasation or otherwise is not beyond belief.

15 The other issues I will sort of address
16 along the way here into this talk. I should let you
17 know my relevant disclosures. I do sit on a
18 hospital's Medication Use Committee and a large
19 medical center's Pharmacy and Therapeutics Committee.
20 I have received research support from the original
21 manufacturer of Fosphenytoin, which was abruptly cut
22 off after our study, as I will describe.

1 I should also bring up issues of
2 abbreviations. As others have mentioned, most of
3 these have been covered and used across the day so
4 that you are aware what it is I'm talking about.

5 So, in terms of Fosphenytoin, this question
6 maybe also comes to mind that the original reason for
7 our research and interest into this is everything
8 seemed wonderful, that here would be a drug that could
9 provide Phenytoin to the brain, that potentially did
10 not have the local injection reaction issues, that
11 could be administered faster, some other questions of
12 outcomes that might be related to that. And
13 everything seemed wonderful, and then we were
14 approached, this occurred at 80 to 90 times the
15 present cost of Phenytoin that we were using. And,
16 so, this made a large financial impact at the time.

17 Now, as I'll go over cost issues later, this
18 cost issue is much less important, perhaps, available
19 generically. Of course, that doesn't speak to what
20 might happen in the future.

21 And originally it was marketed to replace.
22 The manufacturer of Phenytoin was the manufacturer of

1 Fosphenytoin. Pfizer here today for those--needing
2 the history. Park Davis was acquired by Pfizer
3 shortly after the time of this.

4 Now, the perceived disadvantages have
5 included things that have been described today, and,
6 also, the slower infusion time. The question is:
7 With this conversion of 15 minutes, does this actually
8 mean a slower, effective availability to the brain of
9 the actual active drug? And is this clinically
10 important any time differences that could happen?

11 Phenytoin cannot be given intramuscularly,
12 so therefore, it does provide an area where the lack
13 of intravenous access would allow the drug to be
14 given. And I'll describe some of the issues of
15 attention to safe infusion protocols, and, perhaps,
16 some intelligent prescribing practices that could be
17 used.

18 Obviously, the presence of propylene glycol
19 has been discussed today and the alkaline pH, and the
20 vehicle itself may be a cardiotoxin as much as the
21 drug as a Class 1B anti-arrhythmic is also potentially
22 a cardiotoxin, and in that respect, Fosphenytoin has

1 also been described today as having some of those
2 potential same effects, and these go back to reports
3 even from my chairman going back now some 43 years.

4 The potential advantages were original
5 reports of less frequent serious adverse events and
6 this rapid infusion, the ability to give this
7 intramuscularly, and the improve efficacy was touted,
8 but never quite proven along the way. The issue being
9 efficacy of the active drug being considered
10 equivalent with the addition to the FDA's approval of
11 the prodrug.

12 Now, the rational use of parenteral
13 Phenytoin equivalent-type drugs is another area open
14 for discussion, and has usually been reserved by
15 indication for those who are unable to tolerate
16 parenteral Phenytoin if Phenytoin is to be prescribed.
17 There are also the issue of loading doses to be used
18 for perioperative neurosurgical practice and severe
19 traumatic brain injury, et cetera.

20 Less clear are the indications for
21 maintenance dosing. The known epileptic not taking
22 medication who comes in, perhaps, after a single

1 seizure is awakening and is prescribed nonetheless by
2 emergency physicians, neurologists, internists, and
3 others, is prescribed intravenous Phenytoin where
4 perhaps oral Phenytoin could be given shortly
5 thereafter.

6 I've mentioned the issue of no IV access,
7 and then there is the question of status epilepticus,
8 where the indication for Phenytoin being an old one
9 for "grand mal status epilepticus" and the indication
10 given to Fosphenytoin without clear study.

11 Now, I would argue one thing in considering
12 this when we talk about the emergence of use of this.
13 As has been mentioned for access and availability,
14 Fosphenytoin is to be refrigerated. So, that may be
15 an issue certainly for smaller hospitals or those
16 where an emergency room pharmacy is not available with
17 a refrigerator, for instance.

18 One would argue from studies, the VA
19 Cooperative Study, David Treiman studies, and others
20 that rational use of Phenytoin in the treatment of
21 status epilepticus may be an older concept and that
22 where the goal is to stop the seizures that there is

1 no clear proof that the administration of Phenytoin
2 acutely or Phenytoin equivalence will actually stop
3 the seizures.

4 So, the question is: Do they need to be
5 given acutely in the case of status epilepticus
6 nonetheless. I present for you just a sort of
7 sequential concept of a paradigm that is in use by us
8 and many others.

9 If you look at the Department of Veterans'
10 Affairs Cooperative Study of status epilepticus, in
11 fact, Phenytoin alone was less effective or when given
12 in combination with Diazepam, then the initial
13 installation of Lorazepam. And is well argued,
14 therefore, that this be the initial first line
15 treatment. In those patients who received Lorazepam,
16 given Phenytoin as a second drug only added somewhere
17 between a 3 to 7 percent success, whereas the
18 Benzodiazepine as a second drug gave up to 14 percent
19 added success in patients who received Phenytoin alone
20 initially.

21 Now, one of the things that was discussed in
22 the review of our studies and others is the issues of

1 proper infusion techniques, and, certainly, one could
2 argue without Phenytoin left available that the
3 learning curve for doing this could disappear. One
4 could also argue, in no way badmouthing any of my
5 colleagues, that there may have been certain areas
6 shall we just call them less than perfect infusion
7 techniques either from choosing the wrong site, small
8 hand veins, for instance, or where the patency of a
9 line or the flushing of pooled Phenytoin after
10 administration may not have been complete. This,
11 obviously, could go for potential issues with
12 intravenous Fosphenytoin, as well, when local
13 phosphatase were to breakdown the drug into Phenytoin.

14 At least in this century, and I can go back
15 actually to reviews through 1996, the protocol that is
16 used, it was described earlier and written here, we
17 are without Purple Glove Syndrome patients in our
18 hospital whatsoever, and I would say only that it
19 confirms the safety of our technique, perhaps.
20 Certainly, the drug itself is a different issue.

21 Now, a lot has been made of this, and
22 knowing that Dr. Bleck is going to discuss this in

1 more detail, as well, I'm going to keep short this
2 issue, which is a real problem. As was mentioned in
3 our prospective study, that this was not seen in a
4 review of patients, where we have about a 62 percent
5 return rate for known epileptics, we work at a small,
6 little, quiet, inner-city, level-one trauma center in
7 Detroit. And others have suggested the incidences
8 described.

9 There have been other studies that were
10 described here and certainly using retrospective data
11 from databases is one thing or from hospital records.
12 I just query in doing this why the original
13 publications from the Mayo Clinic were actually review
14 of a period that was seven years prior to the actual
15 publication of the article, and whether that really
16 means what's happening in the modern day. Also, as
17 was mentioned, their infusion protocols were quite
18 unclear.

19 And, in fact, local site reaction pictures
20 are shown with local site reactions in the hand and
21 the more distal forearm. One might argue not the
22 ideal place to infuse these drugs.

1 The financial issues, as I mentioned, are
2 certainly one. So, if you take our hospital, a safety
3 net hospital for the City of Detroit, under current
4 use patterns at the time, and I should say that this
5 was at the time in 2002 that this would have had a
6 substantial on the hospital pharmacy budget. One
7 might argue that it also would make people think twice
8 about the appropriateness, as I've mentioned, what
9 those scenarios might be, for the actual
10 administration or ordering of an intravenous Phenytoin
11 equivalent compound.

12 The acquisition costs today, the base--well,
13 actually, I'm lying, these are acquisition costs from
14 two days ago within our hospital. For instance, from
15 manufacturers that have been mentioned before, that
16 this is now reduced to about a 1.4 fold difference in
17 costs. What is unknown is certainly that some of
18 these pressures may be for reducing the cost not just
19 generic manufacturer, the original manufacturer, as
20 was just described, is now out of the business, but
21 may be in the future, is certainly this doesn't
22 describe what may happen to the price in the future

1 where Phenytoin, perhaps, not giving some pressure for
2 the reduction in cost in Fosphenytoin.

3 And so, the unanswered questions and
4 ramblings that I certainly have with this is the
5 pressure of Phenytoin keeping the price down? The
6 shortage of Fosphenytoin is obviously quite concerning
7 and to be actually happening right now as this
8 committee is meeting really brings up questions to
9 remove the alternative.

10 Phenytoin and intravenous Phenytoin
11 equivalent compounds may not have quite the
12 application I've described, at least the scenario in
13 the time allotted for status epilepticus, yet, they
14 are widely prescribed, and this is sort of the basic
15 mainstay of initial epilepsy or seizure therapy in
16 many patients.

17 All right. Are there alternates for the
18 committee to decide other than discontinuing all
19 manufacturers of the drug? Does it have something to
20 do, perhaps, with the labeling, as I've seen has been
21 described. I was not privy to the same 200-plus page
22 document that you all were.

1 And the irony to me in this whole thing is
2 we use so much Phenytoin, and there appears to be so
3 little acute toxicity in an emergency department such
4 as ours, seeing 115,000 patient visits a year. Where
5 in less than a few months, we can complete a study of
6 279 patients in the prescription of these drugs.

7 If the committee would tolerate me just to
8 go a little deeper into the issues of safety of
9 infusion, I would just go over a bit concerning our
10 study and not for claiming any issues of primacy in
11 any fashion. I'm not aware of the same paradigm being
12 used in any of the other reported studies. My co-
13 investigators included pharmacists, nurses, and
14 emergency physicians, as well.

15 And as was described, we were really looking
16 what happens with routine emergency department use.
17 So, trained nurses and trained in administering both
18 drugs are going to administer in similar fashion.
19 They are not previously aware of Fosphenytoin and the
20 issues behind it, and are now out in the real world
21 and not in a study prescribed. The physician would
22 order Phenytoin and the pharmacy, based on the

1 randomization, would dispense one or the other drugs.
2 So, the nurses, there was an open label, but it was
3 not clear what to do. Save the issue of IM injection.

4 And this was, as I mentioned, carried across
5 in less than 4 months in 279 doses in 256 patients.
6 This was continued until the research gift from Park
7 Davis was completely dispensed. So, a convenience
8 cohort in that respect.

9 And the paradigm, as I say, the nurse was
10 aware, the patients did not know what drug assignment,
11 nor were they told, and we were allowed this form of,
12 if you will, deception and deferred consent by the
13 Human Investigation Committee.

14 At that time, a manufacturer that no longer
15 makes it, a pre-existing contract, was done. No one
16 was charged for the drug, and the manufacturer had no
17 further involvement at that time in the study until
18 its completion.

19 And the drug administration was mentioned
20 before, how it was done, the problem of the important
21 issues is that this is, perhaps, and artificially low
22 rate. Certainly, administration has been shown to be

1 safe, and we often will use it up to 550 mg/min, and
2 the Fosphenytoin issues certainly were that it was
3 stored under refrigeration. The maximum rate that we
4 allowed was 100 mg Phenytoin equivalent per minute.
5 And that was the plan.

6 For adverse events, the rate of infusion was
7 to be decreased as a first action. For the patients
8 receiving intramuscular Fosphenytoin, I leave this
9 here for you to read. It's certainly available to
10 you. That's obviously not the point of discussion
11 today here.

12 And the follow-up, as I mentioned, we went
13 back watching across three months for return of any
14 patients with any sorts of complaints related to the
15 Phenytoin equivalent infusions.

16 All right. The bottom line is that these
17 were patients who were by and large in reasonably good
18 neurological condition. For those of you familiar
19 with the Glasgow Coma Scale, and about 3 percent were
20 considered status epilepticus patients actively
21 convulsing upon an arrival to the ED.

22 The issues that come up in the

1 randomization, just to note, is that we were not
2 always able certainly to administer the Fosphenytoin
3 at the maximum rate allowed. Again, if this becomes
4 an issue for time of infusion and time of availability
5 for internal conversion, and the other thing, that it
6 would bring up similar numbers of patients had to have
7 the rate decreased because of some adverse event at
8 some point.

9 Notice most of the Phenytoin, this is not
10 because we were giving it through central venous
11 catheters. It was actually the vast minority of
12 patients who received the drug through central venous
13 catheters. And another, just as an issue, that
14 certainly the number of IM injections that were
15 necessary even up to four.

16 And going back to the question of status
17 epilepticus, the cessation of seizures is that they
18 didn't really appear to stop any faster with any
19 medication, and certainly, one would argue from the
20 modern treatment of status epilepticus and the
21 application as I showed you of protocol, essentially
22 leading to total intravenous anesthesia hopefully

1 within half an hour that it took well over half an
2 hour for patients to stop convulsing within the
3 paradigm at the time.

4 In the issue of adverse events that were
5 noted, of note, the only serious adverse event that
6 was noted across was one patient who became
7 hypotensive in the Fosphenytoin group with reduction
8 of the infusion rate, this hypotension went away, and
9 there were no other serious adverse events noted.
10 Some patients reporting vein burning more often in the
11 Phenytoin group, and was mentioned the issue of
12 parasthesias, we included, as well, in the lighter
13 side one man who did not really report it as an
14 adverse event. He said that they felt kind of nice.
15 So, nonetheless.

16 I'm just going skip this for the issue of
17 time here.

18 Another thing that was brought up were the
19 pressures and issues regarding emergency department
20 length of stay, and there were clearly factors related
21 other than the time of infusion that would lead to why
22 patients would stay in the emergency department

1 longer. So, it wasn't clearing out the emergency
2 department any faster in particular. But also notice
3 that that was independent of the issue of whether or
4 not patients had any adverse effects from either drug.

5 I mentioned just the intramuscular
6 Fosphenytoin. Obviously, this is a unique issue to
7 this drug and is not available as an issue for the use
8 of intravenous or injectable Phenytoin itself. These
9 are all, obviously, available to you in your handouts.

10 So, one would argue in conclusion what we're
11 able to find that it did not support our formulary
12 conversion. We seem to have a safe way that wasn't
13 adding any time to patients either remaining having
14 seizures or remaining in the emergency, nor leading to
15 any serious adverse events. Again, arguably
16 confirming our protocol more than anything else. And,
17 as such, we left the time restricted to patients in
18 status epilepticus with no intravenous access.

19 And so, I go back that these are the
20 questions I posed to the committee in its
21 availability, and, certainly, one might argue that
22 people would learn to live in a world without

1 Phenytoin. The question certainly with drug shortages
2 is: What happens then if there's no Fosphenytoin, and
3 I thank the committee for its time, for its
4 invitation, and I'm happy to answer any questions.

5 DR. ANDERSON: I guess I might suggest that
6 we let Dr. Bleck go, and then we can bring the two of
7 you back and get to questions at the same time.

8 DR. COPLIN: Yes.

9 DR. ANDERSON: And, so, now our counterpoint
10 from Dr. Bleck.

11 **Counterpoint**

12 DR. BLECK: Thank you for the invitation.
13 For those of you I haven't met, I'm Tom Bleck. I
14 started as an epileptologist many decades ago, and
15 then moved on into critical care. So, as you can
16 imagine, this is a topic that's near to my heart.

17 I have no current disclosures. In 1999, I
18 was a consultant to Pfizer along with Martin Brodie
19 from Scotland to review what were at that time all the
20 reports of potential adverse effects related to
21 Fosphenytoin. The concern at that time actually was
22 that deliberation of formaldehyde during the

1 conversion of Fosphenytoin to Phenytoin was resulting
2 in adverse cardiovascular effects.

3 Our conclusion at the time was that the
4 cardiovascular effects of Fosphenytoin were just the
5 same as those of Phenytoin and that the previous
6 literature that suggested that the vehicle was the
7 source of the toxicity was really a misunderstanding
8 in part because there was no way to give the Phenytoin
9 without the vehicle, and in part because what was
10 reported was respiratory irregularities in dogs, and I
11 think that was primarily from giving them a huge
12 amount of sodium bicarbonate unrelated to the drugs
13 themselves.

14 So, I'll make a few assumptions. The first
15 one I just, I think, explained, that there's not a
16 remarkable difference in their anticonvulsant effects
17 or their cardiovascular toxicity, and that the skin
18 soft tissue in muscular toxicities of Phenytoin aren't
19 an issue when it's given through a central line. And
20 I have to say most of the time when I give it, it's
21 being given through a central line, and, therefore,
22 the possibility of extravasation or of small veins

1 being involved is lost.

2 Well, in order to get this stuff into
3 solution, as has been mentioned, it's basically a
4 solution of sodium hydroxide and propylene glycol in
5 which a little bit of Phenytoin has been dissolved.
6 The toxicities are primarily, in my view, due to the
7 pH, and we'll come back to the one histologic study in
8 just a minute, but I think one of the things to keep
9 in mind is that the extravasation of the drug may be
10 in part responsible for what's been reported, even
11 though the people reporting it don't tell you that
12 it's extravasated. It would only take a small amount
13 of extravasation to produce the toxic effects that
14 have been reported.

15 So, I will follow-up on one of Bill's
16 points.

17 In fact, Bill and I could have just switched
18 each other's slides, so, it's knowing that I'm the
19 only thing between you and lunch, I will skip over the
20 points that he's already made.

21 But, basically, these drugs are not useful
22 for the control of status epilepticus. They're useful

1 for the maintenance of the patient after they're out
2 of status, perhaps in some circumstances less so than
3 in the past. This is a little deeper dive in to the
4 data from the VA Cooperative Trial, looking at the
5 various drugs, but instead of just looking at the
6 aggregate rates here, let's look at the individual
7 arms.

8 So, if you failed Lorazepam, then you have
9 Phenytoin, and Phenytoin was able to convert 7 percent
10 of the patients. If you failed those two, then you
11 get phenobarb. You got 2 percent.

12 Now, what's the issue here? It's not
13 whether one drug is that much more efficacious than
14 the other; it's that you only have time for one drug
15 and, after that you've lost your ability in terms of
16 conventional drugs to control status regardless of
17 what sequence you use. So, if you have phenobarb and
18 you failed, then Phenytoin only got 3 percent,
19 Lorazepam only 2 percent. These drugs didn't become
20 magically less-effective; it's just the amount of time
21 that's gone on with the patient in Status.

22 In addition, in the Diazepam followed by

1 Phenytoin arm, you can see similar results. And,
2 finally, in the Phenytoin-alone arm, Lorazepam looks a
3 little bit better, and although Dr. Twyman and his
4 friends say that I'm wrong about this, I'm convinced
5 that this just means that Phenytoin took a very long
6 time to be infused, and that the effect wasn't seen
7 until the next half an hour passed.

8 So, one of the possibilities for toxicity
9 going forward is that people will become less
10 cognizant of the precautions that Bill mentioned in
11 his talk. I would say, in fact, that this avoiding
12 injection in the glucose-containing solutions, while
13 it's all over the labeling, the one time it was
14 explored and published about as a letter in the *New*
15 *England Journal* in 1976, in which they actually
16 dissolved some intravenous Phenytoin in D5W, and in
17 the first 8 hours, there was essentially no
18 precipitation of it, and in 24 hours, there was a
19 modest amount. So, it's not clear to me that our
20 notion about that is correct at all.

21 You already heard more than you want to
22 about Purple Glove Syndrome. One thing that though

1 hasn't been brought up, Bill touched on it very
2 quickly and let it go by, is how is the drug actually
3 administered?

4 When I was a child, I was taught to give it
5 directly into the IV through a non-glucose containing
6 solution without dilution. There was study done at
7 the University of Illinois by de la Cruz and Leikin
8 published in 1988 in which they made various dilutions
9 not really in a systematic way, but for whatever
10 reason, different concentrations were given, and
11 showed that by diluting it and giving it intravenously
12 in a fresh solution, that they were able to get the
13 expected serum concentration of Phenytoin in the
14 patients, and that has actually caught on in a lot of
15 pharmacies so that even though there is no provision
16 in the labeling for the drug to be diluted, in a lot
17 of places, it actually is diluted.

18 Now, this was started mainly because of the
19 burning that was reported in the veins, and there was,
20 I think, a misapprehension that well, if diluting it a
21 little bit might be good, diluting it a lot is better.
22 But, remember, as you dilute it in solutions that have

1 themselves a pH of around five, as the pH drops, the
2 possibility of the drug coming out a solution becomes
3 an issue, and, perhaps, what we're looking at is you
4 can't tell from the published reports how many were
5 diluted, how many were given as the parent drug. We
6 may just be looking at the drug coming out a solution
7 because of the way it's being infused rather than
8 anything specific to the drug itself.

9 And we've already talked about all this
10 stuff. You don't want to see this again. I do want
11 to show, however, something that will address one of
12 Panayiotis' questions, which is this paper. For
13 reasons that are somewhat unclear, despite the fact
14 that they knew what was going on, this group decided
15 to do some skin biopsies in the area that was affected
16 by this Phenytoin injury.

17 And you probably can't tell what's going on
18 here. I had to read the paper to figure it out
19 myself. But, basically, in addition to the edema you
20 might expect, there is thrombosis in a large number of
21 small vessels, and that, to me, suggests that the
22 mechanism here is likely one that's may not vasculitis

1 in the usual immune sense, but a chemical vasculitis
2 related to the drug, whether it's propagating back
3 from the IV infusion site into the smaller venules in
4 the hand.

5 You really can't tell from this. There is
6 no stain here to help you tease out what's in arterial
7 and what's veinual. But, nevertheless, in the one
8 published report, thrombosis seems to be an important
9 part of this. So, you've all seen all this stuff
10 again here.

11 All right, Bill already showed you some cost
12 data. Mine is older than his. It's from last month.
13 But, nevertheless, depending on where you acquire it
14 from, you can get a pretty good deal on this stuff.
15 The pharmacist who provided the data did add that
16 we've been unable to get Fosphenytoin for the last six
17 months because of the manufacturing problems.

18 So, that's what I had planned to say, but
19 since everybody else has said the rest of what I
20 wanted to do, I want to make a couple of other points.

21 Regarding the equivalence of Phenytoin to
22 Fosphenytoin, in terms of its brain effect, the only

1 study of which I'm aware was done by Nancy Walton,
2 where she sampled extra cellular fluid from animal
3 brains during infusions of Phenytoin and Fosphenytoin,
4 and showed that while the serum levels, when it's
5 given according to the label, go up at essentially the
6 same rate.

7 The extra cellular fluid concentration of
8 Fosphenytoin actually rises more slowly than the
9 concentration of Phenytoin. And she didn't try to
10 explain it, but my guess is working on earlier work by
11 Roger Simon on the affected pH on the partitioning of
12 drugs like this across the blood brain barrier, that
13 the alkalosis of the parent Phenytoin infusion
14 actually favors the delivery of drug into the drug so
15 that although the Fosphenytoin and the serum is
16 producing Phenytoin that looks equivalent, perhaps,
17 the actual penetration of the brain is not as fast.
18 Since I would never again imagine using this drug to
19 terminate status epilepticus, I think that's, to me,
20 not important, but if you were going to use it, that
21 might be important to you.

22 And it may be some explanation in Bill's

1 data why the Fosphenytoin patients actually took
2 longer to come out of status.

3 Although we focused on Purple Glove
4 Syndrome, I think there is actually a lot more just
5 plain extravasation-related injury that never gets
6 reported. I've certainly seen it a lot out on the
7 floors where the drug is being given through
8 peripheral IVs.

9 Luckily, most of those patients don't have
10 more of a problem than the skin ulceration that I
11 passed by in one of these pictures. But that, to me,
12 is an important reason not to be injecting sodium
13 hydroxide subcutaneously.

14 So, I think the real question here is one of
15 safety, and in my current job, I spent a lot of time
16 trying to improve processes that end up having the
17 potential to harm patients. And, to me, as long as we
18 could assure an economical supply of Fosphenytoin, it
19 doesn't make sense to have two drugs when there has
20 been the potential for them to be confused. We've
21 seen that that was at least one of the issues early
22 on.

1 But, more importantly, if you get
2 Fosphenytoin at the Detroit Medical Center, you're
3 going to have people who know how to give it or give
4 Phenytoin there. If you go to many of the small
5 hospitals near where I work, although there aren't as
6 many small hospitals as there used to be, you won't
7 have people who have been trained how to do this
8 properly. Fosphenytoin, I think, is inherently a
9 safer drug than Phenytoin, and, for that reason, I
10 would suggest that the answer to the question is:
11 Should we remove Phenytoin from our formularies, the
12 answer would be yes.

13 So, thank you.

14 **Clarifying Questions**

15 DR. ANDERSON: Thank you very much. And,
16 so, I will just let people know that our 1:00 post-
17 lunch needs to start on time since that's the open
18 public hearing.

19 So, we have say 10 minutes or so that we can
20 go through some questions here and give people a
21 chance have a break and then have our public hearing,
22 and then we should have a little bit of gap of time

1 before we can begin our panel discussions to resume
2 some of these questions.

3 So, clarifying questions from the panel for
4 our point-counterpoint presenters?

5 Dr. Pearl?

6 DR. PEARL: (Off microphone.)

7 DR. ANDERSON: All right, so, Dr. Khatri?

8 DR. KHATRI: A question for Dr. Bleck. If I
9 understand correctly, it sounds like from your
10 experience when Phenytoin has been given by central
11 line, there have been no reported cases of Purple
12 Glove Syndrome or they certainly aren't frequent.

13 DR. BLECK: I haven't been able to find any
14 in which that was the case. True.

15 DR. KHATRI: Okay, so then my question
16 actually is any thoughts? I'd just be interested in
17 your thoughts about the case of the oral Phenytoin
18 causing Purple Glove Syndrome in terms of mechanism.
19 It sounds like you've been thinking about the
20 mechanisms quite a bit.

21 DR. BLECK: Do you want to start?

22 DR. COPLIN: After you.

1 (Laughter.)

2 DR. BLECK: With all due respects, I don't
3 believe it.

4 DR. COPLIN: I'll actually agree with my
5 colleague for a change.

6 (Laughter.)

7 DR. ANDERSON: I think Dr. Fountain?

8 DR. FOUNTAIN: Assume the big picture.
9 Could I ask both of you to comment on your general
10 clinical impression of the significance of Purple
11 Glove Syndrome and the significance of all the other
12 adverse effects of each of the drugs, which you sort
13 of did, but if you could just sort of make it explicit
14 for both of you.

15 DR. BLECK: Okay, well--

16 DR. FOUNTAIN: That is in relative terms.

17 DR. BLECK: So, to me, I mean, these rare,
18 but somewhat disturbing cases of Purple Glove Syndrome
19 have gotten all the press. There are lots of
20 anecdotal reports, meaning not reported and not
21 published presumably because of the feature of
22 litigation of patients, especially infants and small

1 children who have suffered amputation as a result of
2 extravasation without any of the colorful
3 manifestations of Purple Glove Syndrome.

4 To me though, the main issue in toxicity is
5 the same for the two drugs, which is if you give it
6 too fast, you're going to kill the patient from
7 cardiovascular collapse, and I've seen that happen
8 more time than I care to do. That's not going to be
9 any better with Fosphenytoin.

10 In fact, it might even be worse in that if
11 Phenytoin is being given and you see the blood
12 pressure falling or the heart rate starting to drop,
13 you stop giving it. Well, if you stop giving the
14 Fosphenytoin, you've got another five half-lives of
15 conversion before the blood level stops going up. So,
16 from that standpoint, I'll argue with Dr. Coplin here
17 that the safety issue related to cardiovascular
18 toxicity really, perhaps, favors the original drug.
19 All the other toxicities, which are primarily these
20 dermatologic and soft tissue things that are of
21 importance are pretty rare.

22 DR. COPLIN: I'll have to agree with my

1 colleague agreeing with me. But I give as another
2 scenario not to get too far away, but, certainly,
3 there are multiple catecholamines available for
4 infusion in cases, for instance, of shock,
5 distributive shock. There are extravasation issues
6 presented with these drugs. The question might come:
7 Why are we not looking at the issue of phenylephrine,
8 norphenylephrine, you have two drugs, albeit somewhat
9 different mechanisms, and the removal from
10 extravasation.

11 I think, as Dr. Bleck has put it, these
12 rather rare, given the denominator of Phenytoin
13 equivalent infusions, they've gotten all the press,
14 and it's not clear to me that certainly being given
15 properly that these risks need be realized, even
16 today.

17 DR. ANDERSON: Dr. Chapman?

18 DR. CHAPMAN: A question for Dr. Coplin.
19 You talked about your study. Did you include
20 pediatrics at all in that, because I sort of look at
21 them as a little bit special subgroup because getting
22 large bore peripheral IVs in kids is not practical.

1 DR. COPLIN: No, we didn't. Our hospital,
2 we see patients 14 and up, and by the letter of the
3 law, 11 and up by a reality of what shows up. So, I
4 really have no experience, and children come with
5 parents, so, I try to avoid those.

6 (Laughter.)

7 DR. ANDERSON: Dr. Schacter?

8 DR. SCHACTER: In either critical care of
9 medicine or in emergency room, are there other
10 parenteral medications or infusions that contain
11 sodium hydroxide, propylene glycol, or that are buffer
12 to pH of 11 or 12? And, if so, what is the range of
13 adverse effects to see with that that could be
14 relevant to this.

15 DR. BLECK: All right, so, propylene glycol
16 is commonly used as a diluent for many drugs, and if
17 you give too much of it, you'll get a metabolic
18 acidosis from it. As far as I know, this is the only
19 one though that's given it a pH of 12.

20 DR. COPLIN: And, to add to that, among
21 these drugs, is Lorazepam, which we've described, as
22 well, that's diluted with propylene glycol?

1 DR. ANDERSON: Dr. Rogawski?

2 DR. ROGAWSKI: My question is for Dr. Bleck.
3 There is some concern with Fosphenytoin that with
4 cleavage, you get release of phosphate, which could be
5 an issue with patients with end-stage renal disease,
6 and I'm just wondering if we didn't have any Phenytoin
7 to use in those patients, would that be an issue for
8 you?

9 DR. BLECK: Well, there's not enough
10 phosphate in the loading dose to make that much of a
11 difference. I think the formaldehyde issue was,
12 perhaps, more pressing, and it seems not to be
13 concerned any longer.

14 In terms of the maintenance drug, if you
15 can't give it internally, then you can always find
16 some substitute for it if you thought that the
17 phosphorous was an issue.

18 DR. ANDERSON: Dr. Snodgrass?

19 DR. SNODGRASS: In view of perhaps the fact
20 that Phenytoin may not be useful in stopping Status,
21 the issue of refrigeration requirements for
22 Fosphenytoin, is that even an issue in terms of

1 emergency medical services or being on Pyxis and maybe
2 you or others would have some idea of what's the shelf
3 life of Fosphenytoin if it's not refrigerated?

4 DR. COPLIN: We actually conducted sort of
5 our own little completely uncontrolled study of how
6 safe was the Fosphenytoin if left for a year at room
7 temperature, and we lost the bottle.

8 (Laughter.)

9 DR. COPLIN: So, that's how uncontrolled the
10 study was. So, we have queried within Park Davis and
11 Pfizer. We're not able, if you're able to tell us any
12 information from Pfizer, but it was not clear as to
13 the efficacy of available Phenytoin equivalence and
14 stability at that time timeframe.

15 The issue becomes there are lots of other
16 reasons simply other than status epilepticus that the
17 drug might be given. So, the storage certainly say
18 for medics to carry it were IM injections to be used
19 for patients or in emergency departments, I think that
20 is actually a real concern.

21 DR. BLECK: I'll disagree with my esteemed
22 colleague. I can't imagine a circumstance where you'd

1 give this drug at great distance from a refrigerator.

2 DR. ANDERSON: Dr. Varelas?

3 DR. VARLELAS: Yes, looking at the previous
4 presentation in the pie, I could see that almost 47,
5 48 percent of all Fosphenytoin administrations in the
6 ICU. So, we are in good shape to ask this question:
7 In these patients in the ICU, many of them clearly
8 have very low albumin levels, and because these drugs
9 are highly bound to proteins to albumin, you can have
10 a normal, semi-normal total level and a very high,
11 toxic level of free Phenytoin. Do you know any data
12 that actually associate these free level to the
13 cardiovascular, et cetera, side effects or adverse
14 reactions?

15 DR. COPLIN: There is an old report looking
16 at diphenylhydantoin, as the drug was called, and at
17 looking at it in uremic patients in that respect, and
18 it was not clear that there was a direct relation at
19 least at the doses given.

20 DR. BLECK: Yes, I don't know of anybody who
21 drew a blood sample at the time the blood pressure was
22 falling to answer that question.

1 DR. ANDERSON: Okay, so, we'll give the last
2 question maybe to Dr. Nelson for this session.

3 DR. NELSON: I was actually going to answer
4 Wayne's question about stability without
5 refrigeration. It actually has been studied and
6 published in the Annals of Pharmacotherapy, and it is
7 at least 30 days in undiluted form or in multiple
8 different solutions it's stable. Complete, 100
9 percent stable. So, this refrigeration issue I'm not
10 sure where that comes from. I mean, obviously,
11 somebody thought it was important.

12 If I could ask you guys one quick question,
13 the IM benefit of Fosphenytoin has always escaped me
14 because to give a loading dose would require 20 mLs of
15 injecting, which most nurses aren't really comfortable
16 giving more than 3 to 5 mLs.

17 So, you'd be stabbing these people a lot in
18 order to give them 20 mLs of solution. So, have you
19 ever used it? I've never used it that way.

20 DR. COPLIN: I'll give a couple of things.
21 The issues with the Annals of Pharmacotherapy, we
22 didn't consider 30 days, when I was answering the

1 previous question, really as long-term stability issue
2 certainly for a hospital pharmacy to turn over its
3 drug supply of something every 30 days is a little
4 unusual.

5 DR. NELSON: I wasn't criticizing you.

6 DR. COPLIN: Yes.

7 DR. NELSON: Because I know people looked at
8 it particularly for the EMS use.

9 DR. COPLIN: Right.

10 DR. NELSON: To keep it, because they need
11 to carry it for periods of time.

12 DR. COPLIN: The issue with intramuscular,
13 as I said, I presented stuff for you all to read.
14 Certainly, it was beyond the scope, so, I didn't talk
15 about it. We actually, up to four injections, our
16 nurses actually rebelled after the study and have by
17 and large refused for exactly the reason they think
18 that it--a word that starts with T that I probably
19 shouldn't use in the study of medical practice, but we
20 have actually had refusals to administer these four
21 injections to patients.

22 DR. BLECK: So, in their registration

1 trials, a number of nurses declined to give the
2 injections, and, among others, Dr. Eugene Ramsey said
3 he had to give them himself, but he would give 20 mLs
4 in one buttock, and it was tolerated. I don't know
5 what his patient selection criteria were.

6 (Laughter.)

7 DR. ANDERSON: Well, I'd like to thank you
8 both for sharing your expertise with us this morning.

9 We are now going to break for lunch. We
10 will convene again in this room at 1:00 for the open
11 public hearing session. Please take any belongings
12 that you may want with you at this time since the
13 ballroom is secured by FDA staff during the lunch
14 break, and you may not be allowed back into the room
15 until we reconvene.

16 And, panel members, please do not discuss
17 the issues amongst yourselves at lunch, but wait until
18 you returned. There is a buffet in the hotel and
19 there's other things located nearby, but there's no
20 special lunch provision for panel members.

21 (Whereupon, at 11:58 a.m., a luncheon recess was
22 taken.)

1 For example, this financial information may
2 include the sponsor's payment of travel, lodging, or
3 other expenses in connection with your attendance at
4 the meeting. Likewise, FDA encourages you at the
5 beginning of the statement to advise the committee if
6 you do not have any such financial relationships. If
7 you choose not to address this issue of financial
8 relationships at the beginning of your statement, it
9 will not preclude you from speaking.

10 The FDA and this committee places great
11 importance on the open public hearing process. The
12 insights and comments provided can help the Agency and
13 this committee in their consideration of the issues
14 before them. That said, and many instances and for
15 many topics there will be a variety of opinions. One
16 of our goals today is for this open public hearing to
17 be conducted in a fair and open way where every
18 participant is listened to carefully, treated with
19 dignity, courtesy, and respect. Therefore, please
20 speak only as recognized by the chair. Thank you for
21 your cooperation.

22 And we have a single open public hearing

1 speaker today, which is Dr. Kapur. You're on, sir.

2 DR. KAPUR: I thank you for inviting me. My
3 name is Jaideep Kapur. I'm here to represent American
4 Epilepsy Society, which is an association of
5 professionals involved in the care of patients with
6 epilepsy.

7 My travel is paid for by the American
8 Epilepsy Society. I have once received travel support
9 from Pfizer two years ago.

10 What I want to -- my remarks will be brief,
11 less than five minutes, hopefully. I just want to
12 mention our interests in IV Phenytoin and
13 Fosphenytoin. This is currently recommended as first
14 line of therapy after benzodiazepine has failed for
15 treatment of status epilepticus. That's the major
16 gist of my remarks and why though you've heard other
17 speakers mentioned, though it may not be as effective
18 but the truth is current recommendation and FDA
19 approval for drugs after benzodiazepine has failed is
20 Phenytoin or Fosphenytoin. That's the reality.

21 No other drug has an approval for treatment
22 of status after benzodiazepine other than Phenytoin or

1 Fosphenytoin. Other indications you've heard of.

2 Just to give you a sense for those few in
3 the audience who don't know enough about status
4 epilepticus, it is a condition that affects 61 per
5 100,000 Americans. About a quarter of them will have
6 mortality within 30 days after suffering from status
7 epilepticus. And so it is a fairly prolonged self-
8 sustaining seizure rather than a single seizure.

9 Shown to your right is a graph of the
10 incidence of status epilepticus and what I want you to
11 take away from that graph is that the incidence is a
12 lot higher. There are two extremes -- very young and
13 very old suffer from status epilepticus
14 disproportionately. Mortality is higher in the
15 elderly; long-term morbidity is higher in the young.

16 There is -- some of our members have
17 expressed concern with Phenytoin, IV Phenytoin, and
18 Fosphenytoin. That is as I just mentioned, elderly
19 suffer from status epilepticus. Elderly are at a
20 greater risk for developing hypertension and
21 cardiovascular risks due to Phenytoin, although that
22 study has not been done for IV Fosphenytoin.

1 So if, as you consider this, should there be
2 a recommendation for dosing in elderly? Can the rate
3 of 150 Phenytoin equivalents be per kilogram per
4 minute be acceptable or not in elderly is something I
5 hope the panel would consider.

6 Currently, as we reflect the practice within
7 the U.S. and you've heard today, Phenytoin is being
8 gradually replaced by IV Fosphenytoin. In ordinary
9 circumstances I wouldn't be here and worried about
10 this but there is tremendous shortage of IV
11 Fosphenytoin. Our members have repeatedly written to
12 us over the last four to six months. You've heard
13 sporadically throughout the day that there's a
14 shortage of Fosphenytoin. Here is the data from
15 Hospital Pharmacists Association website. Currently,
16 as you can see, the release date for Fosphenytoin is
17 not even available beyond certain dates. So very few
18 hospitals have IV Fosphenytoin right now. Many are
19 scrounging and calling manufacturers.

20 So if this panel chooses to withdrawal IV
21 Phenytoin, it should consider the impact on patients
22 because there is Fosphenytoin not available. In the

1 long-term that may be subtle, but please do. Our
2 society wants you to very strongly consider the
3 possibility that there is no IV formulation available.
4 So if benzodiazepines fail, our members would have
5 nothing to treat their patients with a drug until IV
6 Fosphenytoin is available.

7 I'll conclude my remarks and thank you.
8 Thank you for giving me time.

9 DR. ANDERSON: Thank you very much, Dr.
10 Kapur.

11 So that is the conclusion of the open public
12 hearing portion of this meeting. It's now concluded
13 and we will no longer take comments from the audience.

14 The committee now turns its attention to
15 address the task at hand, the careful consideration of
16 the data before the committee and the public comments.

17 And we have some sort of business left over
18 from the morning session. We asked Ms. Welsh some
19 questions on behalf of Pfizer that she went to try to
20 find some data for us. And so I'm going to give her a
21 couple minutes to do that and then we can resume our
22 questioning of the FDA, both clarifying and otherwise

1 from this morning's session as there were several
2 people who had questions left over for that.

3 **Clarifying Questions (continued)**

4 MS. WELSH: I'll repeat the question.

5 One of the first questions was regarding the
6 origin of the 119 probable -- possible cases of Purple
7 Glove associated with Phenytoin. And I'd like to
8 respond as follows. Of those 119 cases, 101 were from
9 the U.S.; five were from the U.K. There were two each
10 from Germany, India, and Ireland; and there was one
11 each from Canada, France, Israel, Italy, Jamaica,
12 Philippines, and Sweden.

13 The next question that came up was what was
14 the date of the Global Safety Database for Phenytoin
15 and the very earliest date of any case in that
16 database was 1982. The first possible probable case
17 of Purple Glove Syndrome was reported in 1983.

18 As regards the animal model for Purple Glove
19 Syndrome, the response to that is that there is no
20 animal model known at Pfizer. As regards the question
21 of cases of oral Phenytoin and an association with
22 Purple Glove, I do not have that information at the

1 moment.

2 DR. ANDERSON: So, thank you very much for
3 getting that information for us. Dr. Cavazos wanted
4 to make one comment on the animal model regarding
5 something he found in the pre-meeting materials.

6 DR. CAVAZOS: If you look at the Pfizer
7 submitted information in the pre-meeting material, on
8 page 16 under Appendix 3, there is actually
9 information there that talks about the following: in
10 the forewake of IV toxicity in rats study,
11 histopathology identifying transcutaneous necrosis and
12 inflammation at the injection site -- in this case,
13 the tail -- of treated males and females at four
14 weeks. So I will submit to you that necrosis and
15 inflammation are at least some comments, perhaps the
16 tail doesn't become purple but some components of the
17 issue at stake.

18 And so the question that I had earlier for
19 the Pfizer group was if there were similar studies
20 like that of Phenytoin to demonstrate if there was
21 truly a difference between the two incidents.

22 DR. ANDERSON: So I think in the present

1 circumstances we'll have to just note that there is
2 that literature in the material we can consult but it
3 doesn't look like there's additional information
4 Pfizer can give us at this time.

5 So at this point I'd like to go back to the
6 FDA clarifying questions. And I've got three names at
7 the moment on this list and then we can go from there.
8 Yours is not the first. And the first name on the
9 list is Dr. Pearl's. And you're second and you're
10 third, and then I'll get everyone else after that.

11 DR. PEARL: Thank you. Phillip Pearl.

12 I wanted to ask a couple clarifying questions
13 from Dr. Tobenkin's talk on the labeling because I
14 think this is really going to come down to clarifying
15 labeling, especially with regard to AERS that may
16 emanate from confusing labeling.

17 So the first is on Fosphenytoins. When
18 Fosphenytoin came out in '96, there was even this
19 policy, at least among hospitals where I was, that it
20 would be written or ordered as milligrams of
21 Fosphenytoin and the mg PEs. The numbers were
22 different by 1.5 times. It's very confusing. And

1 then as you showed in 2000, the AERS rate really went
2 down, although it hasn't disappeared because of this
3 problem between the conversion.

4 My impression then was that there was this
5 almost universal decision, and I'm not sure on what
6 basis. And that's what I'm asking you -- to longer
7 use PEs in orders. We switched right to milligrams.
8 Everyone uses a one-to-one conversion. Say you're
9 going to load someone with 18 mg/kg of Phenytoin.
10 Well, now all of our people, house staff, attending,
11 right, the same number, 18 mg/kg of Fosphenytoin. No
12 one talks about Phenytoin equivalents. We're
13 pretending -- we're pretending really that milligram
14 is milligram, even though it's not.

15 I thought this was directed by the FDA. And
16 my question for clarification is can you help me or
17 can anyone from the FDA help me understand how this
18 came about? Because it was almost an overnight
19 switch. And yet it really did clarify the practice of
20 use of Fosphenytoin.

21 DR. TOBENKIN: No, as far as I know, excuse
22 me, mg PE is still the standard of how it should be

1 dosed.

2 And in fact, that was part of the problem in
3 a lot of the AERS cases. It did state because of the
4 inconsistent use, practitioners who were actually
5 administering or pharmacists who were transcribing,
6 could not tell what dose was actually intended by the
7 physician. Whether it was -- because I don't know if
8 you remember on the vial, in a vial of 500 milligrams
9 there is 750 milligrams of Fosphenytoin and 500
10 milligrams of Phenytoin equivalence.

11 So if you happened to look at the vial and
12 you were a nurse, it became very unclear about what
13 was supposed to be administered. So we still
14 recommend that it should be mg PE because that really
15 clarifies what amount of Fosphenytoin should be given.
16 I think -- I'm speculating, but I do think probably a
17 lot of hospitals and ones that use computerized
18 programs already have that kind of instilled in the
19 program. And it will say mg PE but I'm sure not
20 everyone has that.

21 So that is part of our concern, that we
22 don't understand how many people really understand

1 that when you're switching from Phenytoin to
2 Fosphenytoin, you need to maintain the milligram that
3 was on Phenytoin.

4 DR. PEARL: Well, I thank you. I just can't
5 emphasize enough how paramount this is because
6 physicians are being trained to order milligrams per
7 kilogram totally oblivious to the fact that the
8 milligrams of Fosphenytoin are not the same as the
9 milligrams of Phenytoin.

10 DR. TOBENKIN: Right.

11 DR. PEARL: And my second question was
12 labeling on the Phenytoin. On the infusion it said
13 not as infusion. I think Dr. Bleck explained what
14 that means to most of us, which is you just give it
15 straight. But it is so confusing. And the fact that
16 people do try to have normal saline boluses, pre and
17 post, I think we need to clarify that. But my
18 question to you is from the FDA perspective, what does
19 that mean, not as an infusion?

20 DR. TOBENKIN: You know, that was before my
21 time. So I cannot answer, you know, who put that and
22 what their intention was. We have requested that they

1 remove that. Perhaps someone from DNP.

2 DR. KATZ: It's even before my time.

3 (Laughter.)

4 DR. KATZ: That has to be very, very old.

5 And I really have no idea what the motivation was for
6 doing that. I mean, everybody knows that it shouldn't
7 be given faster than 50 mg/minute, you know, some
8 maximum rate. And perhaps it was intended to call
9 attention to that. But it's completely misleading.

10 To get back to your first question, I was
11 around when we dealt with Fosphenytoin. And I don't
12 recall there ever being any decision. There would not
13 have been a decision from the Agency to say forget
14 about the PEs, just convert milligram to milligram.
15 It's possible, I suppose, that another source of the
16 confusion is that we do talk about mg PEs. We don't
17 say PE. We say mg PE. And so perhaps that's a source
18 of confusion because we know from other settings that
19 when you put a suffix on a drug, you know, drug X, you
20 know, drug A-XR, you know, extended release. People
21 often don't write the XR.

22 So I guess it's possible people just left

1 off -- leave off the PE and all you're left with is
2 the milligrams. Maybe it'd be less confusing if you
3 just said PEs and didn't include the milligrams. I
4 don't know. But chopping off the PE and just say, oh,
5 look, just substitute milligram for milligram. That
6 did not come from the Agency.

7 DR. PEARL: Thank you.

8 DR. ANDERSON: And so Dr. Schachter is next.

9 DR. SCHACHTER: Thank you. I have a
10 question for Dr. Chai and then a question for Dr.
11 Pinheiro.

12 First for Dr. Chai, if you're here. Okay.
13 You presented utilization Fosphenytoin and IV
14 Phenytoin based on two large databases -- the premier
15 and the SDI databases. And in looking at the slides,
16 both of those databases apparently also include
17 hospital procedures and diagnostic codes that were
18 associated with inpatient admissions.

19 So my question is if there's an opportunity
20 -- or have you tried to query that database in terms
21 of diagnoses of procedures done as a function of
22 patients taking Fosphenytoin or IV Phenytoin?

1 DR. CHAI: I don't know if you can pull up
2 Slide 10. That's the closest one pertaining to what
3 your question is. So once again I'd just like to
4 emphasize that due to the nature of the data that we
5 were able to obtain, this is primary diagnosis with an
6 ICD-9 code related to status epilepticus of 345.3
7 associated with the billing discharge for a drug. So
8 that's the most granular level of information we can
9 get. That's not to say that this drug was
10 specifically used for status epilepticus, but it's
11 associated with that billing discharge.

12 DR. SCHACHTER: I guess what I'm asking is
13 in those patients who had a billing discharge
14 involving Fosphenytoin or Phenytoin, were there other
15 diagnoses or procedures that could indicate that the
16 patient had Purple Glove Syndrome?

17 DR. CHAI: Oh, that was not -- I don't think
18 there's an ICD-9 code for Purple Glove.

19 DR. SCHACHTER: Or, you know, a related
20 diagnosis, much the same as Dr. Pinheiro was querying
21 the VA database.

22 DR. CHAI: Yeah, Dr. --

1 DR. SCHACHTER: It seems like they're both
2 quite large databases.

3 MS. STAFFA: My name is Judy Staffa. I'm
4 the acting director of the Division of Epidemiology.
5 And the reason we did not do that is because we could
6 have done a similar search like what was done in the
7 VA based on the codes but we had no ability to get
8 back easily to the clinical data to be able to
9 validate it. And based on our experience with the VA,
10 I don't know that we could have trusted that the codes
11 were for identifying people who actually had Purple
12 Glove. So that's why we didn't do that.

13 DR. SCHACHTER: Okay. Thanks. And for Dr.
14 Pinheiro, the search strategy or the strategy used to
15 try to uncover cases possibly consistent with Purple
16 Glove Syndrome in the VA database, if you had applied
17 that, and this is totally hypothetical, but had you
18 applied that to the consecutive patients in the
19 retrospective study of O'Brien, et al. from the Mayo
20 Clinic, would those cases have come up as well? I'm
21 just trying to figure out what could possibly explain
22 the difference in incidence rates between different

1 centers.

2 Or conversely, if you had applied O'Brien's
3 definition of possible Purple Glove Syndrome to the VA
4 dataset, would you still have come up with zero in
5 both cases?

6 DR. PINHEIRO: Right. The problem is that
7 we didn't have the capability of doing text string
8 searches in all of the patients in our population. So
9 we had to narrow it down to patients with ICD-9 codes
10 that would serve as a proxy for the severe phenotype
11 of Purple Glove Syndrome.

12 DR. SCHACHTER: I see.

13 DR. PINHEIRO: Had we had the ability to do
14 text string searches throughout all the patients
15 included perhaps that would have been the case.

16 DR. ANDERSON: Yes.

17 DR. HERSHKOWITZ: Yeah, hi. If I recall
18 right from the O'Brien study, one required a skin
19 graft. And I believe was skin graft one of your
20 initial search terminologies?

21 DR. PINHEIRO: Yes, it was.

22 DR. HERSHKOWITZ: So one case would have

1 shown up.

2 DR. ANDERSON: Okay. So now we're to Dr.
3 Wolfe, who has been waiting patiently.

4 DR. WOLFE: I just have a brief clarifying
5 question for Dr. Fine. On Slide 32, where you have
6 the 43 cases of Phenytoin Purple Glove Syndrome,
7 others including you have said that this is mainly in
8 elderly people. It's a risk factor. Of the 37
9 patients in this slide who have age as the range was 3
10 years to 88.

11 So my question is simply how many of these
12 other 35 patients were children? In other words, were
13 under 16 or 18 or however you want to define it? If
14 you could -- if you have that, that's fine. If it
15 could possibly be obtained it would be good because we
16 see this apparent asymmetry. A lot of these overdose
17 death cases are in children and most of the Purple
18 Glove Syndrome with Fosphenytoin and most of the
19 Purple Glove Syndrome with Phenytoin are in older
20 people.

21 So just -- do you know roughly or could you
22 find out how many of these other 35 people, besides

1 the 3-year-old and the 88-year-old were children?

2 DR. FINE: Yes. I would have to consult the
3 raw data just to clarify how many. Just for the
4 audience here, the broad range was important to
5 emphasize that there were cases in very young and very
6 old patients but the median -- the median and mean
7 presented, as well.

8 DR. ANDERSON: I think Dr. Chapman wants to
9 direct something to the pediatric issue, as well.

10 DR. CHAPMAN: Well, you know, I'll just
11 point out that status epilepticus has sort of a
12 bimodal distribution. Right? It's in the very young
13 and very old so it's possible it's just exposure. You
14 just have more patients within that age range that are
15 exposed to the drug is a possibility.

16 DR. ANDERSON: Did you have more to follow
17 up on that, Dr. Wolfe?

18 Okay, so Dr. Lee, please.

19 DR. LEE: Yes. I've just got a quick
20 question on -- actually, it was from a couple of
21 different slides but I guess we can go with Dr. Fine.
22 Of course, just wait till he sits down.

1 Let's see here. Where was it now?
2 Slide No. 18 discussed the Coplin data
3 there. And speaking about the dilution techniques
4 associated with IV Phenytoin, has there been
5 discussion? And where is the FDA as far as, you know,
6 how does the FDA stand as far as possibly adding that
7 dilution-type information into the label? Is that
8 something up for consideration or where are we on
9 that?

10 DR. KATZ: I don't think we've considered
11 it. It's something perhaps to consider. I don't know
12 that we've seen any data submitted about that. We'd
13 have to think about that.

14 DR. ANDERSON: So Dr. Twyman is next.

15 DR. TWYMAN: Yeah. I just want to follow up
16 with a question with Dr. Chai on her slide, I believe
17 15. The data on the distribution of use in the
18 hospitals is quite interesting. It looks pretty
19 similar between Fosphenytoin and Phenytoin. And I was
20 just wondering, is it known if both agents were on
21 formularies for both of these databases? And if they
22 weren't on both, you know, if both drugs were not on

1 the formularies, is it known why one would be there
2 versus another? Is it price or is it a safety review
3 assessment from the formulary committee?

4 DR. CHAI: I was not able to get the
5 granular data that you're asking for in terms of
6 hospital formularies. Perhaps there's somebody from
7 hospital formularies that can answer that question
8 better. This just show the proportion of discharges
9 that we were able to get -- the difference between the
10 two products.

11 DR. TWYMAN: I'm just wondering, you know,
12 what's driving the preference? Because the
13 utilization is the same and if the two drugs are on,
14 you know, are on the same formulary or are they being
15 preferred over one of the other in these hospitals?

16 DR. ANDERSON: Is this related -- yeah, Dr.
17 Avigan.

18 DR. AVIGAN: Yeah, I think that as we
19 discuss these two slides, we actually didn't know for
20 sure and we wanted to ask the Advisory Committee a
21 little bit about this.

22 So the two points that are notable from that

1 slide and the following slide are, one, that the
2 distributions are pretty overlapping. And you can't
3 distinguish a particular drug that's exclusively used
4 for one of those settings. And the other is that if
5 you look at specific hospitals, there's a certain
6 percentage, robust percentage where both are available
7 and utilized, whereas there are some hospitals where
8 you use one or the other.

9 When one reads reviews on this written by
10 experts, it appears that some experts prefer one and
11 some the other. But the reasons for that might be
12 perhaps commented on by the Advisory Committee.

13 DR. ANDERSON: Was it related to this same
14 point, Dr. Woods, or did you have -- ? Okay.

15 DR. WOODS: Just as a matter to maybe get to
16 your question, I think a number of organizations
17 worked with their pharmacy committees, P&T committees,
18 drug use committees, to develop drug use policies that
19 in some cases restricted use of the drug to certain
20 patient populations. I think we saw an example of
21 that in the Detroit receiving data where they now
22 restrict it to certain populations. So I would guess

1 that it's a combination of both drugs were on
2 formulary; one drug was on formulary, one drug was on
3 formulary and restricted.

4 DR. ANDERSON: Dr. Rogawski.

5 DR. ROGAWSKI: All right. Thank you. I'm
6 wondering if I can get some clarification from the FDA
7 regarding the incidence of amputation. And perhaps
8 Dr. Fine could come forward to respond to my inquiry.

9 So when Susan Welch presented the Pfizer
10 data it was, I think, quite dramatic to hear that of
11 the incidence among the 179 cases of possible or
12 probable Purple Glove, there were 11 amputations. And
13 this seemed to be a lot bigger than what we had heard
14 from you, Dr. Fine, with respect to the literature. I
15 think you mentioned that there was only one case of
16 PGS associated with amputation in the literature.

17 But in the briefing documents there was
18 mention of a report that was published in the 1980s
19 from a collaboration, I guess, between the CDC and the
20 FDA where there were five cases of amputation that was
21 reported. And so I'm just wondering how the FDA views
22 this. What do you think is the incidence of

1 amputation in PGS?

2 DR. FINE: Okay. There is some discrepancy
3 in the numbers of 11 and 1. So I spoke prior to the
4 break briefly about how there was some methodology
5 differences and how we searched the database as well
6 as the definitions were different, as well. Pfizer
7 presented their categorization criteria in the four
8 groupings, and we presented a case definition that may
9 have been stricter where especially in the context of
10 cases prior to the more established definition or
11 relatively established definition of Purple Glove
12 Syndrome and the clinical features, so some of those
13 cases potentially may have only sadic (ph.)
14 extravasation and that would not have been captured in
15 our case definition. And it could have resulted in
16 amputation. So that clarifies a little bit.

17 Just to quickly comment on the citation you
18 had about the five cases that were reported in that
19 one document by Spangler. Those cases were not --
20 there's no causality or investigation, detailed case
21 descriptions of these to determine what the event was
22 that led to the amputation. So, again, if those cases

1 would have been in AERS, they would not have been
2 captured by our case definition.

3 DR. ANDERSON: Yes, sir.

4 DR. AVIGAN: Just to clarify, these are --
5 both databases and the ascertainment of the most
6 severe phenotypes with amputation are not measures of
7 incidences; they're rather frequencies within that
8 population of cases which, of course, are
9 spontaneously reported. So there's no -- in none of
10 this is there a measure of incidence.

11 These are still -- one gets the impression
12 that these are rare. There may be some way --
13 differences in each databases of the biases of
14 reporting of the most severe versus the less severe
15 phenotypes. So that's a critically important point.

16 I think what you're concerned about is that
17 at least for those cases that have been reported
18 either in clinical trials or spontaneous reports from,
19 you know, post-marketing cases that we have the
20 maximal ascertainment in the most serious cases. But
21 we don't actually, which is an important point, but we
22 don't actually -- none of these databases actually

1 provide us with a measure of incidence.

2 DR. ANDERSON: Okay, so Dr. Fountain.

3 DR. FOUNTAIN: Mine follows directly on
4 that. If somebody loses a limb, that's a whole
5 different story than everything else. It's kind of
6 the, you know, if you have something temporary, even
7 if it's a severe and painful problem, that's not so
8 bad. But if you lose a limb, that's permanent. So
9 that's kind of the focus of my concentration about the
10 whole issue of Purple Glove Syndrome separate from
11 other safety issues.

12 So I'm trying to figure out not so much the
13 incidence but I'd take the absolute number of
14 amputations known in the world to anybody in any way
15 and so would it be fair to say that by whatever
16 definition of Purple Glove Syndrome that it's fair to
17 say there seem like there have been 11 cases of
18 amputation in the world in one way or another by some
19 definition of Purple Glove Syndrome?

20 DR. FINE: Well, I would agree that there
21 are 11 cases identified by the sponsor that report
22 amputation by Phenytoin; however, it's unknown if

1 those are related to extrapolation in skin necrosis or
2 if they were a direct result of clearly defined
3 clinical definition of Purple Glove Syndrome.

4 So I think it has to do with some
5 discrepancies in the definition itself, especially
6 when you're looking at a case in the 1980s versus
7 post-1991 when there was a more standardized
8 definition, per se.

9 DR. FOUNTAIN: That's the second half of my
10 question. And is do you have any idea of the
11 distribution of the amputations through time? Your
12 database went from 1982 to 2010 and the FDA's went
13 from 1996 to 2010. Right?

14 DR. FINE: 1998. I'm sorry, 1998 to 2010
15 were the cases that we identified.

16 DR. FOUNTAIN: Okay. So about twice as
17 long. About twice as many total cases, a little more
18 than that. But yet the amputation number was
19 substantially different. So it seems reasonable to
20 think that maybe there were more earlier on in the
21 '80s when medicine or life maybe Phenytoin was
22 different, something was different. So do you have a

1 comment on the distribution through time?

2 MS. WELSH: Yes. In terms of the time
3 distribution of the 11 amputations, one in 1983, two
4 in 1984, two in 1985, two in 1987, one in 1989, one in
5 1992, one in 1995, and one in 1996.

6 DR. FOUNTAIN: Three since 19 --

7 DR. ANDERSON: So since 1998 there's been in
8 amputations.

9 MS. WELSH: Not in this association of
10 Purple Glove Syndrome associated with Phenytoin.

11 DR. ANDERSON: And that's when your starts
12 was in 1998?

13 DR. FINE: The cases we identified were
14 between 1998 and 2010.

15 DR. ANDERSON: Do you want to follow up on
16 that?

17 SPEAKER: I just wanted to be sure I
18 understood it.

19 DR. FOUNTAIN: Yes, so none in that interval
20 and three since, in my frame of reference, since 1992.

21 Thank you. I think that clarifies it for
22 me.

1 DR. ANDERSON: Dr. Katz.

2 DR. KATZ: Yeah, just to remind folks, Dr.
3 Pinheiro presented the results of -- the preliminary
4 results, anyway, of the VA study. And she had
5 expressed reservations about it. And you heard what
6 those reservations are. But one of the terms that was
7 searched was amputation. And there were 10,000
8 patients who had received Fosphenytoin and 10,000 who
9 received Phenytoin. There were no cases that folks
10 felt could reasonably be attributed to Purple Glove.

11 So if those data are valid, and again, Dr.
12 Pinheiro who is an expert has reservations about those
13 data, but if they are accepted you can at least begin
14 to think that you might be able to sort of cap the
15 risk based on those sorts of exposures for amputation.

16 DR. ANDERSON: Clarifying question, Dr.
17 Silbergleit.

18 DR. SILBERGLEIT: On the cardiovascular
19 question for Dr. Gatti, I guess, in the conclusion of
20 your report your conclusion was associated with
21 cardiovascular events in health adults and children
22 without underlying comorbidities. But I guess I

1 didn't see in the briefing where that's broken down.
2 I mean, healthy -- we don't usually give Phenytoin in
3 healthy people. So is that from -- where is the
4 healthy people coming from?

5 DR. GATTI: Okay. So your question is to
6 further define what is meant by healthy in the third
7 bullet point of the conclusion? Is that correct?

8 DR. SILBERGLEIT: Yeah, where are we
9 referencing -- where in the data presentation are we
10 referencing healthy people?

11 DR. GATTI: We are referencing the review
12 basically from there. What we mean by that is
13 basically these cases were not associated with
14 comorbidities such as cardiovascular, I believe. Is
15 that correct, Dr. Fine? Yeah.

16 DR. FINE: No cardiovascular disease?

17 DR. SILBERGLEIT: So you're saying --

18 DR. GATTI: I don't mean that they don't
19 have seizures or they don't have, you know, --

20 DR. SILBERGLEIT: And this isn't -- we're
21 not talking about trial data from Phase 1 healthy
22 people; we're talking about --

1 DR. GATTI: No.

2 DR. SILBERGLEIT: -- patients that had
3 cardiovascular outcomes where the causal link was not
4 thought to be cardiovascular comorbidity.

5 DR. GATTI: Correct.

6 DR. SILBERGLEIT: Is that what you're
7 saying?

8 DR. GATTI: Correct. Correct.

9 DR. SILBERGLEIT: Okay.

10 DR. ANDERSON: Okay. Dr. Nelson.

11 DR. NELSON: Question for Dr. Tobenkin.

12 Actually, two parts. The first part is maybe
13 straightforward or maybe it's not. The second part
14 may not be answerable.

15 According to, you know, your Slide No. 6, I
16 get a sense that about half of the medication errors
17 can be very cleanly related to the fact that there are
18 two preparations on the market. Do you have a sense
19 overall what percentage of errors are related to the
20 fact that there are two preparations?

21 DR. TOBENKIN: Wait, sorry. I was trying to
22 look at the slide.

1 DR. NELSON: I'm sorry. Yeah, so, I mean,
2 some of these are very, I mean, obviously wrong drug
3 happened because there's two preparations on the
4 market and probably duplicate therapy as well. But
5 overall, do you have a sense -- would the majority of
6 these errors not have occurred?

7 For example, would the wrong dose not have
8 occurred had there not been an option to give the
9 other drug? Would it have simplified things to such
10 an extent that many of these errors would not have
11 happened?

12 DR. TOBENKIN: I think a lot of the errors
13 occurred because of the way it was labeled, not due to
14 the intrinsic characteristics of the drug. And I
15 don't think it had to do with the availability of two
16 on the market.

17 DR. NELSON: Okay. Well, that actually does
18 address my second part of the question because, you
19 know, kind of the granddaddy of the two drugs on the
20 market problem, I guess, is amphotericin, right, where
21 there's, you know, the multiple episomal forms and
22 then the nonepisomal forms. And clearly when those

1 errors occur they could be devastating and many people
2 have suffered and many people have died because of
3 that.

4 Now, what is available -- and I don't know
5 if this is a question for you or if I could even ask
6 it, but what is available at this point to FDA to fix
7 this labeling problem other than what we've talked
8 about with, you know, drilling into people that they
9 have to order it in PEs?

10 DR. TOBENKIN: Well, the issue with total
11 drug content, with the revised labels that has
12 decreased and there are virtually none of those
13 reported, mg PE I think is -- it's a much more
14 difficult problem because we have to determine why
15 exactly it's not being ordered as mg PE. Is it that
16 people are just dropping the modifier or the PE? Do
17 they not understand what PE represents? Or I think
18 there could be various reasons. And I think we need
19 to determine the exact root cause.

20 DR. NELSON: Yeah, I mean, the reason I
21 bring up the amphi thing is because every hospital is
22 so sensitized to the amphoterism potential error. And

1 despite that, and in my practice as a medical
2 toxicologist I still see these cases, not commonly but
3 that still occur because people give the wrong
4 formulation. They order liposomal form and they give
5 the non and people are getting multifold drug
6 overdoses. And this is something that's so -- we pay
7 such close attention to this and it still causes
8 errors. This is the kind of problem I have a sense
9 that is going to be much harder to fix.

10 DR. TOBENKIN: Yeah.

11 DR. ANDERSON: Dr. Khatri.

12 DR. KHATRI: Yeah, I have a question along
13 the manufacturing lines for Ms. Welsh from Pfizer and
14 anyone else who might have expertise in this. I'm
15 just trying to understand how much -- so the
16 manufacturing of Fosphenytoin versus Phenytoin, how
17 much of it is actually that Fosphenytoin is hard to
18 make and how much of it -- and make appropriately by
19 guidelines -- and how much of it is because of supply
20 and demand? And could we imagine, say, if Phenytoin
21 were not available, suddenly companies would start
22 making Fosphenytoin? I just want to understand the

1 details of that.

2 MS. WELSH: Thank you for the question. I'm
3 not able to comment further. I'm not a manufacturing
4 expert. Sorry, I cannot provide any more information.
5 Thank you.

6 DR. ANDERSON: Does anyone else have
7 expertise on the manufacture of Fosphenytoin that
8 would help us understand the difficulty? Thank you.

9 DR. SILBERGLEIT: No, but I would say
10 there's a huge demand. And there's no drug.

11 DR. ANDERSON: I think it's the supply side
12 the question was related to rather than the demand
13 side.

14 Dr. Marder.

15 DR. MARDER: As far as I can tell, the two
16 reasons to continue to prescribe Phenytoin are that
17 you don't have to refrigerate it and it might be
18 available in places where you can't refrigerate
19 things. And then the supply issue. And on the other
20 side, in favor of the Fosphenytoin is the absence of
21 skin reactions.

22 And what I'd like to ask Dr. Bleck is that -

1 - whether he, first of all, are there any other drugs?
2 Do we know that there are no other drugs that have the
3 same problems? And does he think that the general
4 skin reactions are related to the Purple Glove
5 Syndrome just skin reactions but barring severity?

6 DR. BLECK: In terms of the refrigeration
7 question, the only drug we commonly run into where
8 that's an issue is lorazepam. And the reason it's not
9 carried in a lot of emergency medical systems on
10 ambulances is this requirement which in the actual
11 timeframe that the lorazepam would be used is probably
12 unrealistic in terms of the amount that actually
13 degrades with heat. You have to heat the ambulance up
14 to 40 degrees to make it degrade fast enough to make
15 that relevant.

16 From the skin standpoint, I don't honestly
17 have any other drug to compare it to. This seems to
18 be a unique problem.

19 DR. ANDERSON: Dr. Rogawski. Oh, I'm sorry,
20 did you --

21 DR. MARDER: I also wanted to know if you
22 thought Purple Glove Syndrome was simply in the

1 spectrum of the localized skin necrosis and so on that
2 we see with Dilantin injections when they're not done
3 properly.

4 DR. BLECK: Okay. So I think it is in the
5 spectrum in the sense that they can overlap, but I
6 think that the extravasation resulting in basically a
7 burn without injury to the tissue that wasn't touched
8 by the high pH material is different from the Purple
9 Glove which looks like it's some sort of vasculitis or
10 at least thrombotic disease.

11 DR. ANDERSON: Dr. Avigan has something on
12 this topic.

13 DR. AVIGAN: Yeah, I just wanted to clarify.
14 I presume you meant the local skin reactions because
15 there are, of course, serious skin reactions which are
16 diffuse. Stevens Johnson Syndrome and toxic epidermal
17 necrolysis, which are shared by both drugs. So I just
18 want to be clear that we're not talking about those
19 reactions; we're talking about local reactions.

20 DR. MARDER: Yes. Thank you.

21 DR. ANDERSON: So now back to Dr. Rogawski.

22 DR. ROGAWSKI: Yeah, just on that last

1 point, I think the issue there is pruritis, which I
2 gather is more frequent in Fosphenytoin than with
3 Phenytoin. You know, it's a nuisance; it's not a
4 major significant medical issue.

5 What I wanted to do though is just to
6 clarify in my own mind this issue of the amputation in
7 terms of the numbers that we've been hearing. And
8 just again for complete clarity in my own mind, the
9 Pfizer data that we heard about, I'm assuming all of
10 those patients that had the amputations had possible
11 or probable Purple Glove Syndrome. They weren't
12 including patients who, for example, had gotten the
13 drug but had an amputation maybe for some other
14 reason.

15 In the case of the CDC data that we heard
16 about, the CDC-FDA Report, those five patients who had
17 the amputations, is it possible that some of those
18 patients had amputations that weren't necessarily
19 related to the Purple Glove? Or was there a direct
20 relationship between those five patients that they
21 reported and having definitive Purple Glove Syndrome?

22 DR. FINE: Again, those cases from that time

1 period, I believe it was 1969 to 1984, along those
2 lines, that the one paper with the joint efforts the
3 CDC and FDA are referring to, those cases, of course,
4 are in AERS as the paper specified, but again --

5 DR. ROGAWSKI: They were what?

6 DR. FINE: Those cases were from the AERS
7 database and were evaluated. But again, it comes to
8 the distinction that was the amputation a direct
9 result of events that were adequately defined by the
10 case definition or Purple Glove Syndrome, or some
11 other local reaction, something that was not -- where
12 the report was not necessarily describing the typical
13 features of the Purple Glove Syndrome as predefined.

14 DR. ROGAWSKI: But the patients could have
15 had amputations for some other reason. They could
16 have had gangrene or for whatever reason that people
17 have amputations. Is that possible or --

18 DR. FINE: That is possible based on the way
19 the data is dealt with in AERS, is that an event --
20 it's listed -- the drugs -- the suspect drugs are
21 listed as well as any event described. So it's,
22 again, it's unknown exactly if there's a true cause

1 and effect and what kind of causality there was in
2 each of those implications.

3 DR. ROGAWSKI: Thanks.

4 DR. ANDERSON: Okay, Dr. Cavazos.

5 DR. CAVAZOS: Yes, my question goes back to
6 Dr. Chai in regards to the data for 20 percent of
7 hospitals that are using Fosphenytoin only. Since
8 that's one of the questions that is posed to this
9 panel, so what happens to these hospitals that only
10 have Fosphenytoin? How are they dealing with the
11 supply issues? Do we have any information about that?

12 DR. CHAI: One major point is that the
13 hospital characteristics slide was for year 2009. I
14 think the shortage problem is more of a problem this
15 year.

16 I'm not sure how they're dealing with the
17 problem. I assume that they may use IV Phenytoin but
18 that's purely speculation.

19 This is basically what it is, 2009 data.
20 It's not formulary data. It's just basically the
21 proportion of hospitals reporting the use of either
22 product or both.

1 DR. CAVAZOS: Supply issues are not new for
2 this situation. I mean, there were intermittent
3 supply problems in the past and so to an extent there
4 might have been some information from those
5 individuals from those particular hospitals.

6 DR. ANDERSON: It would be nice to know why
7 the hospitals chose one or the other but from the data
8 you have we don't know why any of those hospitals
9 chose one or the other or whether they used both but
10 only one ended up in the database.

11 DR. CHAI: Exactly. Reasons are not stated.

12 DR. ANDERSON: Okay. Dr. Kindler.

13 DR. KINDLER: Yes, Dean Kindler. This I
14 guess would be a joint question to Drs. Gatti and
15 Fine. And it's more of a clarifying perspective. I
16 want to make sure that I have a clarified perspective
17 on this. Given the limitations that we have with the
18 epidemiology and truly understanding incidence or
19 maybe even prevalence of Purple Glove Syndrome, maybe
20 having a better understanding of cardiovascular
21 complications with both treatments, would it be fair
22 to say or is it a reasonable perspective that in the

1 current patient treated with either agent would be far
2 more likely on the idea of irreversible complications
3 to die from administration of either of these
4 therapies than to develop any significant risk for
5 amputation based on the best information we have right
6 now? Because it seems like the fundamental question
7 is a safety issue here today. And it seems
8 cardiovascular issues with safety predominate and
9 really are equivalent as best as I can tell from the
10 data here in that really the peripheral glove,
11 although, you know, dramatic and certainly anxiety
12 provoking, is a much smaller percentage. And I just
13 want to make sure my perspective would be felt
14 accurate on your review of those data.

15 DR. GATTI: Let me just repeat that. You
16 are asking if the adverse events of cardiovascular and
17 hypertensive events are outweighing or perhaps more
18 serious in sequelae than the perhaps Purple Glove or
19 skin reactions?

20 DR. KINDLER: Yes, I mean, basically on your
21 data here, too, you have cardiovascular deaths, which
22 if I understand the report correctly are believed

1 directly attributable to either Phenytoin or
2 Fosphenytoin administration. And again, a lot of the
3 issues that we've talked about seem to have the
4 greatest implications to cardiovascular complications.

5 DR. FINE: And also the intention of the
6 review of the cardiovascular data is, yes, the
7 seriousness. But also there was a perception that --
8 and many of the speakers had discussed that
9 Fosphenytoin was approved as advantageous in a lot of
10 these cardiovascular side effects. And on top of that
11 a lot of the literature was dose-related, fused too
12 quickly, or in patients who were ill and had severe
13 cardiovascular histories. However, there were
14 significant reports in the AERS database where there
15 were serious outcomes with the therapeutic doses, with
16 therapeutic infusion rates in both groups, Phenytoin
17 and Fosphenytoin. There's no -- based on the data,
18 there's no way to say that one is more than the other.

19 DR. GATTI: I would agree with that. That
20 basically you're more likely to die from the
21 cardiovascular effects.

22 DR. ANDERSON: Dr. Lu. Oh, Dr. HersHKovitz.

1 DR. HERSHKOVITZ: Yeah, I just want to
2 comment. I'm assuming that the references to Table
3 20, where it shows three Fosphenytoin cardiac arrests
4 and five Phenytoin cardiac arrests, and there's a
5 whole bunch of other cardiovascular problems, but I
6 agree with the contention that cardiovascular is a
7 bigger problem but in the setting of status epileptic
8 if indeed this is, it might be difficult to
9 differentiate the disorder, underlying disorder, from
10 the treatment. So just that caveat.

11 DR. AVIGAN: I just would add to that. I
12 think that what we see clearly and easily in clinical
13 trials is hypotension where there is a robust effect.
14 But, you know, so those kinds of effects are easily
15 seen as being much more frequent, common, and easy to
16 measure than having an amputation. But the most
17 severe form of cardiovascular, i.e., death, is also
18 difficult to get at because of confounding.

19 DR. ANDERSON: So that was Dr. Avigan.
20 Please do announce yourself if I've failed to call on
21 you.

22 So we've got about 10 more minutes for

1 clarifying questions. We can go longer than that but
2 I guess I would ask is people -- I've got a few more
3 names on the list -- to sort of think about the
4 questions that -- as we sort of slide into sort of
5 discussing the issues before us, to try to sort of, at
6 this point, get the questions that are going to the
7 meat or something that the FDA presented that we
8 didn't understand or we need them to expand upon and
9 then we can sort of move into the more general
10 discussion subsequent.

11 So, Dr. Lu.

12 DR. LU: Thank you. Ying Lu.

13 I have a question about -- to Dr. Coplin for
14 the prospective trial of 202--is he here? Okay.

15 SPEAKER: He left.

16 DR. LU: He left. So I don't know. I mean,
17 my question was if anybody knows the original design
18 of that trial. What was their primary endpoints and
19 whether the PGS or the other endpoints, and what was
20 the original sample size in terms of what they were
21 looking for the effect size.

22 DR. FINE: I can only comment briefly. It

1 was included in my presentation, and I can only
2 comment on the objective of the study and some of
3 their endpoints. They were really comparing IV
4 Phenytoin and Fosphenytoin on a variety of endpoints,
5 like emergency department length of stay, as well as
6 any difference in adverse events because their
7 objective was to determine whether Fosphenytoin should
8 be added to the hospital formulary. And one of those
9 adverse events that they did choose to compare was
10 Purple Glove Syndrome. I don't know -- that's all I
11 can speak to that study.

12 DR. LU: So the study was not powered based
13 on any of the endpoints -- safety endpoints?

14 DR. FINE: I'm unaware of those matters.
15 I'm sorry.

16 DR. LU: Okay. And also, Pfizer presented
17 some safety data that combined with IV-IM and oral and
18 all these mixtures. Do they have just IV data that
19 show the comparison of the safety data in the Pfizer
20 trials? In your 208 safety review.

21 MS. WELSH: Are you referring to
22 Fosphenytoin?

1 DR. LU: Yeah.

2 MS. WELSH: There is data, I believe, in the
3 label for Cerebyx describing comparative data between
4 IV Fosphenytoin and Phenytoin that may answer that
5 question. But the data does demonstrate similar
6 results to what we've already shown today which is
7 that the cardiovascular side effects are generally the
8 same between the two agents. There is an increase in
9 pruritis, I believe, with Fosphenytoin. And an
10 increase in injection site reactions and pain
11 injection sites in the Phenytoin data. But that is in
12 the current label for the product.

13 DR. LU: Thank you.

14 DR. ANDERSON: So, Dr. Pearl.

15 DR. PEARL: Phillip Pearl. So just to bring
16 a little bit more perspective on this, when
17 Fosphenytoin came out in '96, many physicians, such as
18 myself, went to many hospitals in their areas and
19 explained that this was the better drug for safety and
20 the pharmacies and the hospitals had to swallow a huge
21 price tag to add this to their formulary. And it was
22 usually done under the context of, well, skin

1 reactions to Phenytoin are a common reason for
2 lawsuits in neurology other than spinal cord mishaps
3 and therefore, this is going to pay for itself.

4 And then some years -- well, the price was
5 very high and now the price is much lower. And at the
6 same time, the company, Pfizer, stopped marketing
7 Phenytoin in the U.S. and now we hear that they're not
8 sure about manufacturing Fosphenytoin in the U.S.
9 This presents a real dilemma to the committee.
10 Obviously, we all recognize that there's a shortage
11 and they can't afford to pare down to just
12 Fosphenytoin if we don't have it for our patients.

13 So Susan Welsh came and said for commercial
14 reasons the company decided to stop marketing. I
15 guess that was for Phenytoin. And so there must have
16 been a lot of analysis into that decision. And so I
17 wanted to ask Susan if she wouldn't mind coming up and
18 defining what she means by for commercial reasons and
19 share with us some of the analysis that was done by
20 the company because I think this is going to be very
21 relevant in our subsequent conversation.

22 DR. ANDERSON: Well, so -- is asking her to

1 do this, do you really think going to sort of
2 significantly advance our ability to discuss the
3 questions that were handed to us? I mean, I just --
4 I'm not sure from all the answers we've heard before
5 that she's really going to be able to represent the
6 corporate analysis of Pfizer into all their decisions
7 here. And I don't know that that information is going
8 to substantially enhance. So I guess I'll sort of
9 look for sort of shrugs of shoulders. How many people
10 on the committee would like us to sort of go into this
11 in more detail with Ms. Welsh at this point?

12 Okay. So I'm going to sort of use my sort
13 of chair authority to sort of pass on asking her to
14 defend and respond to that.

15 DR. PEARL: Can I ask a more specific
16 question then?

17 DR. ANDERSON: Yeah, ask.

18 DR. PEARL: And that would just be -- does
19 the company have any more information on the outlook
20 for manufacturing Fosphenytoin in this country? What
21 are the obstacles? Are they going to involve a big
22 hike in the price?

1 DR. ANDERSON: So if she knows anything
2 about the price she can mention it, but Ms. Welsh, do
3 you know anything specific and concrete in terms of
4 specific plans and opportunities for the manufacture
5 of Fosphenytoin for the U.S. market?

6 MS. WELSH: I do not know anything further
7 at this time.

8 DR. ANDERSON: Thank you. Dr. Fountain.

9 DR. FOUNTAIN: Half of my question was
10 answered, which is about cardiovascular deaths. And
11 we already heard from the FDA in review of that. Do
12 you have information specifically about cardiovascular
13 deaths reported to Pfizer from Fosphenytoin parceled
14 out that way? You may have told us but I'm sorry, I
15 don't remember.

16 MS. WELSH: I do not have that information
17 available currently. It could be sought, however,
18 through further analysis of our safety database.

19 DR. ANDERSON: Dr. Naidech.

20 DR. NAIDECH: Thank you. Andrew Naidech.

21 I wanted to draw out a point with the
22 cardiovascular toxicity. As this group knows,

1 patients with status epilepticus are critical and
2 there's a high associated mortality, some of which is
3 due to the status epilepticus and some which are due
4 to other cardiovascular complications. No one treats
5 this with just Phenytoin or Fosphenytoin anymore. As
6 the experts have told us, they're almost always given
7 benzodiazepines. Many of these patients also require
8 mechanical ventilatory supports and the etiology of
9 the status hasn't come up. Are many of these patients
10 septic? Is this in a setting of ruptured aneurisms?
11 Is this in a setting of stroke? And all of these
12 other complications will play into whether or not
13 cardiovascular toxicity or presumed cardiovascular
14 toxicity, hypertension, or other medical complications
15 that may lead to hypotension death occur. It's going
16 to be very messy to sort out what's directly drug
17 related, what's due to status, and what's due to the
18 original cause of the status in the first place.

19 DR. ANDERSON: So is there a question that I
20 could rephrase for the FDA that you'd -- I mean, I'm
21 not trying to be -- I'm not trying to be snippy. I
22 mean, I think you make -- I mean, I agree with

1 everything that you've said and I think those are --
2 personally, I think those are very relevant to
3 deciding sort of portioning out the risk, but I'm not
4 sure from the data that's been presented who I would
5 direct that to to see if they have some information on
6 how they would parcel out those events and those
7 events.

8 **Panel Discussion/Questions**

9 DR. ANDERSON: So at this point I'd like to
10 ask -- so the FDA -- for those of you who are new, the
11 FDA does and will continue to participate with us as
12 we sort of discuss these questions, especially if
13 there's issues where we require clarification of
14 policy or labeling. So it's not as if they can't talk
15 anymore. So what I would like to know is are there
16 sort of more specific questions related to this
17 morning's presentations about data on this slide or
18 here it came from or reconciling things that people
19 would like to ask? Otherwise, I'll suggest we move
20 forward into discussing the questions that they asked
21 us to deliberate on.

22 Okay. All righty. So we have several

1 voting questions. So usually I read them out and then
2 we sort of discuss them until it seems as if we're
3 sort of discussed out and then we take a vote, which
4 we do in sort of private. And then following that we
5 go around the table and read and confirm our vote and
6 read out what the results were.

7 So the first question that's before us is
8 does the committee agree that intravenous Phenytoin
9 causes Purple Glove Syndrome?

10 And so I guess is there anybody who would
11 like to take point of view that Phenytoin --
12 intravenous Phenytoin does not cause the Purple Glove
13 Syndrome -- would like to advance that argument?

14 So if there is nobody willing to take the
15 point that -- oh, you would like to take the point it
16 does not. Okay. Please read your name.

17 DR. VARELAS: Dr. Varelas from Henry Ford.

18 I'm not convinced that the symptom with a
19 questionable definition, okay, one, lack of pathology.
20 Two, and very rare, in fact. I mean, for people like
21 us that are using the IV Dilantin, IV Phenytoin in the
22 ICU, I admit probably 1,000 patients a year and

1 probably one-third of them actually are on Dilantin
2 from the ER from the neurosurgeons already. Have I
3 see anything in my 12 years of experience in the ICU?
4 Never. Okay. So definitely I'm not convinced that
5 we're talking about -- I think it's a moving target
6 here. Very, very rare. We don't have any pathology.
7 There is no -- the only perspective study actually is
8 from my institution. And even then, although they
9 were taking pictures of these patients, I'm not
10 convinced, although I don't have direct access to
11 their data -- I didn't, I didn't want to discuss with
12 one of the senior authors of the paper because I'm not
13 convinced that there is a clear, clear association
14 between these two.

15 DR. ANDERSON: Dr. Green.

16 DR. GREEN: I don't agree with you. For
17 example, Phenobarbital, which is chemically not that
18 different from Phenytoin has a lot of similarities and
19 is used in the same population under the same
20 circumstances. After all these years we've not seen
21 cases like that.

22 DR. ANDERSON: So I guess a rarity in

1 association. Dr. Silbergleit.

2 DR. SILBERGLEIT: So I think approaching it
3 from a data standpoint I'd say that one of the best
4 reviews that we have so far was the preliminary VA
5 information study that was presented to us this
6 morning, which did not identify any cases. And that
7 could be problems with the methodology. But I think
8 that given the quality of that review, at this point
9 I'd say that there is question based on those data
10 whether this syndrome is caused by Phenytoin. It's
11 not to say that it isn't, but I think that there's
12 reason to believe that the data is unclear.

13 DR. ANDERSON: So I'm going to keep going
14 around to the people who have sort of signaled for
15 turns, but I'd like to know is there anybody at the
16 table, given all the epilepsy and ICU expertise that
17 actually has seen a case that they think is a bona
18 fide example of Purple Glove Syndrome? Dr. Naidech,
19 do you want to sort of chime in then as to whether you
20 believe it exists and it's related to Phenytoin?

21 DR. NAIDECH: Without getting sort of Carl
22 Pauper philosophical, it's a question of can you prove

1 something does exist. I have seen a typical case of a
2 young patient with small veins admitted with status
3 epilepticus who has small veins placed in the
4 emergency department because that was the only
5 available venous access was given Phenytoin through it
6 and did develop -- it looked awful like Purple Glove
7 Syndrome. It's sort of a sore point because the
8 previous year I'd had an animated discussion with the
9 hospital pharmacy about whether or not we ought to
10 have Fosphenytoin on formulary because we presumed it
11 to be safer. I was told that in fact I should be
12 using benzodiazepines if we really thought status was
13 a concern. And really there was no cause for it. And
14 I think in anger I said I look forward to testifying
15 against you when we have a case. And sure enough, a
16 couple of months later, we had this case that fit
17 exactly the description.

18 DR. ANDERSON: So it helps to have some
19 personal experience at it since all we've been looking
20 at is numbers and studies.

21 Dr. Cooper, did you want to comment?

22 DR. COOPER: In response to the members

1 speaking about the VA data, I believe, if I read their
2 case definition, they were really looking at the most
3 severe cases -- the amputation, the necrosis -- that
4 really wouldn't capture the broader range of Purple
5 Glove. So I don't think that the absence of cases in
6 that dataset would suggest that there's not an
7 association.

8 DR. ANDERSON: Dr. Fountain.

9 DR. FOUNTAIN: So I had the same perspective
10 and starting thinking, gosh, you know, I've given
11 hundreds, maybe thousands of doses of Phenytoin IV and
12 it doesn't seem like it. And that led me to ask my
13 colleagues that question. Who's seen it. And so
14 among seven epileptologists and others at UVA we
15 decided we'd seen a couple of cases. So then I did
16 the math. So if we say there are 119 cases in 28
17 years and that Pfizer has made five million doses a
18 year, then the incidence is about one per million
19 doses. So if it's one per million doses, realizing
20 that math is, you know, has confidence limits about
21 wider than the numbers but the incidence must be very,
22 very low. So for any one person to see any more than

1 a few cases of at least serious Purple Glove Syndrome
2 would seem unlike. So I think it exists but it's very
3 uncommon, unlike the cardiovascular problem.

4 DR. ANDERSON: Dr. Kindler, no Kandell.
5 Sorry.

6 MS. KANDELL: Ms. Kandell. I'm curious why
7 Question 1 isn't phrased like Question 2. I guess
8 that's a question for the FDA. Given everything I've
9 heard from my lay perspective, why isn't Question 1
10 phrased as does the committee believe there is
11 adequate information?

12 DR. ANDERSON: Well, there's probably lots
13 of reasons but one is probably they don't have anyone
14 with a J.D. degree helping them write the questions.

15 (Laughter.)

16 DR. ANDERSON: Would you like to amplify on
17 that, Dr. Katz?

18 DR. KATZ: Why did we lead the witness on
19 the first question? Is that the --

20 There was actually discussion about that.
21 And some people felt it should be sort of neutral. In
22 other words, like the second question. And some

1 people were so convinced that it clearly does cause it
2 that it seemed perfectly reasonable to take a
3 position, at least from the Agency's point of view,
4 and say we think it causes it; do you agree? At least
5 we're asking the question. So, I mean, we do want to
6 know, and obviously there's some discussion, and more
7 perhaps than we would have anticipated about that.

8 Again, this question doesn't talk about
9 incidence or is it rare? Is it very rare? We just
10 wanted to know whether or not it exists. And as Dr.
11 Fountain said, if you do the numbers, even if you put
12 in a factor of 10 or 100 for underreporting, it's
13 still by anybody's definition, if you believe the
14 usage data, rare. So it's not unexpected that in a
15 study of 10,000 you wouldn't see any or it's not
16 unexpected that any given practitioner would never see
17 a case.

18 So this question absolutely presupposes that
19 the people who wrote it, and most people in the Agency
20 I thought feel that it does cause Purple Glove. And
21 we want to know if you agree.

22 DR. ANDERSON: So we've heard one good

1 coaching argument against the association. Is there
2 anyone else who wants to sort of pick up that side of
3 it and extend the argument that they're -- sort of
4 justify why they think they might vote no or somebody
5 should vote no on this first question besides Dr.
6 Varelas who we've already heard from?

7 So is there -- so can I go ahead and sort of
8 move us onto the voting on this question and then we
9 can sort of move on to some --

10 DR. NGU: Dr. Lu.

11 DR. ANDERSON: Oh, sorry, Dr. Lu.

12 DR. LU: It just says no medical as a
13 layperson, too.

14 I have a question. So basically we see the
15 PGS there. It's happening. Right? So is there -- if
16 it's not caused by this drug, is there a reason that
17 people can think about, you know, for those patients
18 that can cause that?

19 DR. ANDERSON: Dr. Varelas.

20 DR. VARELAS: Yeah, there are many answers.
21 Of course, you need to have better data. And
22 unfortunately, through this database, data or the

1 reports to the company, you cannot go unless you go
2 and really, you dissect the data, you can't find out
3 what's happening. But for somebody who lives in the
4 ICU and has experience with these patients, for
5 instance, it's a different thing to have somebody who
6 goes to status epilepticus because he is noncompliant,
7 doesn't take his drugs, and he comes in the unit in
8 status and you can treat him usually very easily.
9 It's different than if you have a young person who had
10 a MVA, a car accident, or a motor bike accident, comes
11 with multiple fractures, has lost tons of blood, has
12 lacerations in the liver, has fractures, actually, in
13 the arms. Okay? And he's on multiple pressure
14 medications. And again, you know, sometimes through
15 the database you can pick up these details. But
16 sometimes you can't. And you need to go really and
17 dissect one by one these cases and see if there is an
18 association. If you -- I'm not convinced that
19 actually we have all the data about that. I mean,
20 these are very, very sick patients. Otherwise,
21 normally, they wouldn't have received IV Phenytoin.
22 They would have received a pill of Phenytoin if they

1 have missed a dose or not. These are ICU patients.
2 As you can see, half of them actually were in the ICU
3 where they received IV Phenytoin.

4 DR. ANDERSON: Excuse me, Dr. Cavazos, did
5 you still want to come in?

6 DR. CAVAZOS: Well, I was doing some follow
7 up to the same calculations that Dr. Fountain did. We
8 have seven epileptologists at the University of Texas
9 and I asked them, every one of them and, you know, two
10 of us have seen cases. In my particular situation, I
11 saw an individual much later after, you know, the skin
12 grafts had been done so I cannot really testify as Dr.
13 Naidech that this individual had had that situation.
14 But one of my colleagues had done it.

15 But in any case, it's very rare. And in
16 individuals just like in the case of Dr. Fountain at
17 the University of Virginia, you will need to ask very
18 large survey of neurologists to be able to come up
19 with cases. And even though the lack of evidence is
20 not evidence of an association, I suspect that the
21 fact that we don't have reported cases with Phenytoin
22 -- I mean, with Phenobarbital, with valproic or other

1 medication in this population of patients is
2 suggestive that there is dissociation between the two.

3 I will say that perhaps the question should
4 be with medical certainty, you know, just to clarify
5 because, I mean, from a scientific standpoint this is
6 a causality -- a direct causality. But if you relax
7 the clause to say medical probability or medical
8 certainty, I think it's a yes.

9 DR. ANDERSON: So I'll just -- I'll mention
10 since I do know we have a couple new people on the
11 committee, you sort of have -- we sort of vote on the
12 question as written, but then when you go around the
13 table to clarify or to confirm your vote as it was
14 recorded, you do have a chance to add additional
15 comments that you would like to use to clarify your
16 vote, such as I voted no because I didn't feel it met
17 the definition of medical certainty, or I voted yes
18 because I felt, you know. So you can sort of give a
19 nuance to your yes or no after you've had -- after
20 you've made your vote.

21 Did you still want to come in, Dr.
22 Silbergleit? Okay.

1 DR. SILBERGLEIT: (Off mic.)

2 DR. ANDERSON: Yeah, we still have some
3 opportunities for discussion.

4 Okay, then at this point I'll go ahead and
5 suggest that we do the voting on question number one
6 which is -- I'll read it one more time so the language
7 is clear. Does the committee agree that intravenous
8 Phenytoin causes Purple Glove Syndrome?

9 And so you will press the yes, no, or
10 abstain button. And every voting member has to push
11 it. And then we will wait till they confirm they've
12 got all our votes. It will continue to blink after
13 you think you've -- oh, at least it used to continue
14 to blink after we voted.

15 (Voting)

16 The votes are recorded. It's 26 yes, 2 no,
17 1 abstention. And I'll sort of alternate sides but
18 we'll go ahead on this occasion and start over with
19 Dr. Snodgrass. If you'd just read your name, confirm
20 your vote, and give any other comments that you wish
21 to make.

22 DR. SNODGRASS: Wayne Snodgrass. My vote is

1 yes and I really have no additional comments.

2 DR. HOVINGA: Yes, and no additional
3 comments. Collin Hovinga.

4 DR. SOLOW: My vote was yes. And I looked
5 at the evidence presented on both sides and still say
6 yes.

7 DR. LEE: Mike Lee. First, I must say that
8 this is the opinion of Mike Lee and not the opinion of
9 the agency that I work with. So let me say that
10 first. And with that I say my vote was yes.

11 DR. SPRIDGEN: Stacia Spridgen, and I have
12 to disclaim myself as well, that this vote presents my
13 opinion and not that of DOD. But my opinion is yes
14 just based upon the evidence that was presented today.

15 DR. CAVAZOS: Jose Cavazos. Yes but with
16 medical certainty.

17 DR. BALISH: Marshall Balish, yes.

18 DR. SCHACHTER: Steve Schachter, yes.

19 DR. ROGAWSKI: Michael Rogawski, yes. No
20 additional comment.

21 DR. CHAPMAN: Kevin Chapman, yes. I did see
22 it once as a resident and so it sort of jaded me for

1 my future practice. So.

2 DR. PEARL: Phillip Pearl, yes.

3 DR. MARDER: Ellen Marder, yes.

4 DR. KHATRI: Pooja Khatri, yes.

5 DR. KINDLER: Dean Kindler, yes.

6 DR. LU: Ying Lu, yes.

7 DR. FOUNTAIN: Nathan Fountain, yes.

8 DR. ANDERSON: Brett Anderson, yes.

9 DR. GREEN: Mark Green, yes.

10 DR. FRANK: Samuel Frank, yes.

11 MS. KANDELL: Ellen Kandell, abstain in

12 light of my prior question.

13 DR. WOODS: Mark Woods, yes.

14 DR. COOPER: William Cooper, yes.

15 DR. WOLFE: Sid Wolfe, yes. No additional

16 comments.

17 DR. NELSON: Lewis Nelson, yes.

18 DR. HUFF: Stephen Huff, yes.

19 DR. SILBERGLEIT: Robert Silbergleit, no.

20 And just because I think that the syndrome is not well

21 defined with medical certainty and there is question.

22 DR. NAIDECH: Andrew Naidech, yes.

1 DR. VARELAS: Panaviotis Varelas, no.

2 DR. SLEATH: Betsy Sleath, yes.

3 DR. ANDERSON: Thank you all. We will now
4 turn to the second question.

5 Does the committee believe that there is
6 adequate information to conclude that Fosphenytoin
7 causes Purple Glove Syndrome?

8 So how about this one, Dr. Varelas. If you
9 don't -- do you want to start off on this one, too?
10 No? Okay.

11 Well, if it doesn't meet -- if Phenytoin
12 doesn't meet it, how do you feel about Fosphenytoin?
13 I mean, do you --

14 DR. VARELAS: Again, you know, I don't think
15 we have enough understanding of what's going on here
16 but definitely I don't see any clear association
17 between Fosphenytoin and Purple Glove Syndrome. I
18 don't.

19 DR. ANDERSON: So when the FDA has those
20 little -- has the little case report that they give us
21 of the severe cases and they read them out, I mean,
22 that wasn't a motorcycle accident. I mean, so I guess

1 I have to say when I saw those cases, I mean, so
2 before I sort of got my material I sort of thought
3 Purple Glove Syndrome was rare and it existed and it
4 was due to Phenytoin and there was no cases of
5 Fosphenytoin. And I sort of felt like my mind was
6 being shifted when I read the FDA's briefing
7 materials. And so I'm wondering how you sort of felt
8 or what you -- how you sort of computer that evidence,
9 you know, against Fosphenytoin being associated with
10 Purple Glove from those sort of narratives we were
11 given.

12 DR. VARELAS: Again, if I remember well the
13 case, four of them were probable and one was possible
14 or vice versa. So again, you know, none was definite
15 in a certain way. Of course, I think the money is in
16 the definition. And definitely I would like to know a
17 little bit more about what's happening. And I find it
18 also strange that let's say IN Fosphenytoin has never
19 been reported of causing some kind of tissue necrosis
20 or muscle necrosis. So, I mean, putting them all
21 together, again, I'm not very convinced about that.

22

1 DR. ANDERSON: Dr. Cooper, and then I'll get
2 you.

3 DR. COOPER: I agree with you, Dr. Anderson.
4 I think that I was surprised but on looking at the
5 information in the data provided I think that there is
6 some evidence that while it may be exceedingly rare,
7 there may be some association.

8 DR. ANDERSON: Dr. Wolfe.

9 DR. WOLFE: I just want to contrast the way
10 this question is worded with the first one. It's
11 pretty clear but all we're being asked is do we have
12 enough information to conclude that it does cause it.
13 I think that's a much easier question to answer. So.

14 DR. ANDERSON: And so what -- I'm not so
15 sure that I understand the distinction. So could you
16 elaborate on that, please? Why are you feeling --

17 DR. WOLFE: Well, the first one we're being
18 asked does it cause it, and the second one we're
19 saying is there a lack of -- do we have enough
20 information to conclude that it causes it? I mean,
21 it's phrased importantly in a different way. I mean,
22 having an inadequate amount of information is an

1 easier standard to get to than causality. So.

2 DR. ANDERSON: So you're making the point
3 that the first one is establishing causality between
4 Phenytoin and Purple Glove and the second one --

5 DR. WOLFE: And the second one is do we have
6 enough information.

7 DR. ANDERSON: So is that -- was the FDA's
8 intent with the second question for us to focus on the
9 adequacy of the information in the database or to try
10 to make some assertion of, you know, relationship as
11 we did for Phenytoin?

12 DR. KATZ: Well, I'm not sure there's that
13 much of a distinction between your two interpretations
14 of the thing. Look, we explained why we wrote the
15 first question the way we did. We thought there was
16 pretty solid evidence. We thought, or at least many
17 of us thought there was pretty solid evidence for
18 Phenytoin. And there seemed to be less solid evidence
19 for Fosphenytoin. And we were really just trying to
20 get the committee's sense as to whether or not you can
21 make a decision about causality or whether you think
22 we can't tell yet. We're really trying -- we're

1 ultimately I think trying to get at the causality
2 question. Is there enough here for you to say, yeah,
3 there are cases with Fosphenytoin and we think
4 Fosphenytoin causes it. That's really what we're
5 trying to get at.

6 DR. ANDERSON: I'll come back to you, Dr.
7 Hershkowitz and Dr. Temple. I'll get Dr. Schachter.

8 DR. SCHACHTER: I just wanted to better
9 understand the categorization that Pfizer has provided
10 for the likelihood of Purple Glove Syndrome being
11 diagnosed. I mean, when you read the probable
12 criteria, in the absence of, you know, an objective
13 marker and pathology, how much stronger -- what would
14 a definite case look like? You know, in other words,
15 these criteria to me look fairly strong and perhaps as
16 strong was used to define Purple Glove Syndrome in any
17 of the publications that we've reviewed. So I don't
18 quite understand how much stronger a case could have
19 been to be labeled as probable in this classification
20 scheme.

21 DR. ANDERSON: So you're making the argument
22 that you think that based on this sort of description

1 and sort of the clinical evidence, you're leaning that
2 there is adequate information to make an assessment?

3 DR. SCHACHTER: Yes.

4 DR. ANDERSON: Okay. And then back to Dr.
5 Hershkowitz and then Dr. Temple after him.

6 DR. HERSHKOWITZ: Yeah, I only wanted to say
7 that A then deals -- we were interested in relative
8 differences and so if we all agree it causes Purple
9 Glove, the next question is is there adequate
10 information. Then, if there is adequate information
11 you go to A. Can we compare the two, if you follow
12 the structuring of the question.

13 DR. ANDERSON: Yes. And so whichever one of
14 you wants to begin down there.

15 DR. TEMPLE: Well, just to elaborate on what
16 Rusty said. There's a little bit of context. There
17 are no published reports. I mean, you might have
18 thought that if somebody saw a case for a drug that
19 was thought not to do it he'd be more likely to report
20 it but there were no published reports. And there
21 were relatively few reports to us. Again, you might
22 think the reporting rate would be higher where the

1 drug is not known to do it. So with all those things
2 to make you wonder, that's why we asked the question
3 the way we did because there were some arguments
4 against it being real. But you may find the cases are
5 solid enough to say yes, there is. But that's why it
6 was put that way.

7 DR. ANDERSON: So for situations like this,
8 did you or do you have the ability to put out a call?
9 Sort of we're going to be having an advisory committee
10 on this and we would like pharmacists to be aware of
11 or to make sure that these sorts of things are
12 reported in order to try to solicit the sort of cases
13 and information you're looking? Or do you consider
14 that sort of gaming the system?

15 DR. TEMPLE: Well, we don't usually do it
16 before an advisory committee but if we make a public
17 announcement of something, an expression of concern,
18 we sometimes ask for case reports. We have done it.
19 I can't speak to how successful that's been, however.
20 Maybe OSE knows.

21 DR. ANDERSON: Dr. Lu.

22 DR. LU: Ying Lu. I have a question. So

1 for these data, because there are only a few cases,
2 how -- what kind of quality control implemented in the
3 reporting system, you know, that we can trust those
4 cases?

5 DR. AVIGAN: I'll just answer that more
6 informationally. Obviously, that's a very important
7 and large question around spontaneous reports and how
8 the adverse event reporting system works. So it's a
9 democratic system, so anybody can report. Obviously,
10 a case that gets included in a series has to fit a
11 case definition. So the stringency is based really on
12 dose it fit a case definition. The term -- the
13 probable, possible nomenclature that was used is not
14 around causality of the agent; it's around the
15 phenotype. The clinical phenotype in this case.

16 So, but because these cases are
17 distinguished by exposure to Fosphenytoin and not
18 Phenytoin, and because they fit the case definition
19 which was a report that used the term Purple Glove or
20 had other more specific clinical features, they were
21 included. But they weren't necessarily very broadly -
22 - the narratives were not loquacious. You know, they

1 sometimes were short and they were just taken at face
2 value.

3 DR. LU: So there's no verification, no
4 follow up after those reports?

5 DR. AVIGAN: Right. That's correct.

6 DR. ANDERSON: Dr. Kindler.

7 DR. KINDLER: Yes. I'm much more
8 uncomfortable with causality in this case. The case
9 reports may not be loquacious and I would say our data
10 is taciturn for this as far as actually causality. I
11 think there may be an association. I think there are
12 certain -- I'm concerned that there may be an
13 association but I would be very loathe to advocate for
14 causality.

15 DR. ANDERSON: Dr. Fountain.

16 DR. FOUNTAIN: So I'd agree with that, in
17 particular with what Dr. Temple said. You'd think
18 there would be case reports if someone observed this,
19 but I think the fundamental problem we have is that a
20 superiority versus equivalence. Your end needs to be
21 much larger to know equivalence. So if it's just a
22 random association in a few cases reported through

1 AERS that might or might not be Purple Glove Syndrome,
2 you have to have a much larger sample than if there is
3 a positive association, like there is with Phenytoin.
4 In other words, we have a positive number of seemingly
5 more than could possibly occur by chance with
6 Phenytoin but we don't seem like we have an
7 overwhelming number association with Fosphenytoin. So
8 I'm not sure my analogy is quite right but my idea is
9 that we don't know enough about it because it's not in
10 peer review literature because we don't have follow
11 up.

12 So my gut feeling is that Fosphenytoin
13 probably can cause it but I don't think we have a
14 large enough sample. Maybe because it's not been
15 around long enough or whatever to understand whether
16 or not that's for sure or to what degree.

17 DR. ANDERSON: Dr. Lee.

18 DR. LEE: I guess this is more of a
19 clarifying question that just kind of popped in my
20 mind. You know, basically on the data that showed
21 from AERS, you know, talks about the five cases that
22 were reported. And my question, I guess for

1 clarification, would be were the vast majority of
2 those cases that were reported, were they from the
3 early period versus the late period? And my question
4 is based upon the fact -- or my thought that, you
5 know, early on I think you would probably get greater
6 reporting of data of this type of information as
7 opposed to later on in the dataset just because
8 people, you know, may think that, hey, this has been
9 around a little longer. I'm going to -- you've
10 probably seen some underreporting. And granted, I
11 heard that, you know, underreporting was a possibility
12 but is there any clarifying information on that?

13 DR. FINE: The reports in Fosphenytoin in
14 the AERS database were reported between 1990 and 2007.
15 One case in 1999, one case in 2003, one case in 2006,
16 and one case in 2007. The fifth case, I don't have at
17 the exact moment because that was one submitted by
18 Pfizer.

19 DR. ANDERSON: Dr. Frank.

20 DR. FRANK: So when I look at this question
21 and turn it around, I mean, is there enough -- is
22 there adequate information to conclude that

1 Fosphenytoin never causes Purple Glove Syndrome? I
2 don't know that I can say that, especially if there
3 are five cases sitting in front of us. And I think
4 that just in terms of reporting, when providers give
5 Fosphenytoin, there's a lower probability, there's a
6 lower expectation that they're going to find Purple
7 Glove Syndrome. So I'm not sure that they're looking
8 for it as much as they should. So there may be some
9 underreporting.

10 DR. ANDERSON: Since the question is written
11 the other way around, how does that help us?

12 DR. FRANK: Well, I mean, I think that with
13 five cases, I think that we -- there -- I can't say
14 that there's adequate information because there's --
15 there are only five cases. But on the other hand, I
16 don't know that I'm, comfortable saying that there's
17 no association, that there's not any -- that
18 Fosphenytoin never causes Purple Glove.

19 DR. ANDERSON: Dr. Katz, did you --

20 DR. KATZ: Yeah, a couple of points. There
21 are five cases in AERS that have met our case
22 definition. I had mentioned that there are four

1 others that were severe cases. Didn't quite meet our
2 case definition but you might think of them as
3 possible as opposed to probable. So I wouldn't
4 completely dismiss those.

5 The other point I want to make relates to
6 the assessment of causality. I think as a general
7 matter, when you give a drug and then at some point
8 afterwards something happens, it's very difficult to
9 make an assessment about causality by reading the
10 actual case description because lots of things happen
11 after people get drugs that have nothing to do with
12 the drug, but of course you make that association in
13 your mind. So a lot of things are difficult to assess
14 from a point of view of causality that happened after
15 drug. And in those cases we compare incidence, you
16 know, compared to some control or reporting rates or
17 whatever we do to try to figure out causality.

18 I would just make the point for something
19 like this where a patient receives an infusion and
20 then two hours later things start happening in that
21 limb and then they progress, I think it's fair to say
22 absent any other obvious competing cause, I think it's

1 fair to say that looking at the individual cases, I
2 think it's quite possible to make an assessment about
3 causality, even on a case by case basis. So just
4 throw that out there.

5 DR. ANDERSON: Dr. Rogawski.

6 DR. ROGAWSKI: I guess what I'm struggling
7 with are these oddball cases. For example, the oral
8 Phenytoin where they got a syndrome that looked a
9 little bit like Purple Glove and then there was that
10 one where it was injected, I guess, into the hand.
11 And there was a foot issue. And if these are to be
12 believed, and I'm not suggesting that they should be
13 believed, particularly the oral one because there have
14 obviously been millions of doses of Phenytoin given
15 and this really hasn't generally been reported, but if
16 for a moment we say that those oddball cases, you
17 know, are real, then that would suggest it's really
18 not the excipient or the pH or the polyethylene glycol
19 or whatever, that it's actually the Phenytoin itself
20 that's causing this. And in that case then, you know,
21 all bets are off. I guess you'd have to assume that
22 Fosphenytoin would be able to do it as well since it

1 produces blood levels of Phenytoin.

2 So I guess that's a bit what I'm struggling
3 with. But given the fact that there have been so many
4 oral doses of Phenytoin over the years and it's only
5 been reported this one time as far as we're aware, I
6 guess I'd have to go along with our two debaters and
7 suggest that perhaps that was a red herring and maybe
8 that was really not to be believed.

9 DR. ANDERSON: Dr. Naidech. We've made much
10 the fact that there aren't any published cases of
11 Fosphenytoin and Purple Glove or what looks like
12 Purple Glove, but that doesn't say there weren't case
13 reports that an editor decided weren't worth
14 publishing or said everyone knows Fosphenytoin is
15 safer and decided not to publish it. I don't know if
16 anyone on the panel is an associate editor of one of
17 the journals that might receive such a case like
18 neurology, epilepsy, or if there were going to be a
19 call for cases would it be worth contacting the
20 editors of journals that might be expected to get
21 these cases and ask have you received anything that
22 smelled like Purple Glove from Fosphenytoin but didn't

1 meet the standards for publication?

2 DR. SILBERGLEIT: So I'm the decision maker
3 for everything that would have been neurological for
4 both case reports and manuscripts for Annals of
5 Emergency Medicine and in the last five years we have
6 not gotten anything like that. Whether it happened
7 before that I could ask the other person.

8 DR. NAIDECH: I wish I had known. I would
9 have asked you. You're sitting right here.

10 DR. ANDERSON: So that was Dr. Silbergleit
11 who was responding to Dr. Naidech's question. And Dr.
12 Solow.

13 DR. SOLOW: Excuse me if we've mentioned it,
14 but has Purple Glove ever been -- have we had any case
15 not with these drugs? Or has it only been reported to
16 the FDA with these drugs? Do doctors not report to
17 the FDA Purple Glove on another medicine?

18 DR. ANDERSON: Do any of the clinicians here
19 have experience with something that they would have
20 called Purple Glove with any medicine or when they
21 polled their colleagues something else? Has the
22 Agency had something that met its criteria for Purple

1 Glove or sounded purple glovish that was associated
2 with another agent?

3 DR. NAIDECH: And is it on any other drug,
4 you know, morning? Or is it only on Phenytoin?

5 DR. ANDERSON: Do you know if there's any
6 labeling for Purple Glove Syndrome for any other
7 medications?

8 DR. KATZ: I'm not aware of it being on any
9 other --

10 DR. AVIGAN: I actually have to say that as
11 far as I know we haven't looked for other agents
12 besides these two.

13 DR. ANDERSON: So, yeah --

14 DR. SOLOW: Because that would be important.
15 I mean, what if there was -- I mean, we know they're
16 not in the literature perhaps but it would be
17 interesting to see if you had six here, three here,
18 two here. It would be interesting to know.

19 DR. ANDERSON: Yeah, I mean, it would be a
20 way, I guess, you could sort of pick another one at
21 random and see if you got the same number of
22 Fosphenytoin cases or whatever. But the data we have

1 is the data we have. And so I think the next one was
2 Dr. Snodgrass.

3 DR. SNODGRASS: The issue of other drugs
4 causing this, there might be a confusion and it could
5 be potentially related to this. But certainly we see
6 this in neonates and other children is calcium
7 gluconate and calcium chloride. And almost always
8 those are extravasations usually at the site. But
9 there may be some further progression to, you know,
10 tissue destruction that might have been -- might
11 appear somewhat similar and may not have been labeled
12 as Purple Glove. So calcium perhaps are another known
13 risk.

14 DR. ANDERSON: Okay. Dr. Silbergleit.

15 DR. SILBERGLEIT: I guess to follow up on
16 Dr. Katz's assessment of causality, do we know that
17 there aren't other -- I mean, what you said is that if
18 you see this absent other explanations and other --
19 and I guess that's my problem with these narratives,
20 is that these narratives are so short that I don't
21 feel that I have adequate information to know that
22 there wasn't other things going on as well because

1 there is a well known cognitive blinding where once
2 you know about a certain syndrome and you see a set of
3 data you fit the data to what you know to be true.
4 And it seems that you could easily end up having
5 people say, gosh, what's going on? This weird thing
6 with this hand. Oh, I remember, Purple Glove
7 Syndrome. And so, you know, certainly I think it's
8 quite possibly true. I think it's even maybe even
9 likely true. I think what Dr. Fountain said. But do
10 I have adequate information to say that it is true
11 based on this one page of narratives? And these are
12 the full narratives, right? I mean, this is what you
13 were working on? I mean, that's a very little bit of
14 information, I think.

15 DR. ANDERSON: Yeah, but it's not -- it's
16 not academic. I mean, they're going to make policies
17 and they're going to make decisions. And this is the
18 information they've got. And --

19 DR. SILBERGLEIT: Is this information
20 adequate is the question.

21 DR. ANDERSON: Right. Right, so --

22 DR. SILBERGLEIT: I'd say this one page --

1 in my mind this one page of information is not
2 adequate to make public policy on.

3 DR. ANDERSON: Okay. Dr. Temple.

4 DR. TEMPLE: There have been other drugs
5 that perhaps when put into arterially by mistake have
6 caused peripheral necrosis. I mean, there's the big
7 phenergan scandal everybody knows about because of the
8 violinist. So drugs put in the wrong place can do it.
9 That's not quite the same thing I gather but there
10 might be some overlap.

11 DR. ANDERSON: Okay. So I've got a couple
12 more names down here. We can keep going but if we're
13 sort of making the same points then at some point we
14 may want to vote and move on. But I just throw that
15 out there.

16 Dr. Cavazos? Dr. Fountain? So at this
17 point is there somebody who would like to -- who feels
18 they need to make an expansion on what we've discussed
19 so far before we can -- all right.

20 So question number two reads does -- and so
21 we do this in two parts. We vote on two and then
22 based on our response to two we move down to the A

1 question.

2 Does the committee believe there is adequate
3 information to conclude that Fosphenytoin causes
4 Purple Glove Syndrome?

5 (Voting)

6 DR. ANDERSON: The answers are 11 yes, 18
7 no, 0 abstain. And we'll start on the other end this
8 time. So start with Dr. Sleath, I guess. You're the
9 voting member furthest away.

10 DR. SLEATH: I vote no, and no additional
11 comment.

12 DR. ANDERSON: We're just going to move sort
13 of around in sort of sequential order. And I'll try
14 to pick on a different person each time.

15 DR. VARELAS: No. And this time Michigan is
16 in the majority, I guess.

17 DR. ANDERSON: Yes, please state your name.
18 I did like the joke but take credit for it.

19 DR. VARELAS: Panaviotis Varelas.

20 DR. NAIDECH: Andrew Naidech, yes. I think
21 Phenytoin likely causes Purple Glove. I think there's
22 enough in these five cases that Fosphenytoin is likely

1 to cause it, although probably less often.

2 DR. SILBERGLEIT: Robert Silbergleit. No, I
3 think it might but I don't think there's adequate
4 information.

5 DR. HUFF: Stephen Huff. Adequate
6 information to suspect association; inadequate
7 information to include.

8 DR. NELSON: Lewis Nelson. I voted no. I
9 think we need more information as well.

10 DR. WOLFE: Sid Wolfe voted no. Nothing to
11 add.

12 DR. COOPER: William Cooper. I voted no. I
13 originally thought of yes but when I thought about
14 whether this was enough information to determine
15 causality, I don't believe that's the case.

16 DR. WOODS: Mark Woods. I voted yes. And I
17 appreciated Dr. Frank's comments about never because I
18 do think that the answer to this question will help
19 the FDA hopefully make labeling changes that may alert
20 practitioners to the possibility that this could
21 occur.

22 MS. KANDELL: Ellen Kandell. I voted no.

1 DR. FRANK: Samuel Frank. I voted yes,
2 although from an academic sense I don't think that
3 there's adequate information. I think from a
4 regulatory sense five cases is enough for me to want
5 to warn my patients and have it on the label.

6 DR. GREEN: Mark Green. I voted yes. I
7 think that the syndrome is very distinctive and I
8 think that class labeling is often done with far less
9 information than we have now.

10 DR. ANDERSON: Brett Anderson. I voted yes.
11 And I guess I just felt like I could sort of outthink
12 myself a little bit on this one. I think probably
13 Phenytoin causes Purple Glove Syndrome. Fosphenytoin
14 is very similar. There's five cases. It seemed to me
15 that I felt there's probably a reasonable suspicion of
16 a similar association so I chose to vote yes.

17 DR. FOUNTAIN: Nathan Fountain. I voted yes
18 because if the answer is yes I get to vote on A. That
19 is, I think there's clearly a differential between the
20 two. And I particularly agree with Dr. Woods'
21 comments.

22 DR. LU: Ying Lu. I vote no. Just the

1 adequacy, you know, the part that makes me think it's
2 not adequate right now.

3 DR. KINDLER: Dean Kindler. I voted no. I
4 think if it had been worded "may cause" I might have
5 voted yes.

6 DR. KHATRI: Pooja Khatri. I voted yes for
7 many of the same reasons that others have mentioned,
8 particularly Dr. Anderson and Dr. Green. It's a very
9 distinctive phenomenon and it's hard to come up with
10 much else with a differential diagnosis for that.

11 DR. MARDER: Ellen Marder. I voted yes for
12 all the reasons stated.

13 DR. PEARL: Phillip Pearl. I voted no
14 because the question is for adequate information. And
15 there's so really so skimpy clinical detail given on
16 these cases that it's hard to know what to do with it.
17 It needs more vetting and peer review. But on the
18 other hand I'm quite concerned that it causes it. And
19 I just want to express that sentiment.

20 DR. CHAPMAN: Kevin Chapman. I actually
21 agree with Dr. Pearl.

22 DR. ROGAWSKI: So Michael Rogawski. I voted

1 no. I don't think the information is adequate. But
2 I think there's something really important to say here
3 and that is that that does not imply that I believe
4 that Purple Glove does not cause -- that Fosphenytoin
5 does not cause Purple Glove. I think there's a
6 possibility that it does and we have to keep that in
7 mind when we consider a decision regarding intravenous
8 Phenytoin.

9 DR. SCHACHTER: Steve Schachter. I voted no
10 but I agree with all the comments made by people who
11 voted yes. It's just I felt the wording of this
12 question led me to vote no.

13 DR. BALISH: Marshall Balish. I voted no
14 and I echo the comments of Mike Rogawski and Phillip
15 Pearl.

16 DR. CAVAZOS: Jose Cavazos. I voted yes to
17 the question of probable causality but I do believe
18 that we need to have more information. And I will
19 encourage that to have the information collected
20 because the question I think was poorly worded and the
21 vote is actually reflecting not exactly what was
22 intended. So probably causality; need more

1 information.

2 DR. SPRIDGEN: Stacia Spridgen. And again,
3 I'm voting or commenting on my behalf and not DOD. I
4 also voted yes. I do believe that there's probably
5 more information that should be gathered to understand
6 the causality but I think that there's sufficient
7 evidence to show that it does cause it and hopefully
8 labeling changes will be considered.

9 DR. LEE: Mike Lee again commenting on
10 behalf of myself and not the Indian Health Service. I
11 voted yes, similar reasons as already listed.

12 DR. SOLOW: Brian Solow. I voted no without
13 any further comments.

14 DR. HOVINGA: Collin Hovinga. I voted no
15 largely because I don't believe there's sufficient
16 information to conclude.

17 DR. SNODGRASS: Wayne Snodgrass. I voted
18 no. Again, I agree with others that further
19 surveillance or attempting to find cases in the future
20 would be worthwhile.

21 DR. ANDERSON: Since the no votes carried
22 the day, we're not sort of obliged to vote on Question

1 A but I would ask whether you -- would the Agency like
2 me to still open this up for discussion or do you feel
3 that sort of the preceding discussion has given you
4 enough sense of how people rate the --

5 DR. KATZ: I think some explicit discussion
6 about it. I don't think there needs to be a vote.

7 DR. ANDERSON: Okay.

8 DR. KATZ: But again -- but it would be
9 useful to get a sense whether or not people -- because
10 a lot of people who voted no still believe that it
11 could.

12 DR. ANDERSON: Sure.

13 DR. KATZ: Or it might. And it would be
14 useful to hear whether or not even if you think --
15 what you think about the relative incidence, if you
16 think it could cause it.

17 DR. ANDERSON: So I think Dr. Fountain
18 should start with this one.

19 DR. FOUNTAIN: I get to talk about A anyway.

20 So I think in my mind it's absolutely clear
21 that the instance of Purple Glove Syndrome must be
22 much lower in Fosphenytoin. As I've been scribbling

1 away the numbers, how many years at various times the
2 FDA and Pfizer have been keeping track of things and
3 how many doses. So my calculation is based on the
4 current assessment that about two million doses of
5 Fosphenytoin and a little more than two million doses
6 of Phenytoin are prescribed annually. But previously
7 it was five million doses of Phenytoin before. So
8 Phenytoin clearly has been prescribed a lot more than
9 Fosphenytoin, of course, for more years and more per
10 year until recently. But they both are prescribed a
11 huge amount.

12 So in my mind it's clear that Purple Glove
13 Syndrome, that Fosphenytoin may cause Purple Glove
14 Syndrome. But if it does, in my mind it must be at a
15 much lower incidence. Because if you calculate the
16 instance is one per million for Phenytoin, even at one
17 per million, at two million doses a year, and it's
18 probably more than that now, you would think you'd
19 find more than five cases. And just like Dr. Temple
20 said, you'd think somebody would report it. And as
21 it's newly approved, you'd think there'd be that much
22 more vigilance to report it.

1 So in my mind, among the things we've talked
2 about, that's the one that I feel most strong about.
3 And then I guess a corollary of that is so could it
4 really be that it's not Fosphenytoin causing Purple
5 Glove? Well, you know, I think if you just went to
6 the hospital and showed somebody a limb and say what
7 happened? They say, well, he's got an ischemic arm.
8 So I think we heard down there how, you know, this
9 tends to happen to neonates. They just get -- or
10 young children just get dehydrated. So maybe there's
11 other reasons why people get an ischemic arm. If you
12 injection things into their vein that we don't think
13 about because we don't call it Purple Glove Syndrome
14 if you inject lasix, we call it, line ischemia or
15 something else. So kind of as corollary to that, if
16 it happens it must be very rare. But I personally
17 think it probably could happen.

18 DR. ANDERSON: Dr. Varelas.

19 DR. VARELAS: One more comment regarding
20 that. I mean, the period of reporting, let's say for
21 Fosphenytoin between I guess 1996 and now versus the
22 period for Phenytoin that goes back to '56, 54 years

1 ago, I mean, I would expect if the association was
2 much or the causality was there in the times of
3 internet, you know, it would be much easier for people
4 to report an adverse event than in the time of, you
5 know, in the '60s. I don't know if that's true, and
6 actually, I don't know if you have any data to support
7 that, but nowadays, you know, every student can
8 Google. Not PubMed anymore. Google Purple Glove
9 Syndrome if they see something and then they will have
10 an answer. And then it will be much more easy for
11 physicians to have this information on the internet
12 days than in the last, I don't know, 40 years, 50
13 years ago.

14 So my point is that if a causality was
15 stronger or as strong as with Phenytoin as you
16 believe, then you would have had many more reports of
17 Purple Glove during the last 15 years than with
18 Phenytoin before.

19 DR. ANDERSON: So the discussion and the
20 change in the votes would seem to suggest to me that
21 sort of the group leans towards the fact that if
22 Fosphenytoin is related, it's probably less likely.

1 There's less of a relationship or less severity. Is
2 there somebody who wants to sort of oppose that or
3 sort of feels that they want to make a case there's
4 more equivalence here? Because it seems to me the
5 default is that we either think there's no adequate
6 information or it's iffy but it's probably not of the
7 same magnitude as the relationship.

8 So Dr. Silbergleit.

9 DR. SILBERGLEIT: I think just with the
10 basis of the, you know, how think the information is
11 altogether, I think that the available data would be
12 consistent with either interpretation. That the
13 available data would be consistent with them being
14 different or with being the same. I think that
15 there's clearly got to be some compounding, some of
16 these cases with this high rate of extravasation are
17 from local effects other than this, you know,
18 vasculitic-type systemic effect. And that that's
19 probably going to be partially responsible for the
20 difference because you're going to see more of that
21 with the Phenytoin.

22 So I think that given the vagaries of the

1 case definition, the vagaries of the amount that we
2 have, I think that the available data are consistent
3 with there being a similar incidence or a different
4 incidence.

5 DR. ANDERSON: I'm not sure many people
6 would argue against it being consistent with, but what
7 would surprise you more? If you sort of found out the
8 answer was that Fosphenytoin was just as likely or
9 that Fosphenytoin was less or not at all likely to do
10 it, I mean, based on what you've heard.

11 DR. SILBERGLEIT: Which would surprise me
12 more? I don't have a feeling for which would surprise
13 me more. I would not be surprised by either.

14 DR. ANDERSON: Okay. Dr. Sleath.

15 DR. SLEATH: I think it would help in the
16 future to have data by time because I'm -- you know,
17 we've heard this and not really clearly on any slides
18 or anything like that. But if the FDA could monitor
19 by year the cases of each, that would help control for
20 some of the biases that I think are going on over
21 time.

22 DR. ANDERSON: Dr. Lu.

1 DR. LU: Yeah. I'm just not sure if we have
2 the base to compare the two because even for the
3 incidence of Phenytoin, and we don't have a good
4 number, right, because Meyer's studies 5.7 percent.
5 If that's the rate and the randomized trial was 202
6 patients you should see at least one. And we didn't
7 see anything. And the actual rate is perhaps lower.
8 And so all these reporting data, we don't have a
9 proper denominator and we don't have a comparable time
10 window and the risk factors. So the prospective data
11 is so limited. And so to say, you know, Fosphenytoin
12 is much less information. So I don't know what the
13 base we can say the risks will be comparable or not
14 comparable at this time. And I think it's probable
15 the Fosphenytoin may cause that. But there's no
16 adequate information. So it does not exclude it at
17 lower risk.

18 DR. ANDERSON: So I hope that gives you the
19 pulse of the group. Do you want to elaborate some
20 more?

21 DR. SILBERGLEIT: I thought of a different
22 answer to your question. Before what you had said

1 was, well, you know, there's not much new information.
2 No one would argue with that but people have to make a
3 decision and so we should offer an opinion on how they
4 should proceed making a decision. And I think -- I do
5 not feel that they should make a decision -- based on
6 these data that they should make a decision that
7 there's a difference and act in a policy manner on the
8 basis of their clear difference.

9 DR. ANDERSON: Okay. It sounds well put.
10 So I am going -- we do need to take our 3 o'clock
11 break because there are people who do need that break,
12 but we might be able to move on to say one of the
13 three -- one of Question 3 here before we take a 3
14 o'clock break. If not, we'll take the break just a
15 few minutes late.

16 Is there adequate information to determine
17 how often severe Purple Glove Syndrome with clinically
18 significant outcomes such as surgical intervention
19 occurs as opposed to the milder and moderate forms?

20 And so we're given each agent separately to
21 consider. So for Phenytoin, is there adequate
22 information to determine how often Phenytoin causes

1 severe Purple Glove Syndrome with clinically
2 significant outcomes as opposed to the milder and
3 moderate forms?

4 Some of this has been touched on in our
5 earlier discussions. If someone feels like they have
6 a new take on whether they feel like for Phenytoin the
7 information is adequate to make this sort of an
8 assessment.

9 Okay. Is there any objection to us moving
10 ahead with the vote? All right.

11 So at this point we're voting on Phenytoin.
12 Question 3 reads is there adequate information to
13 determine how often severe Purple Glove Syndrome with
14 clinically significant outcomes such as surgical
15 intervention occurs as opposed to the milder and
16 moderate forms?

17 Yes, please.

18 DR. SCHACHTER: A clarifying question.

19 DR. ANDERSON: Yes.

20 DR. SCHACHTER: If you answer this -- well,
21 to answer this do you have to assume that the veracity
22 of the information for -- that the relationship

1 between the kinds of reports we've seen today and
2 ground truth is just as strong for severe Purple Glove
3 Syndrome as it is for the milder forms?

4 DR. ANDERSON: I'll let them sort of amend
5 what I'm about to say but I think they would like you
6 to vote based on whatever you think is sort of the
7 sensible clinical sort of way to use your expertise to
8 read this question and sort of -- and then give them
9 an amplification of sort of why you said this or why
10 you said no and that will probably be what helps them
11 decide how to sort of interpret that as well.

12 Dr. Rogawski.

13 DR. ROGAWSKI: So we don't really know how
14 often Purple Glove Syndrome occurs in general, right?
15 So are we talking here about assuming that number is a
16 number that we don't know, you're asking what the
17 ratios here are? Is that what you're trying to get
18 at?

19 DR. ANDERSON: I think -- so I would like
20 you all to answer. You're not asking us simply to
21 decide whether we think they're different, right?
22 You're not asking us to say whether we think severe

1 events are less likely. So.

2 DR. KATZ: Yeah. And I can argue if you
3 answer yes there is adequate information that there
4 should be a follow up which is, you know, what do you
5 think? Is it a small percentage of the cases? But,
6 yeah, we're trying to get a sense of in your -- as Dr.
7 Anderson, in your judgment, are 90 percent of the
8 cases mild and, you know, extraordinarily rare cases
9 are bad with serious sequela? Or can you tell? I
10 mean, we're just trying to get a sense of how bad you
11 think this is in effect.

12 DR. ANDERSON: Yes, Dr. Cavazos.

13 DR. CAVAZOS: But the question is about is
14 there enough information for severe versus mild? So
15 are you asking us do we know what is the frequency of
16 the milder forms?

17 DR. KATZ: Yeah, again, in this question
18 we're not asking for a number. We're just saying can
19 you tell, are half the cases severe? You know, are
20 most of the cases severe? Can you tell? I mean,
21 that's sort of why we asked the question. When we
22 think the data -- when we've sort of made a

1 preliminary judgment that the data aren't necessarily
2 great, we want to know whether or not you think you
3 can tell something about how bad this problem is
4 globally.

5 DR. ANDERSON: Dr. Wolfe.

6 DR. WOLFE: Just a quick clarifier. I think
7 that this is a qualitative question, not a
8 quantitative. I mean, people are not really
9 comfortable here saying it's 5 percent or 10 percent.
10 I mean, to me one way of answering the question or
11 looking at it is does it happen very often or not very
12 often? The that being the severe form compared with
13 all the cases. I mean, I don't think we've been given
14 any more data to answer anything other than that. If
15 that's not the way the FDA wants the question answered
16 then they should say that. We don't have numbers that
17 are really valid. We can say of X number of cases,
18 not very often do they result in amputation or a
19 severe form.

20 DR. ANDERSON: Yeah, I think they might be
21 interested in knowing whether you feel like the
22 information is adequate even to go that far. So I

1 think that's -- the vote will help them if you can
2 sort of make your vote and clarify what you sort of
3 feel the information provides, you know, what the
4 adequacy is. It is what it is. The information is
5 what they've got.

6 Okay. So just so we don't lose the thread
7 again, let me read the question. Well, let me ask
8 again. Are there any other questions before I read
9 the question again? Okay, Dr. Rogawski.

10 DR. ROGAWSKI: Let me just rephrase the
11 question in a very simplistic way and ask is the
12 Agency simply asking us when Purple Glove Syndrome
13 occurs in some patients is it really severe and a bad
14 problem? And if that's the question, I think it's a
15 pretty easy answer. We've been --

16 DR. KATZ: It's not what -- we know there
17 are some bad cases. The question is in general is
18 Purple Glove -- just globally, everything that's
19 subsumed under Purple Glove, is that something we
20 worry about a lot because I think as Dr. Wolfe said,
21 are most of them bad? I mean, is this generally a
22 very dangerous thing? Or is it as rare as the global

1 syndrome is? Are the really bad cases a small subset
2 of that? It's not really -- we're not asking for
3 quantization, but we're trying to get a sense of
4 whether or not you think Purple Glove Syndrome is a
5 very, very bad thing.

6 DR. ROGAWSKI: You know, it would be helpful
7 for me if you could clarify what you're going to use
8 that information for. What is the reason for the
9 question?

10 DR. KATZ: For example -- you're going to
11 use it actually because we ask sort of the definitive
12 questions later on. But we're just trying to go sort
13 of stepwise and we're trying to sort of figure out
14 what the reasoning is along the way to the definitive
15 question which is more or less at the end. So the
16 idea is if -- well, maybe Phenytoin has more Purple
17 Glove than Fosphenytoin if that's what you conclude.
18 But it's a trivial matter and it doesn't really inform
19 the decision about whether or not Phenytoin ought to
20 come off the market. We're just trying to build the
21 building blocks to the final question.

22 DR. ANDERSON: Dr. Cavazos.

1 DR. CAVAZOS: By analogy, what I'm thinking
2 here is that you're asking like a question of rash in
3 Stevens-Johnson when rashes is a much larger group and
4 Stevens-Johnson is the one that you end up being
5 reported to because those are the severe cases. And
6 so the problem is the lack of information. We can
7 give you that as feedback but, I mean, I think that's
8 what you're getting at.

9 DR. KATZ: But that's what we asked for. Do
10 you have enough information to conclude that -- to
11 conclude that? That's what we're asking for.

12 DR. ANDERSON: Really?

13 (Laughter.)

14 DR. ANDERSON: Okay. Please, Dr.
15 Hershkowitz.

16 DR. HERSHKOWITZ: Yeah, if I can clarify.
17 What we're concerned about is if you just simply say
18 Purple Glove Syndrome is common or reasonably common.
19 It doesn't give us a regulatory handle. But if you
20 say there's a certain type that's common or highly
21 expected, that does give us -- or to add to the tough
22 regulatory question, that is which comes later on. So

1 we kind of want to get an idea of the serious nature
2 of the phenomena. Or at least that's what I think.

3 DR. AVIGAN: The other thing to think about
4 is think of it as a pyramid. And the question we're
5 in a way asking is the shape of the pyramid because
6 later on if there's, say a labeling effect, for
7 example or another kind of regulatory action, the way
8 it's described has to do with what we mean by Purple
9 Glove Syndrome. We're talking about transient and
10 mild phenotypes. We're talking -- with an occasional
11 rare effect or are we talking about something which is
12 actually a little? So the relationship between mild
13 and severe should be flushed out a little bit.

14 DR. ANDERSON: Dr. Frank.

15 DR. FRANK: Just a quick comment. I think
16 that we're having some trouble with this because of
17 what Dr. Lu highlighted. There's no denominator. And
18 so I think if Dr. Fountain is at the table doing back
19 of the envelope calculations of how often this
20 happens, I think that's enough to answer whether
21 there's adequate information.

22 DR. ANDERSON: All right. Question 3 reads

1 -- Question 3A reads is there adequate information to
2 determine how often severe Purple Glove Syndrome with
3 clinically significant outcomes such as surgical
4 intervention occurs as opposed to the mild and
5 moderate forms for Phenytoin?

6 So please vote yes, no, or abstain.

7 (Voting)

8 STAFF: Can we ask everybody to press their
9 button one more time please? It will continue to
10 blink. We have 28 of 29. Can everybody try it one
11 more time, please?

12 DR. SOLOW: We have one absent over here.

13 (Off microphone conversation.)

14 (Laughter.)

15 DR. ANDERSON: Okay. So we have 28 of 28.

16 Dr. Snodgrass is absent for this vote.

17 COMMITTEE MEMBER: (Off microphone.)

18 DR. ANDERSON: No, no. We don't want you to
19 push Dr. Snodgrass's.

20 (Laughter.)

21 DR. ANDERSON: The record will just reflect
22 that Dr. Snodgrass was absent when this vote was taken

1 and we have 28 votes for 28 voting members.

2 STAFF: Okay. We've reinitialized this
3 vote. Can you go ahead and vote one more time,
4 please?

5 (Voting.)

6 STAFF: There we go. Thank you.

7 DR. ANDERSON: We have 9 yes, we have 18 no,
8 and we have 1 abstention.

9 Can we start with Dr. Hovinga?

10 DR. HOVINGA: Collin Hovinga. No, I don't'
11 think there's adequate information.

12 DR. SOLOW: Brian Solow. Thank god we voted
13 three times so I could switch each time and get back
14 to no. I voted no. I don't think we have enough
15 information. I think it must be severely
16 underreported that most docs would not report any mild
17 forms when they probably have not heard of it. And
18 then we don't know about any other cases with any
19 other drugs.

20 DR. LEE: Mike Lee commenting on behalf of
21 myself and not the Indian Health Service again. I
22 voted no.

1 DR. SPRIDGEN: Stacia Spridgen commenting on
2 myself and not the DOD. And I also voted no. I don't
3 think we have enough information.

4 DR. CAVAZOS: Jose Cavazos. I voted no
5 because there's complete absence of reporting in the
6 milder forms.

7 DR. BALISH: Marshall Balish. I voted yes
8 because there is some literature that allows you to
9 make some estimate of -- so based on the literature.

10 DR. SCHACHTER: Steve Schachter. I voted
11 yes because I think the available information suggests
12 severe forms are very infrequent compared to mild
13 forms. And even if you -- I agree that mild forms are
14 probably grossly underestimated but that would only
15 further make the incidence of severe forms less
16 likely, you know, less frequent. So I voted yes.

17 DR. ROGAWSKI: Yeah, I voted yes for the
18 exact reasons that Dr. Balish and Dr. Schachter
19 expressed. I think the Agency was asking us just for
20 a very rough idea, not for any quantitative
21 information. And as Dr. Balish points out, there is
22 at least one prospective study. So we have some sense

1 of what the ratios might be.

2 DR. CHAPMAN: Kevin Chapman. I voted yes as
3 well. I guess I agree with my three colleagues in a
4 row here that voted yes. It just sort of seemed like
5 the FDA was asking sort of a broad question and I
6 think that if you believe the AERS system is a valid
7 system that people who have bad outcomes are reported
8 in that system, I think they do a decent job of trying
9 to capture that data.

10 DR. PEARL: Phillip Pearl. I voted no and I
11 agree that the data we saw looks like most cases are
12 mild. But I'm not sure about the adequacy of the
13 reporting. And the numbers are so small that if there
14 was just an occasional extra case that required
15 surgery, such as an amputation, it would change the
16 whole balance of the discussion. So for that reason I
17 voted no.

18 DR. MARDER: Ellen Marder. I voted yes
19 because the serious cases seem to be extremely rare no
20 matter what the denominator is.

21 DR. KHATRI: Pooja Khatri. I voted yes.
22 And I was kind of looking at this from a practical

1 standpoint. It's pretty rare. It would be hard to
2 capture this more accurately and this in any
3 meaningful way would take a very, very large study.
4 And I think we have a pretty good sense of what's
5 going on.

6 DR. KINDLER: Dean Kindler. I voted no. I
7 think the data is still confusing, especially the
8 Pfizer database with the 11 amputations versus the FDA
9 presented. So I'm still confused by that. My
10 clinical hunch is that it's very rare divided by rare.
11 But I'm not sure.

12 (Laughter.)

13 DR. LU: I abstained because I think it's
14 low but it seems this one will have implication into
15 practice and I don't see patients. I don't know what
16 the implication will be. So I abstain.

17 DR. FOUNTAIN: Nathan Fountain. I voted yes
18 because I think in prospective randomized trials even
19 just in 79 patients, Greg Barkley found three people
20 that had some purpleness in their hand. So I think to
21 that degree the milder form is probably more frequent
22 and to a degree that we probably wouldn't even

1 recognize or think about. But yet the severe forms
2 are something that we almost never see, whether it's 1
3 in 43 or 11 in 119. So it seems to me the severe form
4 must be more rare. Much more rare than the mild form.

5 DR. ANDERSON: I voted no. I just felt our
6 discussion sort of documented that there really wasn't
7 adequate information to make a strong confident
8 opinion. Brett Anderson.

9 DR. GREEN: Mark Green. I voted no and I
10 don't believe that we have enough information about
11 reporting. There's too many artifacts.

12 DR. FRANK: Samuel Frank. I voted no for
13 exactly the two previous speakers.

14 MS. KANDELL: Ellen Kandell. I voted yes
15 for a number of the reasons previously stated.

16 DR. WOODS: Mark Woods. I voted no for,
17 again, previously stated reasons.

18 DR. COOPER: William Cooper. I voted no.
19 No further comment.

20 DR. WOLFE: Sid Wolfe. I voted no. No
21 further comment.

22 DR. NELSON: Luis Nelson. I voted no. No

1 other comment.

2 DR. HUFF: Stephen Huff. No.

3 DR. SILBERGLEIT: Robert Silbergleit. Yes.

4 DR. NAIDECH: Andrew Naidech. No.

5 DR. VARELAS: Panaviotis Varelas. No.

6 DR. SLEATH: Betsy Sleath. No.

7 DR. ANDERSON: I've been asked to state for
8 the record that Dr. Snodgrass was called away for an
9 emergency phone call and is absent from the room at
10 this time. At this time we're due for our break and
11 several of you have asked me about your planes and
12 things. I will ask that we can start again in 10
13 minutes. It's 20 after, so let's make it a little bit
14 shorter please.

15 (Break.)

16 DR. ANDERSON: All right, if everybody could
17 resume their seats please, then we could begin our--
18 resume our discussions.

19 So, before we move to question 3b, there
20 were a couple of items brought up as questions
21 regarding Pfizer and Pfizer has a brief statement that
22 they've asked me if I will--if they can read into the

1 record which I would like them to do at this time and
2 then we'll move on to item 3b.

3 MS. HALEY: Hello, my name is Carol Haley.
4 I'm from Pfizer Regulatory Affairs and in response to
5 some questions we got today on manufacturing I'd like
6 to read the following statement: Pfizer withdrew
7 Cerebyx or Fosphenytoin Sodium Injection from the U.S.
8 market due to the lack of a cost-effective source to
9 manufacture the drug product. We are actively
10 evaluating a replacement source and plan to reenter
11 the market once we identify one. All product we
12 market is manufactured to the highest quality
13 standards and in full compliance with approved
14 specifications and GMP requirements.

15 Thank you.

16 DR. ANDERSON: Okay, so, I guess we need to
17 also recognize that Dr. Snodgrass has--yes, so Dr.
18 Snodgrass has returned to the room. I have to do that
19 for the--so, now we have 3b to vote upon which is the
20 same forward as the last time but now we're doing it
21 for Fosphenytoin. Is there adequate information to
22 determine how severe Purple Glove Syndrome outcomes

1 are and how they occur as opposed to the milder forms
2 for Fosphenytoin?

3 DR. KATZ: I think given the answer to the
4 previous question about is there enough information to
5 tell if Fosphenytoin causes it, we don't really have
6 to vote on this question. I think it's moot at this
7 point.

8 DR. ANDERSON: Okay. That's fine. And I've
9 also been asked to reorder the questions and move to
10 the discussion of number seven and then return to the
11 discussions of questions four, five, and six. And so
12 that's what we'll do.

13 So, now we are going to move to the
14 following: with the above in mind--which will be
15 discussed later, so, those of you leaving will fill in
16 that blank--would the committee request marketing
17 suspension of Phenytoin? So, is there anybody on the
18 committee who would like to act as an advocate for--
19 based on whatever expertise they brought with them or
20 the information we've heard today--who would like to
21 advocate for the suspension of Phenytoin?

22 Dr. Solow?

1 DR. SOLOW: Yeah, I'm sorry, because my
2 question might relate to question four, so I
3 apologize. I was going to ask why they switched
4 orders but I gave up asking. What drugs from the--I'm
5 a family doc, probably the only one in the room, but--
6 from the experts--what other drugs with the same FDA
7 indications do we have that if both these drugs were
8 removed would take their place--could take their
9 place?

10 DR. ANDERSON: I think the motivation for
11 the question is really that when Dr. Katz was doing
12 his introduction this morning it was sort of brought
13 to FDA, why would you have Phenytoin on the market
14 when you've got Fosphenytoin which is so much better,
15 basically, and so the question for re-suspension of
16 Phenytoin, I think, is sort of implying that
17 Fosphenytoin remains, sort of, the question is
18 phrased, are you going to suspend Phenytoin and not
19 suspend Fosphenytoin?

20 DR. SOLOW: And I understand that, but in
21 the back of my mind as I process all of this, are
22 there other drugs--because I heard different opinions-

1 -that would take the place of both of these drugs?

2 DR. ANDERSON: So, for the standpoint of
3 status epilepticus, we have several epileptologists
4 who could tell us if there was no Phenytoin or
5 Fosphenytoin--

6 DR. SOLOW: Correct.

7 DR. ANDERSON: --would you be able to treat
8 status?

9 DR. SOLOW: Or for the other--and then I
10 heard that we don't use it so much--rarely now for
11 status, we use it for maintenance or post-surgical.
12 What would we use in that case?

13 DR. ANDERSON: Right, so the--I guess I
14 should have broken it down more. Like neurological--
15 because there are also sort of non-neurologic
16 indications that are less common as well but we can
17 ask some of our epilepsy representatives and those who
18 deal in neuro intensive care units, you know, could
19 you get by, or what would you do if neither of these
20 agents were available?

21 DR. SOLOW: Thank you.

22 DR. ANDERSON: Dr. Cavazos, want to start?

1 DR. CAVAZOS: Sure. Well, parenteral drugs
2 that we have available that are using refractory
3 status epilepticus, meaning good prospective evidence,
4 Class I, only exists for the VA Cooperative Study.
5 Essentially that's it in the benzodiazepines and
6 Phenytoin.

7 Having said that there are small studies,
8 some, for example, there some study in India that
9 compares Phenytoin versus Valproic and had similar
10 responses. People have also used for refractory
11 status epilepticus infusions of Midazolam, infusions
12 of Propofol or Phenobarbital. And, you know, there
13 are differences of opinion about what's best to use.

14 And then we have the two other medications
15 that are being used off-label, one of them with
16 significant penetrance due to the time that has been
17 used which is levetiracetam again, no significant--or,
18 no indication, no prospective class I or class II
19 studies that demonstrate effectiveness in this
20 particular situation but clinically have been used in
21 a sequential manner once the status epilepticus has
22 not been controlled.

1 The problem with that, as Dr. Black
2 indicated earlier, is that the predictor for
3 refractor-ness is time and so every time that you use
4 another drug and you are adding to the pile, I mean,
5 that drug is being compared in an unfairly way with
6 the other ones.

7 So, to answer the question is, there are
8 some alternatives, unfortunately the alternatives are
9 not--do not have supportive or definitive supportive
10 evidence for use.

11 DR. ANDERSON: Any other epilepsy experts
12 want to elaborate on those options or opportunities?

13 So, you can go first, Dr. Fountain, and
14 we'll move around.

15 DR. FOUNTAIN: I just want to say that I'm
16 not aware of any other drugs approved for the
17 treatment of status epilepticus and that the standard
18 practice in the United States, despite what all of us
19 think, the most common second line drug give after
20 benediazapines is still Phenytoin and not Fosphenytoin
21 and that in a survey of neurologists in the United
22 States, they still would use Phenytoin first and that

1 there are ongoing designs for clinical trials to
2 compare Phenytoin as the gold standard to Valproic and
3 levetiracetam and I guess some people thinking of
4 lacosamide, because those are available parenteral
5 drugs, but the direct answer to your question is that
6 if you didn't have Phenytoin available, the average
7 practicing neurologist would not find an easy
8 replacement, even if we think there might be some.

9 DR. ANDERSON: Dr. Green had something.

10 DR. GREEN: I'm not an epilepsy expert,
11 however I would suspect that if a patient was on oral
12 Phenytoin and went into status epilepticus because
13 they stopped the drug, that there would probably be no
14 more effective treatment for the status epilepticus
15 than this drug. So, short of a generation of patients
16 and doctors who have no one out there on oral
17 Phenytoin, this is very relevant.

18 DR. ANDERSON: Dr. Naidech?

19 DR. NAIDECH: I think if it were to come to
20 pass that Phenytoin IV were removed from the market
21 and Fosphenytoin were not to become available and a
22 patient with status did not have those options

1 available as part of the armamentarium, we wouldn't
2 feel--I'd feel regretful if that came to pass.

3 DR. ANDERSON: I'm going to get all of you
4 who have raised your hand, but I wanted to ask Dr.
5 Solow if he could maybe frame his--in light of that,
6 do you want to reframe the question or extend it a
7 little bit so that we make sure we address what you--
8 what's going to help you cover it?

9 DR. SOLOW: No, I think I'm hearing a common
10 theme, that there's not a lot more out there, that if
11 these were both removed, we would probably be in
12 trouble and doing a disservice because we only have
13 the other. That's what I'm hearing, at least for FDA
14 indication, so I'm not sure that anything else can be
15 added except if that comes into play during our
16 questioning about the shortage.

17 DR. ANDERSON: So, then, does anyone want
18 to--so, Dr. Rogawski?

19 DR. ROGAWSKI: Well, I think that's a fair
20 assessment of the situation. It's clearly the case
21 that Phenytoin at the moment--or Fosphenytoin--are the
22 standard of care for the treatment of status

1 epilepticus, but, you know, we've heard today that
2 neither of these drugs is ideal and there's
3 considerable anecdotal and limited clinical trial
4 information with other agents that are available as
5 intravenous--in intravenous delivery forms, such as
6 Valproic acid and levetiracetam and basically what we
7 really need now are adequate and well-controlled
8 studies of these agents in status epilepticus. If we
9 had those studies, those agents could very easily
10 supplant Phenytoin and Fosphenytoin and in certain
11 settings, levetiracetam is certain more popular among
12 neuro surgeons and so forth because of ease of
13 administration without major drug interactions and so
14 forth. So, I see that as the future moving away from
15 Phenytoin and Fosphenytoin, but at the moment we're
16 stuck with the data that we have that really don't
17 support the adequacy of these other agents.

18 DR. ANDERSON: I think Dr. Lu, you were
19 next, and then I'll--

20 DR. LU: Okay. I have a question about--you
21 know, because beyond the Purple Glove Syndrome, if you
22 look for the FDA slides--I mean, on the 18th and the

1 death--overall death associated with CV and
2 hypotension since marketing seems to comparable (sic)
3 when Fosphenytoin is 35, IV Phenytoin is 36, but one
4 has been on market much longer time and the more
5 exposure time. Because we discussed earlier about,
6 you know, the PGS based on the AERS report data. I
7 mean, you know, there were spontaneous reports in all
8 those problems, but I think death perhaps will be much
9 less likely to be missed.

10 So, given that--I mean, besides PGS should
11 we also looking to the death when we consider the
12 suspension of the one versus the other?

13 DR. ANDERSON: Dr. Spridgen?

14 DR. SPRIDGEN: Again, I'm speaking on my
15 experiences and not on behalf of DoD, but from a DoD
16 perspective I do have to think about those service
17 members that are in theater currently and are
18 traumatized on the battlefield and they need the
19 options available to them, and irregardless of the
20 Fosphenytoins shortage or unavailability, and the
21 refrigerator issue is a big concern in those austere
22 environments. So, I would consider that these drugs

1 do need to be made available because that does affect
2 our opportunity to perform our mission in theater.

3 DR. ANDERSON: Dr. Snodgrass?

4 DR. SNODGRASS: This is in the context of
5 what's been mentioned about the so-called future of
6 this and levetiracetam and maybe Valproic were brought
7 up. Another consideration, not immediate, but is the
8 animal data that exists, some of which I'm aware of is
9 that apoptosis--brain apoptosis--is produced by
10 Phenobarbital, Phenytoin, but not by levetiracetam as
11 an example, so I suspect down the road as someone has
12 already said, that this is--usage is going to change.

13 DR. ANDERSON: Dr. Silbergleit?

14 DR. SILBERGLEIT: I think pertaining to this
15 I'm very concerned about unintended consequences from,
16 certainly getting rid of the drugs, but even just in
17 certain types of labeling. It's very common that
18 physician behavior gets modified, out of proportion,
19 to the extent of the actual labeling change so the
20 labeling change can be very reasonable and
21 appropriate, but it gets a new black box warning sends
22 people running away from the drug as an unintended

1 consequence and I think given the trends toward
2 increasing use already certainly in status epilepticus
3 of these other parenterals that have not been shown--
4 have not been tested in appropriate and well-
5 controlled clinical trials, I think there's a real
6 concern that if we're not careful about labeling
7 regarding a relatively small safety concern, we could
8 dramatically increase the use of inadequately tested
9 medications that are already on the rise for off label
10 use and so I think that those laws of unintended
11 consequences can have an overwhelming effect and
12 should be thought of very carefully.

13 DR. ANDERSON: Dr. Pearl?

14 DR. PEARL: Phillip Pearl. Thank you. At
15 least in the pediatric neurology literature there are
16 increasing reports of patients with unrecognized
17 mitochondrial disorders being treated with Valproate
18 in status and getting tripped up, and there's one
19 recent article saying people should be screened for a
20 mutation such as the pOG-1 for the preliminary
21 polymerase mutation. And I bring this up in terms of,
22 if we alter the balance of what's available for status

1 epilepticus, there would be unanticipated consequences
2 such as if we started using Valproate in a more wide
3 spread manner in these patients we're going to get
4 into trouble.

5 DR. ANDERSON: Dr. Nelson?

6 DR. NELSON: You know, somebody brought up
7 the issue of other non-neurologic indications. Is
8 that for discussion at this point?

9 DR. ANDERSON: Yes, I mean, I think it would
10 been sort of lead through, but at this point if we
11 suspend the marketing of Phenytoin it's going to have
12 implications for more than epilepsy, so please address
13 it.

14 DR. NELSON: Yeah, what I wanted to say--
15 kind of two things. In emergency medicine I think
16 that, you know, the use of Phenytoin has really fallen
17 fairly low on the scale of use and I think you saw the
18 data--we all saw the data--looking at lorazepam and
19 other things and I guess our use of it may be
20 different than the use of a neuro intensivist, for
21 example, in trying to control Status. The vast
22 majority of people, I think, that we give it to are

1 probably just being reloaded after having had a
2 standard seizure and they could probably get reloaded
3 with either medication probably equally effectively.

4 The use of Phenytoin for non-neuro
5 indications is almost absent. You know, I think for
6 arrhythmias, I can't imagine anybody even uses it.
7 For digitoxicity, it's been done for 20 years since
8 Digoxin FAB has come out and it's never really used.

9 I don't think there's any other--maybe there
10 are some other indications that I can't really come up
11 with, but I think that there would be no harm in not
12 having it for those non-neuro indications and again,
13 from my perspective, the neuro indications are kind of
14 minimal. I mean, I don't think--it's on our list, but
15 most people probably really never get to it other than
16 as a reloading.

17 DR. ANDERSON: All right. That was pretty
18 lively. So, does--so the question still reads, with
19 the above in mind would the committee request
20 marketing suspension of Phenytoin? Is there somebody
21 who wants to act as the advocate of that because I've
22 just been hearing lots of reasons why even though it

1 may not be used, sort of, in the non-neurological
2 world as much as it used to, it still seems to have a
3 role in the neurological one. Is there anyone who
4 wants to change everyone's mind?

5 All right, then maybe we can put this--7a to
6 a vote. I'll read the question one more time and then
7 you vote yes, no, or abstain.

8 With the above in mind, would the committee
9 request marketing suspension of Phenytoin?

10 (Voting.)

11 And the vote is: Yes-0, No-29, Abstain-0.
12 We'll acknowledge our votes. We'll start on the left
13 side this time, please, so that's Dr. Sleath.

14 DR. SLEATH: Betsy Sleath, no.

15 DR. VARELAS: Panaviotis Varelas, no.

16 DR. NAIDECH: Andrew Naidech, no.

17 DR. SILBERGLEIT: Robert Silbergleit, no.

18 DR. HUFF: Stephen Huff, no.

19 DR. NELSON: Lewis Nelson, no.

20 DR. WOLFE: Sid Wolfe, no.

21 DR. COOPER: William Cooper, no.

22 DR. WOODS: Mark Woods, no.

1 DR. KANDELL: Ellen Kandell, no.
2 DR. FRANK: Samuel Frank, no.
3 DR. GREEN: Mark Green, no.
4 DR. ANDERSON: Britt Anderson, no.
5 DR. FOUNTAIN: Nathan Fountain, no.
6 DR. LU: Ying Lu, no.
7 DR. KINDLER: Dean Kindler, no.
8 DR. KHATRI: Pooja Khatri, no.
9 DR. MARDER: Ellen Marder, no.
10 DR. PEARL: Phillip Pearl, no.
11 DR. CHAPMAN: Kevin Chapman, no.
12 DR. ROGAWSKI: Michael Rogawski, no. And I
13 just wanted to elaborate on the shortage issue which I
14 think is a compelling reason not to remove Phenytoin
15 from the market. At our own institution we haven't
16 had any Fosphenytoin for quite a while and I just got
17 the names of our suppliers from our pharmacy and
18 called them up and tried to find out whether they had
19 any plans of resuming sales into the marketplace and
20 virtually all the suppliers that we use have made a
21 decision, really, not to reenter the marketplace. So,
22 I think there's going to be problems going forward

1 with the supply of Fosphenytoin.

2 DR. SCHACHTER: Steve Schachter, no.

3 DR. BALISH: Marshall Balish, no.

4 DR. CAVAZOS: Jose Cavazos, no.

5 DR. SPRIDGEN: Stacia Spridgen on behalf of
6 Stacia Spridgen, no.

7 DR. LEE: Mike Lee on behalf of Mike Lee,
8 no.

9 DR. SOLOW: Brian Solow, no.

10 DR. HOVINGA: Collin Hovinga, no.

11 DR. SNODGRASS: Wayne Snodgrass, no.

12 DR. ANDERSON: Question 7b, with the above
13 in mind would the committee allow continued marketing
14 of Phenytoin without changes to the labeling? So, is
15 there--excuse me, Dr. Katz?

16 DR. KATZ: Yeah, I'd like to--and maybe this
17 pertains to the next question. We've talked a lot
18 about deficiencies in the labeling of Phenytoin and
19 we're interested in what the group thinks about that,
20 but I think there's much to be done to fix the
21 labeling of Phenytoin. But I'd like to amend this or
22 the next question to ask specifically whether or not

1 the committee thinks that Phenytoin should be
2 indicated as second line. In other words, when
3 Fosphenytoin isn't--well, I don't know isn't
4 available--try Fosphenytoin first, kind of thing.
5 Again, if you think that there's no other difference
6 except in the incidence of Purple Glove Syndrome, you
7 might do that.

8 So, that specific question would be
9 important for us to hear your views on.

10 DR. ANDERSON: So, for question C you would
11 like us to perhaps discuss specifics of the labeling
12 or instructions for infusion, but for B--

13 DR. KATZ: Yeah, at some point--at some
14 point, to--because a lot of the other changes, you
15 know, where it says no infusion on the bottom, it's
16 completely confusing and we understand that a lot of
17 those things need to be fixed, but we haven't asked--I
18 don't think we've asked explicitly in any A, B, C, or
19 D, whether or not it should be sort of second line.

20 NH: Could it be a vote?

21 DR. KATZ: Well, we don't have to vote on
22 that but I do want to get a sense of what the

1 committee thinks about that specific labeling change.

2 DR. ANDERSON: So, is there--how many--I
3 guess maybe we could do it by asking sort of the
4 people who administer Phenytoin and Fosphenytoin with
5 regularity how many of them would advocate that
6 Phenytoin ought to be explicitly listed as second
7 line? Not necessarily would you prefer to use
8 Fosphenytoin first or in your practice or something,
9 but would you, you know, encourage it to be listed on
10 your hospital formulary as only available if
11 Fosphenytoin wasn't available or couldn't be used or
12 required special permission for a physician to
13 prescribe it if he wasn't going to prescribe
14 Fosphenytoin?

15 BS: Isn't that number 4(a)?

16 DR. ANDERSON: Number 4(a) says all
17 indications and therapeutic uses--can they be used
18 interchangeably? I think the question is not
19 necessarily whether they can be used interchangeably,
20 but whether the agency should advocate for a role in
21 prioritizing one in favor of the other and to make
22 that explicit in the way they label the products.

1 And so, Dr. Cavazos?

2 DR. CAVAZOS: The question is, second line
3 to what? I mean, I know benzodiazepines is the first
4 line, but I mean, would--

5 DR. KATZ: Using Fosphenytoin first.

6 DR. CAVAZOS: I'm sorry?

7 DR. KATZ: I mean, use Fosphenytoin first if
8 it's available.

9 DR. CAVAZOS: Oh, so second line--

10 DR. KATZ: Yeah, second line may not be the
11 right language, but, you know, try Fosphenytoin first.

12 DR. ANDERSON: They're going to put
13 something in the little--you know, in the instructions
14 that basically says Phenytoin should be only used in
15 X, Y, and Z, and one of those things is going to sort
16 of make explicit the prioritization of Fosphenytoin
17 first.

18 I mean, is that what it should say? Is that
19 what the agency should do? I mean, I'm sure there's
20 people who use it a lot more than I do over there.
21 Dr. Chapman?

22 DR. CHAPMAN: I guess, you know, I take care

1 of pediatric patients and so I think they make a
2 special population. It is challenging to get IV lines
3 in them, they're very rarely in the antecubital fascia
4 and especially in neonates and they're almost never
5 large bore, and so I think all of those are risk
6 factors for having, you know, Purple Glove Syndrome,
7 and so I would make an argument that--and this is how
8 I practice--that Fosphenytoin should be considered for
9 any child that's administered peripherally and I think
10 that it's--I've used it--phenytoin, IV Phenytoin--
11 through central catheters, and so that's sort of what
12 I teach the residents that, you know, part of the
13 issue is, is you have postictal kids who may not be
14 verbal who may not be able to tell you that they have
15 burning and pain, and so you can't really adequately
16 assess whether they're actually being injured as you
17 infuse the medication.

18 So, I think the pediatric subset, I would
19 prefer to see the Fosphenytoin as considered drug of
20 choice over IV Phenytoin.

21 DR. SILBERGLEIT: (Off mic.)

22 DR. ANDERSON: Were you done, Dr. Chapman?

1 DR. CHAPMAN: (Off mic.)

2 DR. SILBERGLEIT: Well, I don't understand--
3 we're talking about labeling changes, though, right,
4 and the Fosphenytoin isn't labeled for use in that
5 population at all. So, you're talking about changing
6 the label to say Fosphenytoin in preference to
7 Phenytoin in kids except that Fosphenytoin is not
8 labeled for use in kids at all.

9 DR. CHAPMAN: Correct.

10 DR. ANDERSON: So that was Dr. Silbergleit
11 who was asking the question. Dr. Temple?

12 DR. TEMPLE: It is worth noting, we saw what
13 the labeling currently says about Fosphenytoin and as
14 labeled, it's second line, so I think that's something
15 we probably need to change. We'll fix that.

16 DR. ANDERSON: The next person on the list
17 is Dr. Khatri?

18 DR. KHATRI: Yeah, I just wanted to answer
19 that question as well. So, in my clinical practice I
20 would chose Fosphenytoin over Phenytoin and that's
21 what I was doing before I came here.

22 Having reviewed this literature, I think the

1 weight of the evidence is that Purple Hand Syndrome is
2 less common with Fosphenytoin. Knowing that I feel
3 very much in favor of making Fosphenytoin first line
4 and Phenytoin second line. We need more information
5 on Fosphenytoin but based on what we know now, that's
6 what I'd be up for.

7 DR. ANDERSON: I can't read that--Naidech.

8 DR. NAIDECH: I would encourage not to make
9 Phenytoin specifically second line to Fosphenytoin.
10 Dr. Coplin's study shows that when you're watching
11 carefully and have a protocol do it carefully it can
12 be done very safely and in a cost conscious era, I
13 don't think we should essentially mandate the use of a
14 significantly more expensive product.

15 DR. ANDERSON: Dr. Silbergleit?

16 DR. SILBERGLEIT: I just want--Dr. Kindler,
17 I think, earlier said--made the case that--from a
18 safety consideration, that the safety of both these
19 drugs is going to be primarily driven by the
20 cardiovascular safety and that what we've learned is
21 that despite popular belief, we think the
22 cardiovascular safety is probably about the same, and

1 in fact if there's any teaching that we need to do the
2 world, it's that. And if that's the case, then I
3 don't see recommending one over the other.

4 DR. ANDERSON: Dr. Nelson?

5 DR. NELSON: I think I was going to pretty
6 much say the same thing. The only other issue would
7 be in terms of the quality of the IV and, you know,
8 those types of things. I think kind of too much
9 telling people what they're supposed to do could get a
10 little bit complicated, but the recommendation that if
11 the IV is of any questionable stability perhaps you
12 should choose one over the other with this potential
13 safety issue. And that may be the issue with children
14 as well, it's just--you know, a lot of it really comes
15 down to the quality of the ability to infuse it.

16 DR. ANDERSON: So, I'll get to the next
17 couple people on the list but I want to rephrase to
18 make sure I'm understanding. So, it sounds like a lot
19 of the issues are related more to the infusion
20 characteristics than sort of necessarily saying that
21 Fosphenytoin should be number one and Phenytoin should
22 be number two, that there should be some latitude for

1 choosing amongst them in the circumstance.

2 Okay, Dr. Snodgrass?

3 DR. SNODGRASS: I certainly would be in
4 favor of what's been proposed, Fosphenytoin first,
5 Phenytoin second. It's clear, and it's already been
6 stated, in children, young infants and children, you
7 really do have an issue about this. The other aspect
8 of this is the off label concern about one not even
9 being indicated. Forty percent of all drug
10 prescribing in the United States in all age groups
11 combined is off label and in the PDR right now, 70
12 percent plus of all drugs don't even have an
13 indication for children.

14 So, what we do in pediatrics is, the
15 majority of drug use is off label and it has to be,
16 and if you go to the official compendia of the United
17 States of America, which is the USPDI, United States
18 Pharmacopoeia Drug Information, it's the only source I
19 know of, in the back is an off label indications index
20 in the official compendia of the United States,
21 meaning it's been reviewed by expert committees, and
22 you'll find lots of drugs with a USP indication that

1 it's off label. So, I don't think that's an issue.

2 DR. ANDERSON: Dr. Katz?

3 DR. KATZ: Yeah, let me just talk for a
4 second about this specific issue saying you should use
5 it first in kids and it's not approved in kids. That
6 will be a problem for us. I don't see how that's
7 doable. If we get pediatric dosing recommendations--
8 obviously, there's lots of off label use and lots of
9 other organizations provide dosing recommendations for
10 kids when it's not on the label, that's all well and
11 good. I don't see how we could put something in the
12 label that said, use this first in kids, and it's not
13 indicated in kids. If we get pediatric dosing
14 recommendations, if we get data we think--reliable and
15 put those in, then of course that becomes possible.

16 DR. ANDERSON: Dr. Fountain?

17 DR. FOUNTAIN: Well, that was my first
18 comment is it would seem reasonable that the FDA would
19 ask the manufacturers and marketers of Fosphenytoin to
20 have that data and of course historically, maybe at
21 the time it was developed, the kind of data they
22 needed was less specific or detailed than needed now,

1 and so the data you got didn't quite lead to the data
2 that's needed in the label, that maybe as a result of
3 other discussions they could require that and so it
4 would inform common clinical practice.

5 But the second comment would be that the
6 context where I give IV Phenytoin isn't very often in
7 ongoing generalized convulsive status as an
8 epileptologist, it's for other kind of urgencies, and
9 so I don't give it myself. I tell the resident or
10 fellow or somebody, they give it. I come in the next
11 day and see what happened, and the thing that happened
12 the next day isn't very often that they've died or
13 their limbs necrose, but what happens is the next day,
14 they always say, that really hurt and now I have this
15 big red spot that hurts. So, I find superficial
16 phlebitis in those kind of things or even occasionally
17 local necrosis, to be more of a problem, and we
18 haven't really talked about that. So, in my mind,
19 that problem is--sort of outweighs any other aspects
20 of Fosphenytoin to make it seem like Fosphenytoin in
21 my mind is first line before Phenytoin, whether or not
22 that plays into the label that way. I don't know that

1 we've had much discussion about sort of those kind of
2 practicalities that are really bothersome that add
3 beyond the super safety issues to the other
4 information that weighs towards using Fosphenytoin
5 before Phenytoin all other things being equal.

6 DR. ANDERSON: So, it seems though, to me,
7 that if you have the FDA make Fosphenytoin first line
8 and Phenytoin second line, then people like Dr. Coplin
9 who want to use Phenytoin and have a protocol for its
10 use and administration are going to have a difficult
11 time opting for that approach in their over the age of
12 11 patients, so I guess I'd like to know how strong
13 the advocacy is for sort of a regulatory status of
14 first line Fosphenytoin, second line Phenytoin,
15 knowing that it's going to impact in those sorts of
16 ways for those sorts of practitioners.

17 We still have a couple people on the list
18 who maybe can help me as we go along here, but next is
19 Dr. Lee.

20 DR. LEE: Again, expressing the opinion of
21 myself, not the agency, but you know, the thing that
22 kind of resonates in my mind is that, you know, I find

1 it difficult as I'm thinking of us recommending one
2 product versus another, and a potentially mixed
3 message that we would be sending out if we're sending
4 out a message that the product we are recommending is
5 a product we ca not get right now, and is a product
6 that, according to what I've heard today, is that we
7 don't have an idea as to when we are going to be able
8 to get that, so, you know, how will that message come
9 out if we were recommending Fosphenytoin over the use
10 of Phenytoin?

11 So, that's one thing that I would ask you to
12 consider. And then the second thing, completely
13 different, is that, you know, I certainly appreciated
14 the Dr. Coplin data and the information that he
15 presented as far as--and I mentioned it earlier as
16 well, that you know, I appreciated the protocol that
17 they used for the dilution factor with the use of
18 Phenytoin and I would certainly find it interesting to
19 see how that data would look in a larger, you know,
20 study population if we could get that type of data in
21 a little bit larger numbers, it would be nice to see
22 as well.

1 DR. ANDERSON: Dr. Rogawski?

2 DR. ROGAWSKI: Right. So, you know, just in
3 general, the issue of this package insert, I
4 downloaded it from the internet and it's this massive
5 document with microscopic type. I'm sure, you know,
6 in the form that it's in very few people actually sit
7 down and read it, so, you know, it seems to me that
8 there really does need to be a change in the labeling
9 and it would be very helpful to have sort of a few
10 bullet points up front and in thinking about what
11 these bullet points might be, I had some ideas. One
12 thing would be to say, you know, use oral Phenytoin
13 when you can instead of any of these intravenous
14 products given the uncertainties. Secondly, I don't
15 really have a problem based upon the evidence that
16 I've heard today to gently suggest that Fosphenytoin--
17 that the physician might consider Fosphenytoin instead
18 of intravenous Phenytoin, and just sort of lay out
19 what the issues are.

20 And then there are some other things I
21 thought too that you might want to include as sort of
22 bullet points to pay particular attention to the issue

1 of Purple Glove Syndrome in the elderly patient. We
2 heard that they might be at higher risk. Perhaps use
3 lower infusion rates in elderly patients. The fact
4 that, perhaps, multiple doses are a problem; if you
5 give it once, maybe that's not such a big issue, but
6 if you give it multiple times, you may be at higher
7 risk of having Purple Glove and you might just let the
8 physician know that if the patient starts complaining
9 of these symptoms you might have to discontinue it and
10 try something else.

11 So, I think, you know, having some helpful
12 bullet points up front in the package insert could go
13 a long way to improving therapy and perhaps reducing
14 the risk, and while you're at it, why not have,
15 instead of this complicated milligrams per minute kind
16 of a calculation that you have to do when you
17 administer the drug, why not just have a little table
18 that has the patient's weight and then says how many
19 milliliters of the solution for that weight range do
20 you administer, and also in that table you could say,
21 well, you shouldn't give it faster than over a certain
22 number of minutes and make it just sort of idiot

1 proof, so to speak, and I think that would really
2 improve the chances that this would be given safely
3 and not have adverse consequences.

4 DR. ANDERSON: Dr. Silbergleit, then Dr.
5 Woods.

6 DR. SILBERGLEIT: No, he covered my point.
7 I think especially encouraging oral use instead of IV,
8 I've heard that a lot today.

9 DR. ANDERSON: Dr. Woods, you're next.

10 DR. WOODS: I guess as I think of this
11 globally, I really believe when you have safe and
12 effective drugs that are similar, that drug use policy
13 has to be made at the local level and that
14 organizations need to take into account their patient
15 populations, the economic factors, the expertise of
16 their staff, their ability to build safe medication
17 use practices into their systems, and it would seem to
18 me that if I'm running a pediatric hospital or a neo
19 natal ICU, that you bring your group together and, you
20 know, you come to the conclusion that Fosphenytoin
21 probably is best. If you're primarily an adult
22 hospital and you have a big ED and you see a lot of

1 neurologic cases there and you feel like you can build
2 the systems to safely administer Phenytoin and you're
3 a public hospital that's squeezed for funds, that
4 maybe that would be the rational choice, and so I
5 guess, I personally think these kind of drug policy
6 issues probably are best left to a local level and to
7 kind of prescribe--or be very prescriptive of this in
8 the product labeling is maybe not the best approach.

9 DR. ANDERSON: Dr. Pearl.

10 DR. PEARL: Phillip Pearl. I want to--these
11 comments are very thoughtful, I want to second what
12 Dr. Rogawski said, but also in light of what Dr. Woods
13 said, I think the current situation is problematic in
14 that Fosphenytoin is right now labeled more as a
15 second tier to use when Phenytoin is not available,
16 and I think that should be switched, but I can
17 understand the local level situation. I just want to
18 be clear that we don't--the current situation really
19 has to be changed. And there is enough compelling
20 safety evidence, I think we discussed today, to make
21 Fosphenytoin the choice--a physician, I think, should
22 be made aware that if it's available that it is

1 available and that there is a higher--there is a
2 stronger association with Purple Glove Syndrome with
3 Phenytoin than Fosphenytoin, so instead of dictating
4 which to use first and which to use second, I think
5 this--I really feel strongly that this idea of a
6 gentle directive to a physician that Fosphenytoin has
7 certain attributes so that if one considers
8 intravenous Phenytoin they should hesitate and
9 consider intravenous Fosphenytoin.

10 DR. ANDERSON: Just one moment. So, does
11 that sort of--should we continue on this line? Okay,
12 so we'll give you the last word, Dr. Varelas.

13 DR. VARELAS: Again, as a physician who has
14 treated status--grand mal statuses, and I'm not
15 talking about non-convulsive, in the ICU and I'm sure
16 my colleagues in the ER share the same idea--it's not
17 easy to treat somebody who's convulsing in front of
18 you and you need to stop this patient from convulsing,
19 even to have a peripheral IV. I think it should be
20 some kind of algorithm in our mind, in essence, if you
21 have somebody that doesn't have a PIV, a peripheral
22 IV, then Fosphenytoin IM is probably the drug of

1 choice. If you have a PIV and you are sure that the
2 PIV is intact, you know, it's not extravasating or
3 anything, then probably would be safer to use, again,
4 Fosphenytoin in case there is Purple Glove Syndrome,
5 okay, in case.

6 And if you have a central line, then I don't
7 have any reason to believe that, you know, I cannot
8 give IV Phenytoin in this patient. I don't know if
9 you agree with this algorithm or if we can put it in
10 an FDA labeling or something like that.

11 DR. ANDERSON: So, thank you everyone for
12 that discussion. We don't vote on that one. So,
13 let's see, so now B reads, continue marketing without
14 changes to the labeling. It seems to--I mean, do you
15 want us to vote on this--I'm sort of asking our agency
16 down here--because it seems like people have suggested
17 a lot of specifications about when it should be used
18 and how it should be used and those sorts of things
19 that seem to dovetail very much with C about the, sort
20 of the nature of labelings and warnings that it
21 should--should we vote on B separately now in light of
22 that discussion?

1 Okay, so let's move on to C as a voting
2 question and that will allow us to expand our
3 discussion a little bit. Allow continued marketing of
4 Phenytoin, which we voted to do, with revisions to the
5 current label, and so now this is where people could
6 suggest whether there are specific recommendations
7 they would make to the agency in terms of populations--
8 --we've heard about pediatrics--additions of more
9 detailed administration instruction. So, is there
10 sufficient information that people feel they have that
11 they would recommend to the agency specific
12 instructions that should be included in the label
13 about catheter size or infusion? And we can use that
14 as a preamble to whether we should vote in favor of
15 that or against it.

16 Dr. Solow?

17 DR. SOLOW: Just a request. Could they put
18 up the slide number nine on--of Dr. Fine's talk,
19 please?

20 For those who can't--I can't read it in the
21 slide--and then blow it up five times?

22 (Laughing.)

1 DR. ANDERSON: Yeah, I don't think it can be
2 blown up five times, actually. Did you--I'm waiting--
3 I thought you were going to make a statement?

4 DR. SOLOW: No, I just wanted to--I was
5 trying to look at it here. I thought that the
6 committee should all see that, though, if we're
7 talking about labeling, this is what's already in
8 there regarding Purple Glove.

9 DR. ANDERSON: Yeah, it's a lot more and a
10 lot smaller. So, Dr. Schachter?

11 DR. SCHACHTER: Would you like suggestions
12 on specific labeling changes?

13 DR. ANDERSON: So, it sounded like we voted--
14 -in fact, it was unanimous that we voted that
15 Phenytoin should continue to be marketed and we
16 discussed in general it's prioritization related to
17 Fosphenytoin and Phenytoin, which the agency has
18 heard, and so now we're sort of moving to a discussion
19 of whether or not the labeling should be changed, and
20 rather than sticking with the generic statement of B,
21 we're moving to C, where we can sort of discuss
22 individually what recommendations we would make for

1 labeling changes, if any, and then once we've sort of
2 heard the group, we can vote, sort of, as a general
3 sort of response whether we're in favor of labeling
4 changes or no labeling changes along the lines of
5 administrations, instructions, boxed warnings, those
6 sorts of things.

7 DR. SCHACHTER: So, in that light, I think
8 the risk factors that we've discussed today need to be
9 in there in some shape or form in a way that doesn't
10 overstate the strength of the association and I think
11 then the prescriber can be in a better position to
12 determine the risk/benefit ratio of using IV Phenytoin
13 in a particular situation, whether it's a--in terms of
14 the approved labeling or approved indications for IV
15 Phenytoin and I--the way that this is--the four or
16 five lines dealing with Purple Glove Syndrome now are
17 in the middle of a large general section. I think it
18 needs to be separated out in some way and this
19 information about the potential risk factors or
20 possible risk factors should be in there as well.

21 DR. ANDERSON: So, you think there's enough
22 information about Purple Glove Syndrome, that that

1 should be sort of specifically highlighted in some way
2 or some fashion to attract provider's attention to
3 that?

4 DR. SCHACHTER: I believe so. I mean, I
5 don't think you say that it's been definitively proved
6 that, you know, older age, female sex, and so forth,
7 are definite risk factors, but I think the information
8 is consistent enough across studies to put in there so
9 that the clinician can put the context of the strength
10 of that information into, again, a risk/benefit ratio-
11 -assessment.

12 DR. ANDERSON: Dr. Rogawski?

13 DR. ROGAWSKI: I agree with Dr. Schachter,
14 but I also feel that, you know, when you need
15 Phenytoin in some form or another, you basically need
16 it. You don't have a whole lot of choice at this
17 point, and so that really isn't going to be terribly
18 helpful to the practicing physician and that's why I
19 think the--what would be helpful is this gentle
20 suggestion to the physician that perhaps--that there
21 is some suggestion that Fosphenytoin has a lower
22 incidence of this--what could be a severe side effect

1 in a small percentage of patients, so I think that
2 would be actually what would turn out to be more
3 useful to the practicing physician than to have a
4 black box of some kind of highlighting this problem
5 because if--you know, status epilepticus is a
6 significant condition and if you need Phenytoin,
7 you're going to have to use it.

8 DR. ANDERSON: So, would you suggest
9 something along the lines of something that says,
10 "Purple Glove Syndrome has been reported and in
11 individuals with only peripheral vascular access,
12 Fosphenytoin should be considered as the preferred
13 drug" or something like that? Or what is this gentle
14 reminder going to--what shape and what circumstances?

15 DR. ROGAWSKI: Something like a physician,
16 you know, may wish to consider the use of Fosphenytoin
17 instead of intravenous Phenytoin as there is a
18 suggestion that there's a higher incidence of Purple
19 Glove Syndrome with intravenous Phenytoin. Something
20 of that nature just to get them thinking along those
21 lines.

22 DR. ANDERSON: Dr. Nelson?

1 DR. NELSON: Yeah, I don't want to sound too
2 skeptical, but the vast majority of people don't read
3 package inserts and they certainly don't read them in
4 the midst of somebody having status epilepticus, which
5 means that the only way this is ever going to get in
6 anybody's face is if it shows up on the computer
7 ordering screen when somebody's getting the drug,
8 which means that it has to probably be a boxed warning
9 or some equivalent that's going to be bold enough that
10 the pharmacy is going to demand it shows up in the
11 ordering screen, or the Pharmacy and Therapeutics
12 Committee, otherwise it's going to be just like this
13 and it's going to be invisible, unless it's some--not
14 this, but what was up before--unless it's something
15 powerful enough to really catch people's attention.

16 There are two issues we've discussed, I
17 don't want to dwell, there's the cardiovascular risk,
18 which is really an infusion rate issue, I think, and
19 perhaps dose, or dose rate, and there's the, you know,
20 the quality of the IV and the infusion apparatus and
21 all those other things, and they're both very
22 important to have listed in some very prominent way.

1 DR. ANDERSON: Dr. Fountain?

2 DR. FOUNTAIN: So, I agree with all that. I
3 suppose the question is, what's the basis for choosing
4 one slower infusion rate or another. If we say that
5 as a rule Phenytoin shouldn't be given--wouldn't
6 routinely be given in emergency situations anymore,
7 that more often you'd get something else, then it
8 almost never would need to be driven as fast as it
9 can. So, consequently, maybe we could find some
10 slower infusion rate either through the best estimate
11 or even by soliciting a specific study to see what's
12 safe. It's not just for Purple Glove, but for all the
13 cardiovascular things you were referring to, so, by
14 some systematic method as best you can arriving at a
15 slower infusion rate, and then recognizing in certain
16 emergencies it may have to--the rate may have to be
17 increased, which means if someone really has status
18 and you're giving them Phenytoin or Fosphenytoin,
19 you'd accelerate the rate.

20 And I guess the second thing is to be
21 diluted, which we think somehow might be helpful maybe
22 for preventing Purple Glove, maybe just for making it

1 more tolerable, and the basis for that could be a
2 systematic study or it could be Dr. Coplin's study,
3 and along with that would be infusing in large bore
4 and so forth, and then if we then say it's not given
5 very often in emergencies anymore, we can then say
6 that most of the time it could be given orally except
7 for people who can't take oral medications which is,
8 among the case reports that have Purple Glove Syndrome
9 reported, like in Dr. Barkely's study, they didn't
10 really necessarily give IV, they were walkie-talkies
11 who need to be loaded after a seizure and they had
12 recovered and were awake and that kind of thing.

13 So, I think among the systematic assessments
14 we have, they mostly weren't people who needed IV
15 drug, and so your comment about saying, well, oral is
16 much safer, which I think you can say across the
17 board, regardless of this low instance of Purple
18 Glove.

19 Then the last thing is I'm still fixated on-
20 -were there 11 amputations? If 11 people lost their
21 hand because of Phenytoin, kind of hard to justify to
22 continue to advocate that as first line for anything.

1 If it wasn't really 11, if it was one, then it's
2 harder to know. You know, one's too many, but it's a
3 lot less than 11. So, it seems to me if that can be
4 clarified to determine what that is, then I'd feel
5 pretty compelled to make some kind of assessment that
6 Phenytoin should be downgraded from the way it is in
7 the labeling.

8 DR. ANDERSON: So, the recommendations we've
9 heard so far are related to infusions, box warnings
10 that show up in the computer system, maybe accenting
11 the risk of any intravenous form of Phenytoin or
12 Fosphenytoin as opposed to oral administration. Other
13 warning labeling recommendations? Dr. Khatri?

14 DR. KHATRI: My impression is that the max
15 infusion rate isn't typically used for Phenytoin or
16 Fosphenytoin. I mean, the reality is, we'll use
17 lorazepam to abort the seizures, and then kick in the
18 Phenytoin or Fosphenytoin with the idea that to create
19 longer lasting effects.

20 So, given that, I'm just curious, I don't
21 see why we wouldn't recommend a slower infusion rate
22 since that's what most of us would do in clinical

1 practice.

2 DR. ANDERSON: And what number would you
3 try?

4 DR. KHATRI: Personally? Half the rate.
5 That's just my personal perspective. I don't know if
6 anyone else would feel strongly about going more than
7 half the maximum rate, in other words, 25 milligrams
8 for Phenytoin.

9 DR. ANDERSON: Dr. Chapman.

10 DR. CHAPMAN: I will just point out that if
11 you're talking about loading a gram of Phenytoin at,
12 you know, just say the 20 milligrams per minute that
13 was used in the Detroit study, that's 50 minutes to
14 infuse Phenytoin, and if someone is actively
15 convulsively, you know, granted you're going to be
16 using benzodiazepines or something else, it's still
17 considered a second line therapy. So, if you're going
18 to say that we're going to cut that time in half,
19 there's a potential that that person could still,
20 while they're waiting to go through their algorithm,
21 because they don't understand it--they're like, the
22 first thing's benzodiazepine, then I do Fosphenytoin,

1 I wait for it to finish, then I do more fos or
2 Phenobarbital--you know, if they go through the
3 cookbook of it, an hour before the Phenytoin is in,
4 you're already, by most all definitions, refractory
5 status and then you're going to anesthetize them.

6 I just--I'm a little hesitant to say, in the
7 absence of good data, to show that it is dependent on,
8 you know, how quickly it's given. It really could
9 lead to potentially slower infusion rates which may
10 impact patient care.

11 DR. ANDERSON: So, you would advocate for
12 sort of general warnings about intravenous use, but
13 not specific sort of infusion rate numbers?

14 DR. CHAPMAN: Yeah, I mean, I think it's one
15 thing if you're loading someone who's in the emergency
16 room and has had a seizure but is now clearly out of
17 it and you're going to plan to send them home with
18 Phenytoin, you don't think they're safe to swallow or
19 something like that, then, yes, you're going to do it
20 slow. But if someone is actively convulsing, I mean,
21 it is still--like we all know, it's still the second
22 drug that's listed on almost all the protocols, and so

1 I would be--I think it would be a little bit remiss if
2 we sort of force everybody to do it at a lower rate.
3 I think it's better to do broad generalizations and
4 say, there may be less hypotension or less
5 cardiovascular side effects with a slower infusion, I
6 think would be appropriate, but dictating a rate--I
7 just--I mean, that seems a bit much for me without
8 better hard data.

9 DR. ANDERSON: Dr. Khatri, did you want to
10 make a response to that? Sure, Dr. Fountain?

11 DR. FOUNTAIN: Only to say that since I
12 suggested that a slower rate is--but I think you're
13 absolutely right, you must say that in seizure
14 emergencies it can be given at whatever rate is
15 necessary up to--although I'm not sure we have a basis
16 for what we use now, but if you want to say up to what
17 we use now, that's fine with me. But that's different
18 than all these people that got the Purple Glove
19 Syndrome in the literature, is the problem.

20 DR. ANDERSON: Dr. Silbergleit?

21 DR. SILBERGLEIT: Yeah, so I think Dr.
22 Chapman's right. I mean, the indication on the label

1 is for treatment of status epilepticus. So, that's
2 what we're talking about. I think that we're really
3 shooting ourselves in the foot if we encourage a
4 slower rate for all these non-status patients who
5 could, in fact, get oral. And so I think that, you
6 know, the label should primarily talk about the
7 treatment of status epilepticus if we take Phenytoin
8 out of all those algorithms that are not changed yet,
9 but have changed for some of us, but I think that the
10 label should encourage the proper use in the emergency
11 use, which is what the label is primarily for anyway,
12 and then all those patients who got Purple Glove
13 Syndrome who could have taken oral shouldn't be
14 encouraged to get a slower rate of IV, they should be
15 encouraged to get oral.

16 And so I think Dr. Rogawski, when you were
17 listing the other suggestions, I think that the other
18 one that Dr. Rogawski said was a table, a dosing
19 table, because in the emergency setting, I'll tell
20 you, when my nurses do pull out a package insert and
21 use it, it's to get at the dosing table so that they
22 don't have to get out their calculator, and a dosing

1 table that says, this weight, this dose, at this rate,
2 which would be the maximal rate--you know, no faster
3 than, but, you know, than this rate, might actually
4 get used and looked at and if right above that it
5 says, if this is not an emergency, use oral, you know,
6 all the more benefit. They whip it out for the table
7 and then what they see is, you know, gosh, maybe we
8 should just do oral instead.

9 I think those are--which all gets back to--I
10 think the labeling changes that I would emphasize
11 would be the ones that encourage improved--reduce the
12 medication errors and reduced cardiovascular toxicity,
13 since those are the major safety concerns that we
14 heard about today, rather than a labeling change that
15 really emphasizes and highlights Purple Glove
16 Syndrome, which I think is going to not do the
17 multiple--the best service for the majority of
18 patients.

19 DR. ANDERSON: So, I've got Dr. Varelas and
20 Nelson on the list and then I'll ask those of you who
21 think about jumping in whether you feel that you
22 really need to before we could vote on question C and

1 then consider D after that. So, Dr. Varelas?

2 DR. VARELAS: Yeah, just to echo Dr.
3 Chapman, I agree completely. I mean, there is, from
4 my experience again in the ICU, it's different, I
5 think, to have somebody who had one seizure or had one
6 seizure to be loaded with dilantin, 1 gram, everybody
7 knows that. And definitely you can do it slower, than
8 if you have somebody in status epilepticus who has a
9 blood pressure of 220, a heart rate of 130, and
10 especially if he's elderly, the risk for complications
11 is based on that and not based on the high 50
12 milligrams per minute infusion of dilantin. So, I
13 think in situation for grand mal status, when you have
14 a tremendous surge from the brain down to the
15 periphery, dilantin can be given and should be given
16 with the fast rate versus if you have a less urgent
17 situation when you can definitely infuse it much lower
18 and you won't see the complications, the side effects.

19 DR. ANDERSON: Dr. Nelson?

20 DR. NELSON: Yeah, my only comment is, and
21 I'm all for oral, don't get me wrong on this, but the
22 time to therapeutic with IV is essentially

1 instantaneous with the administration. Oral takes
2 hours and in many people--many times, people don't
3 ever get therapeutic with oral Phenytoin loading even
4 with substantial doses. So, they're not necessarily
5 really the same thing. Depending on the patient
6 you're dealing with and how sure you have to be that
7 they're actually at therapeutic levels, they may not
8 really be equivalent.

9 DR. ANDERSON: So, I'll go ahead and read 7c
10 again and I guess I would say that when we're voting
11 yes and no, we're sort of voting sort of whether in
12 the abstract you think there's sort of room for
13 improvement in the revisions to the current label
14 rather than having to endorse the specific or the
15 totality of all the little suggestions that we've
16 individually made.

17 With the above in mind would the committee
18 allow continued marketing of Phenytoin with revisions
19 to the current label, for example, the addition of
20 contraindications for some populations, addition to
21 more detailed administration instructions, for
22 example, catheter size, rate of infusion, a boxed

1 warning? Yes, no, or abstain?

2 (Voting.)

3 STAFF: We're missing four votes. Can
4 everybody press again, please?

5 DR. ANDERSON: The results are 29 yes, zero
6 no, zero abstentions. We'll start on Dr. Snodgrass'
7 side this time.

8 DR. SNODGRASS: I voted yes. No further
9 comments.

10 DR. HOVINGA: Yes, no further comments.

11 Please say your names as you--

12 DR. HOVINGA: Collin Hovinga.

13 DR. SOLOW: Brian Solow, yes.

14 DR. LEE: Mike Lee commenting on myself, I
15 voted yes.

16 DR. SPRIDGEN: Stacia Spridgen commenting on
17 myself, I voted yes.

18 DR. CAVAZOS: Jose Cavazos, I voted yes, but
19 specifically for box warning.

20 DR. BALISH: Marshall Balish, I voted yes.

21 DR. SCHACHTER: Steve Schachter, yes and one
22 other labeling change the agency may want to look at

1 is how the dosages recommended for the neurosurgical
2 indication, which is IM at every four hour intervals,
3 I don't think it's given that way.

4 DR. ROGAWSKI: Michael Rogawski, I voted
5 yes. The only comment I might make is that my reading
6 of the documents that were presented to us made a good
7 case of the catheter--the issue of catheter size is
8 not well understood and it might be that smaller
9 catheters are better or bigger catheters are better in
10 some situations, so that particular thing we'd
11 probably have to remain moot on until we have better
12 information.

13 DR. CHAPMAN: Kevin Chapman, I voted yes.

14 DR. PEARL: Phillip Pearl, I voted yes and
15 I'd just like to reiterate that I think Fosphenytoin
16 ought to be included in the labeling for Phenytoin as
17 an important option.

18 DR. MARDER: Ellen Marder, I voted yes.

19 DR. KHATRI: Pooja Khatri, yes.

20 DR. KINDLER: Dean Kindler, yes.

21 DR. LU: Ying Lu, yes.

22 DR. FOUNTAIN: Nathan Fountain, yes, and I'd

1 add that although it's not in the indication, I think
2 everybody would replace oral Phenytoin with IV
3 Phenytoin if you can't take oral for some reason. So,
4 I don't know that's an indication but that would be a
5 case where you might give Fosphenytoin instead of
6 Phenytoin, but that's sort of self evident.

7 DR. ANDERSON: Britt Anderson, yes.

8 DR. GREEN: Mark Green, yes.

9 DR. FRANK: Samuel Frank, yes.

10 DR. KANDELL: Ellen Kandell, yes.

11 DR. WOODS: Mark Woods, yes.

12 DR. COOPER: William Cooper, yes.

13 DR. WOLFE: Sid Wolfe, yes.

14 DR. NELSON: Lewis Nelson, yes.

15 DR. HUFF: Steve Huff, yes.

16 DR. SILBERGLEIT: Robert Silbergleit, yes.

17 DR. NAIDECH: Andrew Naidech, yes, with
18 consideration of a black box warning for Purple Glove
19 and consideration of the location of the infusion
20 site.

21 DR. VARELAS: Panaviotis Varelas, yes.

22 DR. SLEATH: Betsy Sleath, yes.

1 DR. ANDERSON: Question 7d reads, with the
2 above in mind, would the committee require any
3 regulatory action for Fosphenytoin.

4 Dr. Wolfe?

5 DR. WOLFE: Go back to Dr. Katz's statement
6 this morning, just to read it again, cannot write
7 valid dosing recommendations for Fosphenytoin for
8 children. I think that one suggested change is not
9 necessarily to counter indicate in children, although
10 that's a possibility. I think that it needs to be
11 stated clearly that it is not approved in children
12 because at this present time there aren't valid
13 pharmaca--PK data that would allow us to choose the
14 right dosage. That will not stop someone from using
15 it, but I think trying to do fractions of adult
16 dosages and other things--remember, a lot of these--a
17 good proportion of the deaths that have to do with
18 dosage problems are, in fact, in children. So, I
19 think that some change, strengthening, whatever, of
20 that fact in the label for Fosphenytoin would be
21 useful.

22 DR. ANDERSON: Dr. Sleath?

1 DR. SLEATH: I would support labeling
2 changes to try to help reduce these errors that Dr.
3 Tobenkin presented, that there are still errors with
4 the milligrams in Phenytoin equivalents, and to me
5 that's something that definitely could be prevented.
6 I don't know a better way to do it but I would hope
7 the FDA would look into that or sponsor a study on how
8 could we improve that to reduce errors.

9 DR. ANDERSON: Dr. Chapman?

10 DR. CHAPMAN: I would recommend--before I
11 came here I asked my epilepsy colleagues whether they
12 thought that hypotension was just as common with
13 Fosphenytoin as Phenytoin and they actually all
14 thought that it was less and so I think there's a
15 little bit of a misunderstanding amongst us that
16 Phenytoin--that Fosphenytoin has a lower
17 cardiovascular side effect. I think it should be sort
18 of mentioned in here a little bit more clearly that it
19 does appear to be equivalent because I think we're
20 probably administering it and going, ah, it's fos, we
21 don't need to worry about blood pressure as much, and
22 I may not worry about it as much in kids, but maybe it

1 is more of an issue in adults, and so I think it needs
2 to be a little bit more clear that way. And I was
3 also thinking, well, a Dear Doctor letter may be
4 helpful, but maybe that's a bit much. I think it was
5 mentioned somewhere in the handout about that.

6 DR. ANDERSON: Other suggestions? Dr.
7 Rogawski?

8 DR. ROGAWSKI: Yeah, I just wonder whether
9 there's any point to updating the Fosphenytoin package
10 insert to just give the data with regard to suspected
11 Purple Glove. You know, how hard is that to do?
12 Would you have to revise it, you know, more frequently
13 than you could do? I mean, what's the agency thinking
14 on that?

15 DR. KATZ: Certainly some language about it
16 could obviously be put in. We're sort of loathe to
17 put in specific data for these things because tomorrow
18 there will be another case of whatever and, you know,
19 so that's problematic, but certainly obviously
20 language about it clearly can be done.

21 DR. ROGAWSKI: In that case I wouldn't be
22 opposed to having agency require that.

1 DR. ANDERSON: I'll just speak for myself,
2 Britt Anderson. I guess--so, in the spirit of what
3 Dr. Chapman said, I also had sort of the same feeling
4 and so I've been educated here that sort of the
5 difference in cardiovascular toxicities of the two is
6 not as great, if any, as I thought it was, and I think
7 being made alert to the possibility that the Purple
8 Glove Syndrome might exist as well with Fosphenytoin
9 of some provision that there have been cases, you
10 know, reported to the FDA that meet clinical criteria
11 for Purple Glove Syndrome would be useful in
12 maintaining awareness and alertness to something that
13 we might otherwise discount or dismiss or blame on
14 some other secondary cause.

15 Dr. Solow?

16 DR. SOLOW: I had also mentioned about the
17 dosing. I think I was a little disheartened to hear,
18 I don't know who said it, that in their hospital, to
19 their residents, et cetera, how they taught them to
20 dose was different than what's listed about
21 equivalents, so I think there's still confusion
22 despite there's supposed to be no confusion.

1 DR. ANDERSON: Yeah, I don't think they were
2 actually teaching them that. I think that was sort of
3 the de facto--

4 DR. SOLOW: Well, they were teaching them
5 just use milligrams, don't use the equivalent, but in
6 this it sounds like they're not supposed to do that.

7 DR. ANDERSON: I think the residents were
8 teaching themselves to do that, but I also think that
9 we've--that, I found, personally a little hard because
10 it doesn't seem like we know the other end of the
11 equation. I mean, when Phenytoin was the standard and
12 Fosphenytoin came out, it seemed like there was a
13 great risk for the mistreatment of large numbers of
14 patients being under dosed and so we don't really know
15 if we might be having more, sort of, medication errors
16 or poorer clinical outcomes if we went to the
17 alternative. So, I'm not sure it's such a simple
18 decision to say, you know, abandon the Phenytoin
19 equivalent. So, I'd like to know if other people feel
20 like it's such a slam dunk that by going to a straight
21 milligram dosing it would be clear that that would be
22 the better thing to do for patient care.

1 Dr. Nelson?

2 DR. NELSON: Well, I mean--maybe it's along
3 these same lines but you wonder if there's a way to
4 provide a better warning in the Fosphenytoin labeling
5 about this problem, you know, specifically to say, you
6 know, why it's dosed the way it is, what the concerns
7 are, how common or how real the issue of mistaking the
8 two products are in some sort of warning, you know,
9 that actually says, you know, be careful.

10 DR. ANDERSON: Dr. Naidech?

11 DR. NAIDECH: If it was confusing to get
12 everyone to think of Fosphenytoin and Phenytoin
13 equivalents the first time, it's going to be extra
14 confusing to try and re-educate everyone who learned
15 it right the first time to go back and do it a
16 different way.

17 DR. ANDERSON: So, what does that--but now I
18 don't understand what you mean? We should just leave
19 it alone and just do a better job of advertising it?

20 DR. NAIDECH: I explicitly did not imply
21 what was the better solution, only that it's--

22 DR. ANDERSON: Something needs to change,

1 but we don't know what.

2 Dr. Silbergleit?

3 DR. SILBERGLEIT: Well, it was somebody's
4 suggestion earlier that it might be changing mg PE to
5 just PE and getting rid of the mg PE so it's just--and
6 people know, what is the definition of a Phenytoin
7 equivalent, it's the number of milligrams of dilantin
8 that is equivalent to that dose. And so, I don't know
9 who's suggestion that was, but I thought that was a
10 great suggestion. I think that's a source of confusion
11 and so I think mostly keeping it the same but dropping
12 the mg PE and making it just PE.

13 DR. ANDERSON: That was Dr. Tobenkin's
14 suggestion from the FDA.

15 You said that you should drop the PE?

16 DR. TOBENKIN: No, no, no, I said that it's
17 possible that we're dropping the PE because that (off
18 mic).

19 DR. ANDERSON: All right, I'm sorry. I
20 tried to give you credit. If you want to deny it,
21 it's okay. It's a good idea, but it did not come from
22 the FDA.

1 Okay, so we've heard several suggestions.
2 If people want to make another one we can do it now,
3 but otherwise we could vote and I guess if you sort of
4 feel like any of those are reasonable considerations
5 for the agency to include, then you would vote in
6 favor and if you felt like none of those and nothing
7 else that you could think of should be changed then
8 you would vote no.

9 (Voting.)

10 DR. ANDERSON: We had 29 yes, zero no, zero
11 abstentions, and I forget whose side to start on.
12 I'll start on Dr. Sleath, if you can read your name,
13 your vote, and any other comments.

14 DR. SLEATH: Betsy Sleath, yes.

15 DR. VARELAS: Panaviotis Varelas, yes.

16 DR. NAIDECH: Andrew Naidech, yes.

17 DR. SILBERGLEIT: Robert Silbergleit, yes.

18 DR. HUFF: Stephen Huff, yes.

19 DR. NELSON: Lewis Nelson, yes.

20 DR. WOLFE: Sid Wolfe, yes.

21 DR. ANDERSON: Can we pause for a moment?

22 So, can you vote, Dr. Spridgen? And I've been asked

1 to do it out of order because we have two people who
2 have to depart.

3 DR. SPRIDGEN: I voted yes on my behalf, not
4 DoD.

5 DR. ANDERSON: Okay, and who's the other
6 one? Dr. Chapman?

7 DR. CHAPMAN: This is Kevin Chapman, I voted
8 yes.

9 DR. ANDERSON: Okay, thank you. So, now I
10 think it was--thank you, Dr. Cooper.

11 DR. COOPER: William Cooper, I voted yes.

12 DR. WOODS: Mark Woods, yes.

13 DR. KANDELL: Ellen Kandell, yes.

14 DR. FRANK: Samuel Frank, yes.

15 DR. GREEN: Mark Green, yes.

16 DR. ANDERSON: Britt Anderson, yes.

17 DR. FOUNTAIN: Nathan Fountain, yes.

18 DR. LU: Ying Lu, yes.

19 DR. KINDLER: Dean Kindler, yes.

20 DR. KHATRI: Pooja Khatri, yes.

21 DR. MARDER: Ellen Marder, yes.

22 DR. PEARL: Phillip Pearl, yes.

1 DR. ROGAWSKI: Michael Rogawski, yes.

2 DR. SCHACHTER: Steve Schachter, yes.

3 DR. BALISH: Marshall Balish, yes.

4 DR. CAVAZOS: Jose Cavazos, yes.

5 DR. LEE: Mike Lee on behalf of myself, not

6 the IHS, yes. No comments.

7 DR. SOLOW: Brian Solow, yes.

8 DR. HOVINGA: Collin Hovinga, yes.

9 DR. SNODGRASS: Wayne Snodgrass, yes.

10 DR. ANDERSON: All right, so pressing along,

11 now we can return to some of the more specific content

12 questions that led into this.

13 DR. KATZ: Can I just--

14 DR. ANDERSON: Dr. Katz, please?

15 DR. KATZ: Yeah, in light of the votes that
16 have already been taken and the discussion that you've

17 had, I'm not sure that any of the other questions need

18 to be voted on. I mean, the committee can take a

19 quick look and see--look at questions four, five, and

20 six, which are the ones we haven't discussed, and see

21 if there's anything in there that you think you want

22 to tell us, but those were sort of supposed to be way

