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FOOD AND DRUG ADMINISTRATION
PEDIATRIC ADVISORY COMMITTEE MEETING

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Monday, January 30, 2012
Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, MD 20877

The meeting was convened at 8:02 a.m.,
GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding.

MEMBERS PRESENT:

- GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding
- BRAHM GOLDSTEIN, M.D.
- JEFFREY KRISCHER, Ph.D.
- KATHLEEN MOTIL, M.D., Ph.D.
- ALEX RAKOWSKY, M.D.
- MICHAEL D. REED, Pharm.D., FCCP, FCP
- VICTOR SANTANA, M.D.
- KENNETH TOWBIN, M.D.
- JEFFREY WAGENER, M.D.

1 CONSULTANTS/TEMPORARY MEMBERS PRESENT:

2 SUSAN BAKER, M.D.

3 ROBERT CASTILE, M.D.

4 JATINDER BHATIA, M.D.

5 ROBERT DRACKER, M.D.

6 MARILYN EICHNER

7 ERIC FELNER, M.D.

8 ISRAEL FRANCO, M.D.

9 PAULA HILLARD, M.D.

10 SHELDON KAPLAN, M.D.

11 JONATHAN MINK, M.D.

12 LESLIE WALKER, M.D.

13 MICHAEL WHITE, M.D., Ph.D.

14 BRIDGETTE WIEFLING, M.D.

15 JOSEPH WRIGHT, M.D.

16 ALSO PRESENT: WALTER ELLENBERG, Ph.D.,

17 Executive Director and Designated Federal Official

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

2 (8:02 a.m.)

3 WELCOME AND INTRODUCTORY REMARKS

4 CHAIRMAN ROSENTHAL: Good morning, everyone.

5 We are a couple minutes over. I understand that there's
6 been an accident on one of the main arteries on the way
7 here, so some of the members of the committee I'm sure
8 are delayed because of that. But we should go ahead and
9 get started.

10 The first part of our meeting this morning, we
11 have a guest speaker, Dr. Stephen Spielberg. Dr. Murphy
12 is going to be introducing Dr. Spielberg. But before we
13 get started with that, let's go around the table and
14 introduce ourselves, and then a few formalities and then
15 we'll get going.

16 So, Dr. White, you're positioned strategically
17 at the end of the table, so you can get these rounds
18 going.

19 DR. WHITE: Michael White. I'm from Ochsner -
20 -

21 CHAIRMAN ROSENTHAL: I didn't hear you, so
22 make sure that your red light is on when you're speaking

1 at the microphone.

2 DR. WHITE: Is that better? That's better.

3 I'm Michael White. I'm from New Orleans, the
4 Ochsner Health System. I'm a pediatric cardiologist and
5 director of our ethics education program.

6 DR. RAKOWSKY: Good morning. My name is Alex
7 Rakowsky. I'm from Nationwide Children's Hospital in
8 Columbus, Ohio. I'm the IRB chair there. Michael and I
9 think that the bow ties were put on the end of the table
10 here on purpose.

11 (Laughter.)

12 DR. FELNER: Eric Felner. I'm associate
13 professor of pediatrics at Emory University. I'm in the
14 division of pediatric endocrinology.

15 DR. WALKER: Leslie Walker, professor of
16 pediatrics at the University of Washington and chief of
17 the division of adolescent medicine.

18 DR. HILLARD: Paula Hillard, professor of
19 obstetrics and gynecology at Stanford University School
20 of Medicine, where I practice pediatric and adolescent
21 gynecology.

22 DR. FRANCO: Israel Franco, pediatric

1 urologist at New York Medical College, professor of
2 urology, and at Maria Fareri Children's Hospital in
3 Westchester.

4 DR. BHATIA: Jatinder Bhatia, professor of
5 pediatrics at the Georgia Health Sciences University in
6 Augusta, Georgia.

7 DR. BAKER: I'm Susan Baker, professor of
8 pediatrics at the University of Buffalo and section head
9 for the GI and nutrition division.

10 DR. WARD: I'm Bob Ward from the University of
11 Utah, a pediatric clinical pharmacologist and
12 neonatologist.

13 DR. KAPLAN: Sheldon Kaplan. I'm a professor
14 of pediatrics at Baylor College of Medicine, and
15 infectious diseases.

16 DR. CASTILE: I'm Bob Castile. I'm a
17 pediatric pulmonologist from Nationwide Children's
18 Hospital in Columbus, Ohio.

19 DR. TOWBIN: I'm Kenneth Towbin. I'm a
20 psychiatrist in the intramural program at the National
21 Institute of Mental Health.

22 CHAIRMAN ROSENTHAL: My name is Geof

1 Rosenthal. I'm a professor of pediatrics at the
2 University of Maryland School of Medicine, and I'm a
3 pediatric cardiologist.

4 DR. ELLENBERG: My name is Walt Ellenberg.
5 I'm the Designated Federal Official for the meeting and
6 I'm in the Office of Pediatric Therapeutics at the FDA.

7 DR. WAGENER: I'm Jeff Wagener. I'm professor
8 of pediatrics at the University of Colorado, pediatric
9 pulmonologist, and I'm put next to Walt because he has
10 to control me.

11 DR. MOTIL: My name is Kathleen Motil --
12 sorry. My name is Kathleen Motil. I'm a pediatric
13 gastroenterologist at Baylor College of Medicine.

14 DR. SANTANA: Good morning. I'm Victor
15 Santana. I'm a pediatric hematologist and oncologist at
16 St. Jude Children's Research Hospital in Memphis,
17 Tennessee.

18 DR. GOLDSTEIN: Good morning. My name is
19 Brahm Goldstein. I'm senior medical director at Ikaria,
20 Incorporated, and a professor of pediatrics at the
21 University of Medicine and Dentistry of New Jersey, and
22 I'm a pediatric critical care physician.

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DR. HAUSMAN: Ethan Hausman, FDA Office of
Surveillance and Epidemiology. I'm a pathologist and a
pediatrician.

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DR. COPE: Judy Cope. I lead the safety team
for the Office of Pediatric Therapeutics. My background
is adolescent medicine, pediatrics, and epidemiology.

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DR. MURPHY: Dianne Murphy. I'm the Director
for the Office of Pediatric Therapeutics at the FDA. My
background is pediatric infectious diseases.

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DR. LISA MATHIS: Timing is everything.

(Laughter.)

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Hi. I'm Lisa Mathis. I'm a general
pediatrician and I'm in charge of the pediatric and
maternal health staff within the Office of New Drugs in
CEDR.

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CHAIRMAN ROSENTHAL: Dr. Wiefeling, will you
introduce yourself?

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DR. WIEFLING: My name is Bridgette Wiefeling
and I'm a pediatrician. I'm also the CEO of the Anthony
Jordan Health Center, a federally qualified health
center in New York.

1 CHAIRMAN ROSENTHAL: Thank you.

2 Now, one thing that we'd like to do a better
3 job with today than we have during a few of the other,
4 more recent meetings, is we'd like for everyone who
5 addresses the committee, everybody, first please speak
6 into microphones; and also introduce yourself if it's
7 not apparent because we've just gone around the table
8 and introduced ourselves. So people who are stepping up
9 to microphones today, please introduce yourself so that
10 we all can look back into the transcripts and understand
11 who made which statements. So thank you very much about
12 that.

13 The other thing I'd like to just say as a
14 matter of course: first, if you can please silence your
15 cellphones, that's always helpful.

16 One of the principles that we live by on this
17 committee is that we really feel like all sides of
18 discussions, all points, need to be made into the record
19 so that they can be considered fully. So with that in
20 mind, I'd like to ask everyone to please not speak about
21 the matters before us today in our meeting during any of
22 the breaks or during lunch. So please save any

1 comments, any discussion, for time into the microphone
2 around the table. Thank you.

3 Dr. Murphy, would you like to introduce Dr.
4 Spielberg.

5 DR. MURPHY: I'd be delighted to do that.
6 We're actually excited to be able to welcome Dr.
7 Spielberg to open the meeting today. For those of you
8 who do not know Dr. Spielberg, he recently came to the
9 FDA from Children's Mercy in Kansas City, where he was
10 head of personalized medicine. Previously he was also
11 the dean at Dartmouth. He was also, let's say, the guru
12 for pediatrics at JNJ.

13 He's had a remarkable career in pediatric
14 clinical pharmacology. But I know Dr. Spielberg as one
15 of the founding fathers -- and I'm one of the older
16 mothers here -- who actually helped write ICAG-11 in the
17 days when there weren't many people who thought that we
18 actually needed data to treat children, for the
19 medicines that we gave them.

20 So he knows the issues and the concerns and
21 the struggles that we have been through over the last
22 two decades in trying to get more real science behind

1 how we treat children.

2

3 Dr. Spielberg, we look very much forward to
4 your opening the meeting for us today. Thank you.

5 OPENING ADDRESS

6 DR. SPIELBERG: Thank you, Dianne.

7 First and foremost, I want to thank all the
8 members of the committee for your service. I know how
9 much time it takes getting to outer Gaithersburg and
10 doing all the homework necessary to participate in these
11 committees, having served on such committees way back
12 into the last millennium, I suppose, way back when,
13 1978, I suppose, I started on the American Academy of
14 Pediatrics Committee on Drugs, which at that time was
15 the Subcommittee for Pediatrics to the FDA. So it does
16 indeed go back a long ways.

17 As the resident, as Dianne said, senior -- not
18 old; senior -- person around and being really delighted
19 to be able to be here at FDA serving as Deputy
20 Commissioner, but also having the opportunity to advance
21 the needs of children for improved therapeutics, it's
22 indeed an honor for me to be able to be here.

1 What I thought I would do, since I do have all
2 you here for a few minutes, is to provide some
3 perspective on the whole issue of pediatric safety, some
4 new challenges that we face, and more importantly I
5 think new opportunities that we have to advance the safe
6 and effective use of medicines in children.

7 This is a remarkable time in history. The
8 science is changing faster, I think, than any of us can
9 keep up with or, for that matter, I would argue the
10 sociology of medicine can keep up with. Things are
11 changing on two sides with respect to drug safety and
12 they're both influencing how we learn about safety
13 signals and how we study those safety signals, the
14 ascertainment, clinical informatics technology on the
15 one hand and a veritable explosion in biology, which is
16 changing the way in which we look at those molecules
17 that we call medicines.

18 Let me start off with the ascertainment side.

19 How do we find out about safety signals? It's pretty
20 obvious to all of you, we start off with our clinical
21 trials. Just a couple points about clinical trials. We
22 now are blessed, I think, with having electronic ways of

1 recording information about our patients. Electronic
2 health records are now become ubiquitous, and we'll talk
3 about how good or bad they are.

4 But one of the things that we still struggle
5 with in pediatrics and for that matter in adult clinical
6 trials is the EHRs do not automatically convert into
7 case report forms that we use in our clinical trials.
8 Even well-organized groups such as Children's Oncology
9 Group end up transcribing from electronic records into
10 case report forms and then into the summary tables for
11 clinical trials.

12 I would posit that this is wasteful,
13 expensive, and by definition error-prone. But, having
14 said that, it's an opportunity to come up with ways that
15 in fact we can transcribe information directly from what
16 happens to our patients into case report forms,
17 capturing richness better.

18 The other thing that's happening -- and I
19 think this is a good trend and an exciting trend --
20 based on increasing understanding of molecular targets
21 of our drugs and increasing trials aimed, if you will,
22 at individualized therapeutics, is that our clinical

1 trials can and will become smaller. And because of
2 that, we are going to be able to demonstrate efficacy in
3 smaller numbers of patients for registrations of
4 compounds.

5 But that obviously has implications for
6 understanding population and individual issues with
7 respect to safety, because our clinical trials are going
8 to be smaller.

9 Once compounds are on the market, we have our
10 Adverse Event Reporting Safety, the AERS, soon to be
11 converted into FAERS, within FDA. One of the government
12 agencies -- and I'm still not fluent in terms of the
13 letter salad agencies, so I don't know which one it was
14 -- estimated that it takes 40 to 45 minutes to fill out
15 an AERS or a 5300 AERS report form.

16 Of course, all of you have so much time that
17 it's no issue, right? Well, it's a huge issue. Of the
18 nearly 800,000 and growing reports that come in in the
19 AERS system, the richness of information often is
20 lacking in a lot of those reports, because they are
21 difficult to fill out and because of the time that it
22 takes.

1 Shouldn't as well our electronic health
2 records be able to autopopulate that from the pharmacy
3 records in terms of what's dispensed, to the clinical
4 records in terms of what actually happens to our
5 patients in real time? That I am told by any 13-year-
6 old who's good at programming is a trivial undertaking.

7 The question is do we have the will as a
8 health care system, as doctors advocating for our
9 patients, to assure that that indeed happens, so that we
10 do have the richness, so that we do have clinically
11 meaningful information that then can be aggregated and
12 assessed in real time?

13 In addition, we need some more pediatric-
14 specific terminology. Often, again because sick
15 children, fortunately, are a minority of sick patients -
16 - most of our kids are healthy, thank heavens, but those
17 who are not have real challenges in terms of getting
18 their specific information recorded.

19 I remember in my industry days every time
20 there was a report of chest pain it got mapped to
21 angina, and we were stuck with case reports of angina in
22 children, whereas most of the time it was sports

1 injuries, costochondritis, Tietze's Syndrome, what have
2 you. So that we do indeed need better developmental
3 markers of what goes on with our patients, focusing on
4 the things that are the jobs of childhood, growth and
5 development, and interference with growth and
6 development being critical outcomes, be it central
7 nervous system development and learning and behavior or
8 whether it be physical growth and development. Often
9 these things are not well quantified in our records and
10 not easily transcribable into adverse reaction reports.

11 We're now moving to an era of active
12 surveillance, of the Sentinel system, mandated by
13 Congress to be actively involved in looking at clinical
14 -- at clinical experience of patients, up to 100 million
15 patients very soon, across the United States, smaller
16 numbers of children. We need to be sure that children
17 are well represented in the Sentinel efforts. That is
18 an ongoing effort now, but we again need to be sure
19 about the richness of the information that we collect so
20 that we really understand what the phenotype is of an
21 adverse event.

22 Would that, for example, we could have

1 embedded pictures of supposed drug rashes within our
2 reports, so that they could be verified by
3 dermatologists. At Children's Mercy we tried this
4 really hard, but the pictures remain in cameras in the
5 drawers of the dermatologists' offices, not embedded in
6 the record, so that we can in fact use records for what
7 I was taught records were supposed to be about in the
8 1960s, patient care, research, and education. We'll
9 get there. But I think all of us have to work together
10 to assure that that indeed happens.

11 We also have other sources. We have networks,
12 disease-specific such as Children's Oncology Group. We
13 have networks that are increasingly developed on the
14 international front specifically about different types
15 of adverse event outcomes. We have the DILI network,
16 Drug-Induced Liver Injury, which is an international
17 group now. I would posit we need a little bit more
18 pediatric hepatology representation on those groups,
19 again because what we see in our patients can indeed be
20 different than what you see in adults.

21 We have the wonderfully named Itch Network,
22 focused on severe dermatologic reactions and

1 hypersensitivity drug reactions, again working out
2 phenotype and standardized approach to reporting of
3 patients with potential drug-induced dermatologic
4 outcomes. But again, we need a little bit more in the
5 way of pediatrics there as well.

6 We have a number of networks of children's
7 hospitals around the country, in Canada and elsewhere,
8 that are beginning to focus on how do you aggregate
9 information across larger patient populations and get
10 really good clinical information that can be interpreted
11 for the individual patient and for epidemiologic studies
12 as well, things that all of us need to work on.

13 Concurrent with this has been a change in
14 understanding of mechanism. I started my career at
15 Hopkins back in, what year was it, '77, I suppose,
16 looking at mechanisms of adverse drug reactions and
17 trying to understand the genetic basis of predisposition
18 to adverse reactions.

19 Mechanistic thinking about safety is all the
20 more important because of the paradigms of drug
21 development now. Targeted therapeutics, developing
22 drugs specifically against human recombinant targets,

1 has some consequences, because in the old days when you
2 developed a medicine in an animal you saw pharmacology
3 in that animal, you tweaked the medicine trying to
4 optimize it for a human indication, but you saw
5 pharmacology all the way through. Here we have drugs
6 specifically targeted in vitro, high throughput
7 screening, to get molecules that interact with specific
8 targets and dial out other targets.

9 As a pharmacogeneticist, of course, my first
10 question is how does that target vary in the population,
11 because if 40 percent of the people have target that
12 won't interact with that molecule by definition the most
13 you'll ever get is 60 percent efficacy or 60 percent
14 interaction with that target.

15 But the same applies for off-target effects.
16 If you have lots of things that have been dialed out and
17 you have variants in those targets, some are now going
18 to be dialed in, creating side effects. One of the
19 interesting challenges that we have in pediatrics is
20 what is the role of all these new targets in growth and
21 development, because they may well be a source of a new
22 type of safety signal that we should be ahead of the

1 game in looking for.

2 You know, oncology has changed dramatically.
3 It's so unbelievably exciting right now. I wish I was
4 starting a residency at this point, because the world
5 really is changing. But with that, many of these
6 targets are in fact mediators of proliferation and cell
7 growth. How do those targets play out in a regulated
8 sense during ontogeny?

9 You know, in teratology we always think about
10 critical periods. You know, you can't get congenital
11 heart disease after the heart is completely formed, even
12 if a medicine might be associated with congenital heart
13 disease. We don't think as much about critical periods
14 in ontogeny and growth and development, where a variety
15 of different loci are going to be turned on in a
16 regulated way and then turned off.

17 One of the interesting and I think wonderful
18 challenges going forward in developmental biology is
19 going to be understanding when those targets are in fact
20 turned on and turned off, because so many of the drugs
21 that are going to be coming down the pike over the next
22 numbers of years are in fact going to be aimed at those

1 very targets, and we really need to think about how
2 those things will play out in terms of potential safety
3 signals and be ready for them and looking for them
4 actively, be it creative use of pre-clinical models and
5 cell models and increasingly, as we begin to use these
6 medicines in children, how they may in fact lead to
7 changes in development, ontogeny in children.

8 And we're beginning to get some interesting
9 hints about personalized safety approaches, some new
10 hints now, HOA variants in hypersensitivity reactions to
11 medicines like carbamazepine, some interesting hits in
12 the folate pathway, folate pathway variants, being
13 associated with metabolic syndrome, with the use of
14 atypical antipsychotics. Mechanistically they don't
15 make sense now.

16 What's exciting to me about that is it opens
17 up whole new opportunities for biologic investigation
18 and thinking about complex pathways and thinking about
19 clusters of targets and clusters of metabolic pathways
20 that lead to final phenotypic changes, very similar
21 kinds of things -- wonderful opportunities.

22 I would posit that if I was starting out now

1 in pediatrics that one of the most exciting things is
2 linking biology back to epidemiology, careful,
3 thoughtful, clinical ascertainment of phenotype, linked
4 with all the exciting tools that we now have in all of
5 the omics, not just genomics, but really all of the
6 omics, and thinking about how to bring those two
7 together; I know probably at many of your institutions,
8 and it's certainly going on now in multiple medical
9 centers around the country, collecting DNA and other
10 samples on patients, looking at outcomes, and trying to
11 link those together.

12 I suppose as a dean, going to deans meetings -
13 - deans, the only people deans get to talk to are other
14 deans. Your faculty don't talk to you, for God's sakes.

15 So you got to talk to other deans, and you find out
16 what's going on around the country: the increasing
17 concern about not being careful and thoughtful enough
18 about ascertaining and recording phenotype, what
19 patients really look like.

20 I know Ulso had a lot more time on his hands
21 to sit at the bedside and to characterize patients and
22 characterize the natural history of illness. But if

1 we're going to use all the molecular and other tools
2 that we now have, the greatest danger is applying highly
3 specific diagnostic tools to heterogeneous clinical
4 populations. If you expect anything out of entering
5 apples, oranges, and pears into a clinical trial other
6 than fruit salad, I'm sorry; that's what you get.

7 So we have an opportunity here, both in our
8 training programs and in the way that we look at
9 information on both a micro and macro level, of
10 enhancing characterization of our patients, thoughtful
11 understanding of the natural history of complex illness.

12 And natural history is so different than when I
13 started. Most of the diseases that are now making their
14 way into adolescents and into young adulthood patients
15 surviving things that to me were fatal as newborns or at
16 most early childhood, is characterizing what happens to
17 these patients, continuing to be thoughtful in
18 describing phenotype and natural history of illness, so
19 we now pick up not only those things that occur
20 immediately when you give a medicine, like anaphylaxis
21 to penicillin, but the longer term consequences as well.

22 Having said all of that, to me this can be the

1 golden age of pediatrics. I really truly believe that.

2 And I think we have an enormous opportunity because we
3 have tools that we never had before. But, as always, in
4 using those tools it comes down to the "W" word,
5 "wisdom" in terms of how we use those tools.

6 Again, I want to thank all of you for
7 contributing your wisdom to the deliberations that we're
8 about to undergo today and in an ongoing way. Thank you
9 for helping the FDA, thank you for helping the public
10 health in doing this.

11 Dianne, the floor is back to you.

12 DR. MURPHY: Thank you very much, Dr.
13 Spielberg. As I said, we're just delighted Dr.
14 Spielberg has come to the FDA as our Deputy Commissioner
15 and that we have a pediatrician at that level that can
16 help promote pediatric perspective, which I'm sure, for
17 those of you in non-pediatric institutions understand
18 the importance of that.

19 I think what he's outlined for you is where we
20 hope we're going, and I know you guys are sitting here
21 going, but we don't have a lot of that right now. Many
22 of the members who are experienced in dealing with our

1 adverse event reporting know the severe limitations and
2 know that we try the best to enhance the adverse event
3 reporting with as much detail as we can to provide to
4 you an assessment that we can provide to you.

5 Now, because today we have actually more
6 experts who are not members of the committee than are
7 normally here, because we try to often bring similar
8 groups of medicines at one time and it just happened on
9 this meeting we had many disparate types of therapies,
10 so we had to bring in many more different experts, which
11 is wonderful. We enjoy the discussion.

12 But I thought I would take a minute and just
13 go over very quickly for you just a couple of ground
14 rules, if you will, about the meeting. One is that
15 we're not here to discuss the efficacy of a product.
16 The FDA will take your comments about safety and weigh
17 it always with efficacy. But we're here today to talk
18 about the post-marketing safety assessment.

19 Any of you who've been in this pediatric
20 product development arena for very long know what the
21 challenges are. The challenges are that getting
22 pediatric studies done at all, is why we have

1 legislation; it requires that to get it done. When it's
2 done, we then run into the issue of small populations,
3 as Dr. Spielberg was referring to. We already start out
4 with small populations. So therefore a pediatric trial,
5 which we empower as best as we can, is going to be very
6 limited in its ability to detect a safety signal.

7 Once a product is, again, designated as for
8 use in children, it's going to be used, of course,
9 broadly. That's why the post-marketing adverse event is
10 so, assessment for children, is even more important,
11 because we have such small trial sizes. But we are
12 then dealing with all the limitations that you've heard
13 about in trying to make sense out of this.

14 So what we have provided you, the new thing we
15 have provided you, if you will, in your background
16 package is the adverse event, our safety review by our
17 Office of Surveillance and Epidemiology, the drug
18 utilization of this product review, again from our
19 Office of Surveillance and Epidemiology. Then we
20 sometimes will add in any recent or new literature,
21 articles, or relevant prior adverse event reviews for
22 that product. So that's the -- I call that the new data

1 as far as it's put together for this meeting for you.

2 What we also refer you to, though -- and this
3 is why people get confused sometimes with my initial
4 statement -- is we refer you to the trials that were
5 submitted to the agency, and we provide you the medical
6 officer's review. We provide you the pharmacology
7 review and the statistical review. The intent of doing
8 that is to provide you some context in which to put this
9 post-marketing adverse event information, because it
10 gives you the adverse events that were found during the
11 trials. So you often will, hopefully, have a control
12 group or what we consider a comparative group, so you
13 can then look at what we have for that, and the
14 statistical and pharmacology analysis that also
15 accompanied those studies.

16 So for those members, participants today and
17 experts who haven't been on this committee, that's why
18 you get -- only it's electronically; we bring these
19 (indicating) for visual -- that's why you get so much
20 background information, is that we are trying to give
21 you as robust a structure upon which you can feed this
22 new information that you obtain.

1 Today we're also -- for those who are not
2 members of the committee, the committee recently voted
3 on a new process, and we'll discuss that later when we
4 get there. But in that situation we don't expect you to
5 know anything about it. So if you don't understand
6 anything about it, that's perfectly appropriate.

7 So I think enough for me right now. Thank you
8 all.

9 CHAIRMAN ROSENTHAL: Thanks.

10 Before we go on, I'd like to give an
11 opportunity for the people who've joined us since the
12 introductions to introduce themselves. So if you
13 haven't already introduced yourself, why don't we start
14 with Dr. Reed and then work our way around this way.

15 DR. REED: Good morning. I am Michael Reed.
16 I'm director of clinical pharmacology and toxicology and
17 associate chair of the department of pediatrics and
18 director of the research institute at Akron Children's
19 Hospital, and a professor of pediatrics at Northeast
20 Ohio Medical University.

21 DR. WRIGHT: Good morning. Joseph Wright,
22 professor of pediatrics, emergency medicine and health

1 policy at George Washington University, and I'm a senior
2 vice president at Children's National Medical Center.

3 DR. KRISCHER: Good morning. I am Jeff
4 Krischer. I am professor of epidemiology and
5 biostatistics, mostly focused on clinical trials and
6 genotype-phenotype studies, at the University of South
7 Florida-Tampa.

8 MS. EICHNER: Good morning. I'm Marilyn
9 Eichner. I'm the patient-family representative.

10 CHAIRMAN ROSENTHAL: Thank you very much.

11 I'm going to apologize for going out of order
12 a little bit, but I never introduced Dianne Murphy, so I
13 want to just take a moment to introduce Dr. Murphy,
14 because, for those of you who don't know her, she is --
15 I describe Dr. Murphy as a primary driver of many of the
16 processes and ideas that come to this committee. We're
17 very appreciative for her input.

18 But Dr. Murphy is the director of the Office
19 of Pediatric Therapeutics at the FDA. It's in the
20 Office of the Commissioner. She's been with the FDA
21 since 1998. She's also served as the director of the
22 Office of Counterterrorism and Pediatric Drug

1 Development, the associate director for pediatrics, and
2 director of the Office of Drug Evaluation, with
3 oversight for all the divisions involved with anti-
4 microbial therapeutics.

5 She received her medical education from the
6 Medical College of Virginia and completed a pediatric
7 residency at the University of Virginia, as well as a
8 fellowship in pediatric infectious diseases at the
9 University of Colorado.

10 She has numerous articles in peer-reviewed
11 journals. She's made many scientific and policy
12 contributions, many contributions in the areas of
13 pediatric drug development, residency teaching,
14 laboratory diagnosis. She's the editor of a book on
15 office laboratory procedures.

16 So, sorry to do that after you spoke, Dr.
17 Murphy, but I'm glad to be able to get that in, and I
18 appreciate your guidance and wisdom as we go forward
19 through the meeting today.

20 The other thing that's coming up out of order
21 is we're going to be reversing the presentations. We
22 will be presenting Seroquel at 9:00 and then we'll

1 follow with the presentations for Focalin and Daytrana.

2 The reason that we're doing that is just to try to give
3 people whose flights were cancelled the opportunity to
4 participate in the discussions. So thank you for your
5 patience as we rearrange things a little bit.

6 DR. MURPHY: One last thing. I forgot to tell
7 the people who are the invited guests that may not be
8 used to the processes that you'll see individuals coming
9 up to the table and leaving. Those are the individuals
10 from the various technical divisions whose expertise we
11 want to have at the table and various people from the
12 Office of Surveillance and Epidemiology. So that's why
13 people will be coming and going from this side of the
14 table.

15 Thank you.

16 CHAIRMAN ROSENTHAL: Dr. Dracker, will you
17 please introduce yourself to the committee?

18 DR. DRACKER: Thank you. It's a pleasure
19 being here.

20 CHAIRMAN ROSENTHAL: You just need to press
21 the button for the red light.

22 DR. DRACKER: Got it, thank you.

1 Thank you. It's a pleasure being here. I
2 have a sore throat, which is an occupational hazard.
3 Besides that, my flight had difficulties as well. I am
4 a pediatrician, hematologist, and a blood banker. I am
5 from Syracuse, New York. I am in private practice as
6 well.

7 This is my first official meeting. I was here
8 last time just to observe, so I hope I can help all of
9 you.

10 Thank you.

11 CHAIRMAN ROSENTHAL: We appreciate your
12 participation.

13 All right, Walt.

14 MEETING COMMENCEMENT

15 DR. ELLENBERG: This is the opening statement
16 for the meeting. I'd like to say good morning to the
17 members of the Pediatric Advisory Committee, the members
18 of the public, and the FDA staff. Welcome.

19 The following announcement addresses the
20 issues of conflict of interest with regard to today's
21 discussion of reports by the agency, as mandated by the
22 Best Pharmaceuticals Act for Children and the Pediatric

1 Research Equity Act.

2 Based on the submitted agenda for the meeting
3 and all financial interests reported by the committee
4 participants, it has been determined that those
5 individuals who will be participating in each topic do
6 not have a conflict of interest for the following
7 products. The Pediatric Advisory Committee will meet to
8 discuss the pediatric-focused safety reviews as mandated
9 by BPCA and PREA with regards to: Pevnar 13, Cervarix,
10 Focalin XR, Daytrana, Seroquel, Xolair, Benicar,
11 Atacand, Plan B One-Step, and Flomax.

12 At the end of the day, several products which
13 fit the criteria for an abbreviated presentation have
14 been assigned to a designated reviewer for the process
15 of that discussion. These products are: Pancreaze,
16 Zenpep, Creon, Xerese cream, and Mirena.

17 In general, the committee participants are
18 aware of the need to exclude themselves from involvement
19 in the discussion of topics if their interests would be
20 affected, and their exclusion will be noted for the
21 record.

22 Dr. Bridgette Wiefeling is participating as a

1 consumer representative. Ms. Marilyn Eichner is
2 participating is a patient-family representative. Dr.
3 Robert Ward is participating as the health care
4 representative, which is a nonvoting position. Dr.
5 Brahm Goldstein is participating as the industry
6 representative, also a nonvoting position.

7 The following experts at the table will be
8 participating as temporary voting members: Dr. White,
9 Dr. Mink, Dr. Franco, Dr. Dracker, Dr. Castile, Dr.
10 Kaplan, Dr. Baker, Dr. Bhatia, Dr. Hillard, Dr. Walker,
11 and Dr. Felner.

12 I need to make a note that there will be one
13 recusal from the meeting. Dr. Franco will be recused
14 from the table for Seroquel and Atacand, and at that
15 time Dr. Franco will simply just need to slide his chair
16 away from the table and will not participate in those
17 discussions. Otherwise he will be permitted to
18 participate in the rest of the activities of the day.

19 With respect to all other participants, we ask
20 that in the interest of fairness that they address any
21 current or previous financial involvement with any firm
22 whose product they may wish to comment on.

1 We have one open public session, which is
2 scheduled for approximately 1:00 o'clock this afternoon.

3 Copies of the material which were submitted in
4 advance of this meeting are available on the table
5 outside for public viewing. The members of the
6 committee have also received a copy of this information
7 and it's been placed at each individual's seat.

8 Just a reminder for the members of the
9 committee: Please remember that when you get ready to
10 speak, turn your microphones on; and then when you
11 finish turn them off, because there's a limitation with
12 regards to the number of open mikes that can be
13 accommodated at any time. And again, introduce
14 yourselves so that we have a clear record in the
15 transcript.

16 Also, just to reiterate what Dr. Rosenthal
17 said earlier, if you'd please silence your cell phones
18 and any kind of pagers we'd appreciate it.

19 Thank you very much and we'll get ready to go
20 ahead.

21 CHAIRMAN ROSENTHAL: Thank you, Walt.

22 First, Dr. Mink has arrived from Dulles in

1 what might have been the fastest cab that is in this
2 area. So, Dr. Mink, will you please just introduce
3 yourself real quickly for the committee.

4 DR. MINK: Sure. My name is John Mink. I'm
5 from the University of Rochester. I'm a pediatric
6 neurologist.

7 DR. MURPHY: Why don't we just go ahead and go
8 with the schedule, because the technical division should
9 be here. So if we could have the neuropsych division.

10 CHAIRMAN ROSENTHAL: Dr. Murphy?

11 DR. MURPHY: Yes?

12 CHAIRMAN ROSENTHAL: Shall we just go ahead
13 with the agenda as previously described? Shall we go
14 with Focalin and Daytrana and then Seroquel? Or would
15 you like to do Seroquel first?

16 DR. MURPHY: Is Beth Durmowicz here? Okay. I
17 didn't see her. That was my hesitation. Okay, Beth,
18 are you ready to go, then?

19 DR. DURMOWICZ: Yes.

20 DR. MURPHY: Fine. We will go back to the
21 original schedule, then.

22 DR. COPE: That's Hari.

1 DR. MURPHY: It's Hari. Okay, we're set.

2 Okay, Hari, where are you? There you are. Thank you.

3 We will go into the Federal Register order,
4 which is always better. Thank you for our confusion
5 with shuffling people.

6 CHAIRMAN ROSENTHAL: All right. So just to be
7 clear, we will go through the presentations for Focalin
8 and Daytrana first, and our presenter will be Dr. Hari
9 Sachs, who's the team leader of the Pediatric and
10 Maternal Health Staff, Office of New Drugs. She's been
11 with the FDA since 2002 as a member of the Pediatrics
12 Group.

13 She's a graduate of the University of Maryland
14 at Baltimore Medical School and she completed her
15 internship and residency at the Children's Hospital
16 National Medical Center. She's been a practicing
17 pediatrician for over 20 years and she continues to see
18 patients one day per week. Good for you. That's a sign
19 of -- I like that.

20 All right, Dr. Sachs.

21 DR. MURPHY: Geof, could we introduce the
22 division people too, please?

1 CHAIRMAN ROSENTHAL: Yes, please. Those
2 colleagues and friends joining us at the table, if you
3 could please introduce yourselves.

4 FOCALIN XR (DEXMETHYLPHENIDATE HYDROCHLORIDE)

5 STANDARD REVIEW OF ADVERSE EVENTS

6 DR. LAUGHREN: Tom Laughren. I'm the director
7 of the Psychiatry Products Division, FDA.

8 DR. MITCHELL MATHIS: Mitchell Mathis, deputy
9 director, psychiatry.

10 CHAIRMAN ROSENTHAL: Thank you.

11 Dr. Sachs.

12 (Screen.)

13 DR. SACHS: Thank you guys very much and
14 welcome.

15 (Screen.)

16 Before presenting the specific product
17 information and adverse events for Focalin and Daytrana,
18 I'll be presenting some additional background
19 information regarding some previous discussions at
20 advisory committees about safety concerns for ADHD
21 medicines, as well as the results of a joint FDA-AARQ
22 study on cardiac adverse events that were associated

1 with ADHD medicines.

2 After this additional background discussion
3 and information, I'll move on to the adverse event
4 reviews for the specific products.

5 (Screen.)

6 Two meetings were held in close succession in
7 2006. The first, in February, was a meeting of the Drug
8 Safety and Risk Management Advisory Committee, which
9 discussed cardiovascular safety issues; and the second,
10 in March, provided a more in-depth follow-up on the
11 cardiovascular as well as additional discussions about
12 potential safety concerns in the psychiatric and
13 endocrine realm.

14 (Screen.)

15 The advisors at the DSARM meeting, which
16 included at that time cardiologists, internists,
17 statisticians, and only a few pediatricians,
18 pediatricians, supported adding warnings regarding
19 potential cardiovascular risks with the stimulant
20 classes of drugs, but consensus was not reached
21 regarding a boxed warning at that time. The vote was
22 pretty close, I believe 8 to 7.

1 (Screen.)

2 One month later, the Pediatric Advisory
3 Committee met to discuss a number of potential adverse
4 events, including the cardiovascular ones, along with
5 psychiatric and endocrine adverse events. At that time,
6 an analysis of the clinical trial data as well as the
7 post-marketing reports was presented.

8 (Screen.)

9 I'm going to summarize the recommendations
10 from the previous Pediatric Advisory Committee for these
11 events because you guys are going to be grappling with
12 the same kind of issues as you hear about the specific
13 products today. With respect to psychosis and mania,
14 the clinical trial data did confirm a statistically
15 significant increase in psychosis or mania in patients
16 that receive stimulant agents, and these did seem to be
17 drug-related, particularly hallucinations.

18 (Screen.)

19 So the Pediatric Advisory Committee
20 recommended that labeling include information that
21 quantified the risk, in other words the rates, as well
22 as some additional information about the occurrence of

1 visual and tactile hallucinations. You will see that
2 the rates and the possibility that emergent psychotic or
3 manic symptoms may occur, including hallucinations and
4 delusional thinking, is outlined in the current warnings
5 for these products.

6 (Screen.)

7 Looking at aggression, the clinical trial data
8 also suggested there was an increasing frequency of
9 aggression for some products, including Daytrana, but
10 not others. So the Pediatric Advisory Committee
11 recommended that aggression should be -- that labeling
12 should note that aggression can be a feature of ADHD and
13 that a MedGuide or equivalent should inform patients,
14 parents, and physicians about the potential risk and
15 encourage notification of physicians if change in
16 behavior is noticed. You will see that labeling for
17 both Focalin and Daytrana include such a warning and a
18 MedGuide.

19 (Screen.)

20 Now, importantly, for suicidality, unlike the
21 analysis that was performed around the same time on
22 SSRIs, there was not an association for an increased

1 risk of suicidality in patients receiving stimulants,
2 although one was noted for atomoxetine, which is also
3 used to treat ADHD. The labeling at that time for
4 Strattera, or atomoxetine, already contained a boxed
5 warning. So consequently the Pediatric Advisory
6 Committee did not recommend any changes for the
7 stimulants as far as suicidality goes.

8 The PAC members also recommended that FDA
9 should consider adding more information about the
10 effects of these medications on growth and, as you will
11 see, the potential for growth retardation is also
12 described in the warnings for both the products you'll
13 hear about.

14 (Screen.)

15 The Pediatric Advisory Committee also had
16 several recommendations regarding the potential
17 cardiovascular adverse events. A boxed warning was not
18 recommended, although the committee did recommend the
19 following: strong warnings for patients with underlying
20 cardio disease se be placed in highlights; performing a
21 baseline assessment, including family history, to help
22 detect undiagnosed cardiac disease; and to place some

1 additional warnings about concomitant medicines that
2 might impact treatment with these products.

3 Finally, the PAC recommended that additional
4 pharmacoepidemiologic studies were necessary to help
5 clarify the risk.

6 (Screen.)

7 Well, we now have the results of such a study,
8 and this was published in the New England Journal
9 November 2011. This was a large retrospective cohort
10 study of about 1.2 million children and young adults,
11 and this did not show any association between ADHD
12 medicines, including methylphenidate and
13 dexamethylphenidate, and serious cardiovascular adverse
14 events such as MMI or stroke or sudden cardiac death.

15 Although I'm not showing this on the slide,
16 this finding was replicated in adults and that was
17 published in December.

18 (Screen.)

19 Now that you have some idea of what the
20 previous discussions focused on -- forgive the pun; I'm
21 sorry, I like to pun a little bit -- let's focus to the
22 specific products we're going to discuss, starting with

1 Focalin. You will see that the discussion for Focalin
2 is going to be a little more detailed. The Daytrana
3 discussion will go a little faster.

4 (Screen.)

5 You will become familiar with this outline
6 during the day. We start generally with a background
7 about the specific agent, describe the pediatric studies
8 that resulted in the labeling changes, review any
9 relevant safety information that may be in the warnings,
10 precautions, or adverse events that help put the adverse
11 events you see in the review in context, and then
12 summarize this all for you.

13 (Screen.)

14 Focalin, or dexamethylphenidate, was originally
15 approved in November of 2001 for the treatment of ADHD
16 in pediatric patients 6 to 17 years of age. The long-
17 acting product, Focalin XR, was approved in May 2005,
18 also for the treatment of ADHD, but this time in
19 patients 6 years and above, including adults.

20 Both of these products are marketed by
21 Novartis, and the pediatric labeling change that
22 triggers this particular safety review was associated

1 with a new dosing regimen approved in October of 2009.

2 (Screen.)

3 The initial approval of Focalin was based on
4 two short-term studies, one with an active control in
5 132 patients 6 to 17 years of age and a second, 2-week
6 trial that was a withdrawal study in 75 responders.

7 (Screen.)

8 Similarly, Focalin XR was approved in
9 pediatric patients based on two trials, one a double-
10 blind, placebo-controlled study in 103 pediatric
11 patients and another with a crossover laboratory-
12 classroom study in the younger patients.

13 (Screen.)

14 Now, the Focalin XR labeling has been updated
15 a number of times since May 2005 to include new
16 information regarding the duration of action, the onset
17 of action, and some individualized dosing
18 recommendations. But I'd like to focus on some of the
19 labeling changes which have occurred in part due to the
20 advisory committees you heard about.

21 In April of 2006, the warning and precautions
22 section was updated to include the cardiovascular

1 warnings, or actually stronger cardiovascular warnings.

2 In 2007 the medication guide was added, which includes
3 information about the psychiatric and cardiovascular
4 adverse events.

5 (Screen.)

6 And in May 2010 there was some additional
7 information added about the lack of an effect on the QT
8 interval, which is often associated with arrhythmias if
9 that occurs.

10 (Screen.)

11 To put some of the adverse events you're going
12 to hear about in context, I want to draw your attention
13 to several contraindications and important warnings and
14 precautions for this product. Focalin XR is
15 contraindicated in patients with hypersensitivity to
16 methylphenidate products, as well as those with marked
17 anxiety, tension, and agitation, as those symptoms may
18 be aggravated.

19 Focalin is also contraindicated in patients
20 with tics or a family history of Tourette's.

21 (Screen.)

22 Now, you can see the first three warnings

1 capture the important cardiovascular adverse events, and
2 the next four capture the important psychiatric adverse
3 events. These warnings do include information about the
4 rates as well as that you can see new symptoms,
5 including hallucinations and delusional thinking.

6 (Screen.)

7 Since careful follow-up of patients treated
8 continuously with stimulants shows a slowing of height
9 and weight, labeling recommends monitoring growth. And
10 because seizures can lower the -- I mean, because
11 stimulant treatment can lower the seizure threshold,
12 that warning is also captured. There's an important
13 limitation of use for patients less than six years of
14 age, where the safety and efficacy has not been
15 established. Finally, it is recommended that if
16 patients take stimulants for a long time people check
17 their blood counts to make sure there's no leukopenia or
18 anemia.

19 (Screen.)

20 Now that you guys are familiar with the
21 labeling, let's look at how these products are used.
22 Unlike most of the products you will hear about today,

1 dexamethylphenidate is used largely in the pediatric
2 population. You can see that the use is 80 to 85
3 percent, 13 -- sorry about that --

4 (Screen.)

5 13.7 million out of the 16 million
6 prescriptions dispensed. Then there were 1.8 million
7 pediatric patients who received the products out of 2.2
8 million.

9 CHAIRMAN ROSENTHAL: Dr. Sachs, when you are
10 facing your slide it's hard to hear you.

11 DR. SACHS: You can't hear me, okay.

12 The use in pediatric patients is the majority,
13 over 80 to 85 percent, no matter how you look at it.

14 For all you compulsive number counters, if you
15 try to add up the last row the market share seems to be,
16 the XR products, these numbers will not add up to 100
17 because patients can use more than one product at a
18 time, and they also age and can be counted in two
19 cohorts.

20 (Screen.)

21 You can see graphically in this slide the
22 changes in drug use from 2006 to 2010. You can note an

1 increase in the long-acting product as well as the
2 generics. If you look at the use across the pediatric
3 age cohort, you can see that about 6 to 8 percent of use
4 does occur off label in patients less than six.

5 (Screen.)

6 Not surprisingly, the top prescribers for
7 these products are pediatricians and psychiatrists, and
8 pediatricians account for 30 to 40 percent of all the
9 prescriptions for these agents; and the top diagnosis
10 was ADD, over 95 percent of the time.

11 (Screen.)

12 Now that you have the use information -- and
13 please keep the use in mind -- let's look at the adverse
14 events. You can see the total number of adverse events
15 on this slide -- let's see if this works a little
16 better. There are 196 pediatric reports. These do
17 represent the majority, with 172 serious adverse events
18 and 2 deaths. These are total reports; that may include
19 duplicates or misclassifications.

20 (Screen.)

21 When we did the hands-on review, we actually
22 identified 167 reports, including three deaths, and that

1 was because there was one death that was
2 mischaracterized as simply a serious adverse event and
3 five duplicates.

4 (Screen.)

5 You can see the case characteristics for the
6 serious cases on this slide. The majority of them are
7 occurring in 6 to 11-year-olds, in males. These were
8 pretty much U.S. reports. The overwhelming diagnosis
9 was ADHD and the duration of therapy ranged from one day
10 to three years, with a median of about one month, in a
11 way paralleling the use -- we saw a little more adverse
12 events with the long-acting formulation.

13 (Screen.)

14 The following slides provide the details of
15 the three fatalities. The first two are labeled. One
16 was a sudden death in a 10-year-old with a known cardiac
17 problem who died during a sporting event. Of note, the
18 patient did receive a higher than recommended dose of
19 dexamethylphenidate. The maximum is about 20 milligrams
20 for the short-acting and 30 for the long, and they got
21 20 milligrams twice a day.

22 The second was an eight-year-old male who

1 died, potentially from a seizure, after treatment with
2 both a short and long-acting product for three months.
3 He was taking concomitant medicines which are also
4 labeled for seizures, specifically risperidone and
5 fluoxetine. Both of these adverse events are among the
6 warnings and precautions for the products.

7 (Screen.)

8 The last fatality was a seven-year-old male
9 who hung himself and, although he had a history of
10 behavioral issues, he was not on any concomitant
11 medications.

12 Now, the occurrence of suicide, completed
13 suicide, in this age group is low, but unfortunately not
14 unheard of.

15 (Screen.)

16 Now that you have heard about the fatalities,
17 let's examine the non-fatal serious adverse events. The
18 majority of adverse events were either psychiatric or
19 neurologic. There were also 18 cardiovascular adverse
20 events, 9 related to weight loss and 8 cases related to
21 insomnia, plus a handful or a variety of miscellaneous
22 adverse events. What I'm going to do is describe the

1 adverse events for each category, but focus primarily on
2 the unlabeled events since the majority of them are
3 labeled.

4 (Screen.)

5 So here's a further breakdown of the 55
6 neuropsych adverse events. The majority of these are
7 labeled, specifically hallucinations, psychotic
8 disorders, aggression, and mood disorders. So I won't
9 present the details of those cases, but will spend a
10 little more time on suicidality, panic attack, and OCD.

11 So there were eight reports that described
12 suicidal ideation. Four of them had a positive
13 dechallenge. That is, the suicidality disappeared when
14 the medicine was discontinued. But two of the remaining
15 cases had comorbidities associated with suicidality.
16 And although labeling does not specifically mention
17 suicidality except in the context of screening for
18 bipolar disorder, there are clear warnings for
19 monitoring for behavioral changes.

20 (Screen.)

21 This slide presents the details of the four
22 cases of suicidality that resolved when

1 dexamethylphenidate was discontinued. All of these were
2 males between the ages of 8 and 11. One patient had
3 been on therapy for six months, the others for less than
4 a week, and two had prior reactions to other stimulant
5 medications.

6 As mentioned, suicidality was not found to be
7 a signal from the meta-analysis of the clinical trials
8 of the stimulants, although it was detected for
9 atomoxetine; suicidality, although rare, is not unheard
10 of in the pediatric population. For this reason or
11 these reasons, the previous Pediatric Advisory Committee
12 did not recommend a labeling change and we had agreed.

13 (Screen.)

14 Two patients with OCD -- or two patients were
15 diagnosed with OCD after taxing dexamethylphenidate. One
16 was a seven-year-old who had trichotillomania and her
17 symptoms of touching herself on the face and hands
18 recurred after the medicine was stopped and restarted.
19 The other was an 11-year-old with autism. There were
20 two patients who experienced panic attacks.

21 Again, although labeling does not specifically
22 describe OCD symptoms or panic attacks, it does alert

1 practitioners and patients to report new symptoms and
2 thought problems. In addition, Focalin is
3 contraindicated in patients with agitation or anxiety
4 due to the potential to exacerbate that, and anxiety is
5 listed as a common side effect.

6 (Screen.)

7 So now turning to the 39 neurological adverse
8 events. There were 14 reports of seizures, 12
9 neuromuscular adverse events, 7 headaches, and 6
10 miscellaneous neuro events. Again, the majority of
11 these are labeled, so I'll focus on the unlabeled
12 events.

13 (Screen.)

14 10 of the 12 neuromuscular events included
15 reports of extrapyramidal or EPS-like symptoms, with a
16 single report each of tics and muscle spasms. The
17 adverse events section of labeling includes tics,
18 dyskinesia, and muscle twitching, but EPS is not
19 specifically labeled.

20 (Screen.)

21 So looking a little more closely at these
22 extrapyramidal neuromuscular adverse events, you can see

1 that there's a range of symptoms that occurred in the
2 patients. The median age of the report was expected six
3 years of age. The median dose was about 10 milligrams,
4 and the median duration of treatment was a month. Four
5 out of the ten patients were taking concomitant
6 medicines that are labeling for EPS events.

7 (Screen.)

8 The six remaining neurological events included
9 two reports of hyperactivity and one report of a stroke,
10 which are labeled, and four other miscellaneous events.

11 And while aura, cerebral palsy, and lethargy are not
12 specifically labeled, these are single events and the
13 causality is not clear.

14 (Screen.)

15 There were 18 reports related to
16 cardiovascular adverse events. The majority of these
17 are labeled, except for two patients, a 12-year-old and
18 a 14-year-old male, who had EKGs that showed possible
19 ventricular hypertrophy, and a 14-year-old female who
20 was on multiple medicines that are labeled for
21 hypertension, who had intermittent hypertension and was
22 diagnosed with mitral valve prolapse, or mitral valve

1 incompetence.

2 (Screen.)

3 Nine patients experienced weight loss, which
4 is a labeled event, and although three of the patients
5 required hospitalization, their symptoms are a little
6 atypical. One had cyclic vomiting and abdominal pain.
7 Another was related in part to a manic episode, which
8 resolved after the product was discontinued. And the
9 third had dehydration, generalized weakness, and
10 abdominal pain, but he had been on therapy for quite a
11 bit of time.

12 (Screen.)

13 Eight patients experienced insomnia, which is
14 a labeled event. One of the patients was a seven-year-
15 old who had parasomnias, night terrors, somnambulism,
16 which is not specifically labeled.

17 (Screen.)

18 Finally, let's look at the miscellaneous
19 adverse events. Once again, the majority of these are
20 labeled or they're single reports of an unlabeled event,
21 and you can see the range of labeled events on this
22 slide.

1 Three of the unlabeled events are reported
2 more than once -- Stevens-Johnson Syndrome, Raynaud's
3 Phenomenon, and neutropenia -- and there were four
4 reports of Stevens-Johnson Syndrome. Two appeared to be
5 related to other factors, specifically a viral illness
6 or an antibiotic, but two cases occurred and resolved
7 after the dexmethylphenidate was discontinued.

8 (Screen.)

9 There are four reports of Raynaud's
10 Phenomenon. Two of the patients were taking other
11 methylphenidate products that are labeled for Raynaud's
12 and the other two had either a personal or a family
13 history of a connective tissue type disorder.

14 (Screen.)

15 There were two reports of neutropenia, which
16 may not be specifically labeled, but the label clearly
17 does have a warning for monitoring patients for
18 leukopenia.

19 You can see the variety of the remaining
20 adverse events listed. Most of them again are single
21 reports, but we do actually want to focus your attention
22 on the one case of angioedema. This was a 16-year-old

1 who basically developed angioedema and then symptoms of
2 anaphylaxis and required emergency treatment with epi,
3 diphenhydramine, and steroids. Because of that report,
4 we did an additional review of angioedema and
5 anaphylaxis and identified another report in adults.
6 Since both these cases were temporally associated with
7 the Focalin treatment and included both angioedema and
8 anaphylaxis as symptoms, we have recommended that
9 angioedema and anaphylaxis be added to the labeling and
10 that actually, because of the cross-reactivity between
11 the methylfenidate products, that the labeling be
12 harmonized. The sponsor for Focalin has agreed to do
13 this, actually.

14 (Screen.)

15 This concludes the pediatric focused safety
16 review for Focalin XR. As you know, this was triggered
17 by the new dosing regimen. We do recommend a change in
18 the labeling regarding angioedema and anaphylaxis, which
19 is going to happen. We don't recommend any other
20 labeling changes and we would expect that this product
21 can return to routine monitoring, but we're very
22 interested in hearing your discussion and opinion.

1 May I say that the Daytrana profile is pretty
2 similar, so you could hear that presentation and then
3 discuss it. Or you can start with this one, which is a
4 little more complex.

5 DR. WARD: Could I ask, Dr. Towbin, does
6 dyskinesia capture extrapyramidal symptoms adequately?

7 DR. TOWBIN: I appreciate the question and it
8 speaks to one of the things I wanted to talk about.
9 Actually, I was going to raise that in a somewhat
10 different way, which is to say what would be the
11 threshold for adding language related to extrapyramidal
12 symptoms to the labeling?

13 Given what we're seeing, the mechanisms about
14 those extrapyramidal symptoms that we know, and how this
15 drug works, it certainly would make sense that this drug
16 could cause those kinds of symptoms, given the way that
17 it works. So, thinking about practitioners being alert
18 to the occurrence of extrapyramidal symptoms would make
19 sense to me.

20 I'm delighted Dr. Mink is here because, of
21 course, he may have some observations about this as
22 well.

1 DR. MINK: Unfortunately, the category of
2 extrapyramidal side effects or extrapyramidal symptoms
3 includes both things that are related to excess dopamine
4 and to dopamine blockade. It's very hard to know what
5 is being described by reports of extrapyramidal side
6 effects. Tics are dyskinesia. Tics are an
7 extrapyramidal side effect, and we know that in some
8 individuals tics can worsen with this.

9 So in the absence of better information, it's
10 very hard to determine whether dyskinesia as a separate
11 category should be included. I will tell you in my
12 practice, where I see very many children referred for
13 concerns of tardive dyskinesia or other movement
14 disorders, the great majority of them have tics, but
15 were misrecognized or mischaracterized by their
16 referring physician.

17 So I guess my thought is at this point I think
18 it would be difficult for me to advocate specific
19 labeling for dyskinesia, given that dyskinesia includes
20 something that's already there.

21 DR. WARD: If I read it correctly, dyskinesia
22 is already part of the label, if I read this correctly.

1 My question is, does that adequately warn a prescribing
2 physician about the potential for extrapyramidal
3 movement disorders?

4 DR. MINK: I think so. I think that the
5 movement disorders, the extrapyramidal movement
6 disorders that are the most likely to be associated with
7 this medicine, though we don't know specifically, are
8 dyskinesias, including tics.

9 DR. TOWBIN: It just seems to me -- oh, this
10 is Dr. Towbin back again; sorry -- that the events that
11 were listed were such that, although someone with Dr.
12 Mink's erudition understands the relationship between
13 those kinds of movements and experiences and the term
14 "dyskinesia," that many practitioners who would be using
15 these agents may not. So I might be of the opinion that
16 expanding that list could be useful.

17 The experience of an oculogyric crisis, some
18 of the kinds of things that are described -- a
19 pediatrician who is not a neurological expert of the
20 caliber of Dr. Mink might not consider that to be
21 related to the drug, and one would want, I would think,
22 something like that, or at least I would raise the

1 question about it. I actually am on the fence about it.

2 I do have one other comment to make, but I
3 just want to go one at a time here.

4 CHAIRMAN ROSENTHAL: Any other? Yes, Dr.
5 Laughren?

6 DR. LAUGHREN: Drugs that cause acute
7 extrapyramidal symptoms of the kind that we're used to
8 thinking about, like dystonic reactions and Parkinsonian
9 syndromes, are the dopamine blockers. This drug has an
10 opposite effect. So it would be very surprising, and of
11 course it doesn't show up at all in controlled trials.
12 These are rare, spontaneous reports and it is hard to
13 make sense of them.

14 One thing that you might be seeing -- and this
15 is pure speculation -- but some -- as you know, many of
16 these children do get atypical antipsychotics, which can
17 cause extrapyramidal symptoms, and with prolonged use
18 could cause tardive dyskinesia, which might be uncovered
19 by giving a dopamine agonist.

20 So it's very difficult to capture that sort of
21 thing in labeling. But I think the consolation is that
22 these events are quite rare. We don't see these. I

1 mean, consider the very widespread use of these drugs
2 and the rarity of these reports that we're seeing.

3 DR. TOWBIN: This is Dr. Towbin back. I
4 actually am content with that. I just thought this was
5 a little more of a signal in this system than I would
6 have expected for these, and indeed, given some of the
7 quality of the information that we get, we really don't
8 know whether some of these children may have been on
9 things that were -- even metoclopramide or other kinds
10 of things that may have had similar sort of effects and
11 then got stimulants and these reactions.

12 I would like to raise a second point, if that
13 would be okay, and that is, what is the threshold for
14 reconsidering a contraindication? Because I do believe
15 that the field in the treatment of tic disorders has
16 changed in its view of the use of these agents, and that
17 when these drugs first came onto the market there was a
18 very strong concern about their propensity to either
19 cause or bring forth tics in vulnerable individuals or
20 exacerbate them in individuals that had tics and
21 Tourette's.

22 I think there is now a good body of literature

1 to suggest that a majority of individuals with tic
2 disorders will not experience an exacerbation of their
3 symptoms, and so it would seem that the label is
4 somewhat out of phase right now. I was wondering at
5 what point the agency would reconsider a
6 contraindication, but still of course leave the labeling
7 that there may be an increase in tics in some
8 individuals as a warning?

9 DR. LAUGHREN: It's a very timely question.
10 It turns out that we are actually now reconsidering all
11 the contraindications. We're looking at the somnolents
12 as a class from a labeling standpoint and systematically
13 going through the different sections and trying to
14 update the information.

15 That is one contraindication that will
16 probably go away, because you're right, it isn't -- it
17 doesn't really make sense any more.

18 CHAIRMAN ROSENTHAL: Thank you, Dr. Laughren.

19 I just want to remind people to please state
20 your name into the record.

21 Dr. Mink.

22 DR. MINK: I am indeed Dr. Mink.

1 Two things. Let me just echo what Dr. Towbin
2 said about the tic, and I very much advocate
3 reconsideration of that, as you've already stated.

4 Back to the extrapyramidal side effect
5 description, do we have data whether those ten reports
6 were one type or was it one of each of those different
7 ones that was listed?

8 (Screen.)

9 Actually, the slide you were on.

10 (Screen.)

11 DR. SACHS: No, I'm sorry. I didn't mean to
12 hit it.

13 DR. MINK: So Slide 37 had the EPS
14 descriptions in ten individuals: dysarthria, muscular
15 spasticity or spasms, etcetera, etcetera. Was it one
16 report of each of those or was it ten reports of EPS,
17 and you're saying EPS includes these following things?

18 DR. SACHS: I will ask Vicky Huang, who actually
19 did the review and has the individual reports, to answer
20 that one.

21 DR. HUANG: Hi. My name is Vicky Huang. I'm
22 a safety evaluator with the Office of Surveillance and

1 Epidemiology.

2 These ten reports actually had a mixture of
3 these adverse events. I would say that for the most
4 part these reports actually reported one to two adverse
5 events per report. So the n of ten actually included a
6 different combination of these adverse events.

7 Does that answer your question?

8 DR. MINK: Sort of. So I think that if it
9 were a majority of these reports were oculogyric crises,
10 I'd say that that's a surprise and really should be
11 pursued more and reviewed again shortly. But if it's
12 across the board I'm less concerned about this as a
13 worrisome phenomenon.

14 DR. MURPHY: Is there any more information, I
15 guess we're asking, than what's on page 10 of the
16 report, where it does go through some of these
17 individual cases, where you do describe eye-blinking,
18 sticking -- I mean -- what I'm trying to say is they
19 usually put in these reports all the information they
20 have. Sometimes they will condense them a little bit,
21 but I'm asking is there anything that's not in this
22 report that could help the committee?

1 DR. HUANG: Well, in regards to the oculogyric
2 crisis, there was only one case reporting that event.
3 Is there anything else specific that you would like to
4 know about, so that I can narrow down?

5 DR. MURPHY: Any others?

6 DR. HUANG: It says on the slide that there
7 were four cases that received concomitant medications.
8 It's already labeled for dyskinesia or tardive
9 dyskinesia, etcetera.

10 DR. MURPHY: So the committee should assume
11 that for the other six we don't have information. It
12 doesn't mean that they weren't on it. It just means we
13 don't have any information.

14 DR. HUANG: One case reported no concomitant
15 medications.

16 DR. MURPHY: Sorry.

17 DR. HUANG: And five of the cases did not
18 report concomitant medications.

19 CHAIRMAN ROSENTHAL: Thank you.

20 Dr. Motil and then Dr. Dracker.

21 DR. MOTIL: Motil. I would just like to
22 register my concern in this very area. As a non-

1 neurologist, I am looking at a number of motor type
2 terminologies that raised my concerns. I see a number
3 of children with neurological problems and, while I
4 don't have probably the precision of definition, a
5 cluster of events that involves muscle spasms, muscle
6 spasticity, muscle tightness, nuchal rigidity, some
7 dystonias, tongue movement disorders, it raises an angst
8 that, if nothing else, I think perhaps the agency may
9 wish to come armed with some more precise definitions
10 and monitor if these items are not currently going to be
11 labeled.

12 CHAIRMAN ROSENTHAL: Dr. Dracker.

13 DR. DRACKER: Just a couple comments with
14 regards to the presence of extrapyramidal signs or the
15 appearance of them. Generally speaking from a private
16 practice perspective, as soon as that's noted in the
17 child generally it results in the immediate cessation of
18 therapy. Personally, I've never seen it. We take care
19 of probably over a thousand children with ADHD. It
20 sounds like a large number, but we have 30,000 children
21 in the practice. If that occurs, they are then referred
22 to neurology.

1 In general, I have never seen that occur only
2 when a child is only on a stimulant therapy. Actually,
3 we see it very rarely in general.

4 With regard to the presence of tics or the
5 appearance of tics, if the child has a tic at the time
6 of presentation the child is placed on a stimulant
7 therapy. Parents are generally warned that tics may or
8 may not get worse once placed on therapy. In general,
9 once a child develops tics and is on therapy, did not
10 have tics previously, we don't have to worry about
11 stopping the therapy because usually the parents want
12 the therapy stopped because they don't want additional
13 attention brought to the child. So it becomes a very
14 clinical and socioenvironmental issue for the child.

15 I just want to make one other comment about
16 the angioedema event, and that is in that particular
17 case I wonder if there was a family history taken and
18 whether there was a possibility of a C1-esterase
19 inhibitor evaluation performed?

20 DR. HUANG: Hi. This is Vicky Huang.

21 There was no information regarding that
22 reported in the case. And we actually included all that

1 was reported in the MedWatch form on the slides. That
2 was all the information we received.

3 CHAIRMAN ROSENTHAL: Dr. Wagener.

4 DR. WAGENER: I just want to make one
5 suggestion. This is again coming from somebody who's
6 not a neurologist and has very limited exposure. But it
7 seems that there is a slight difference between the
8 understanding of neurologists, who subcategorize all of
9 these extrapyramidal activity disorders, and those of us
10 who went to medical school many years ago, who were
11 globally told about extrapyramidal problems.

12 I wonder if on the package insert it might
13 simply say extrapyramidal symptoms have been noted, or
14 it's a warning or whatever, and then under that
15 subheading you list all of these other different
16 symptoms that might be considered an extrapyramidal
17 factor by a typical neurologist.

18 CHAIRMAN ROSENTHAL: Dr. White.

19 DR. WHITE: I guess I'm an idealist on this
20 whole area. As a cardiologist, we see bunches of these
21 kids, not because of their neurological problems, but
22 because everybody is afraid they're going to fall over

1 dead.

2 In our community what I see is that the
3 pediatricians that are primary prescribers for these
4 medications and they don't really care about the
5 specific symptoms. If some child comes in that has the
6 least suspicious activity, they don't care what the
7 label is. They're going to send that child off
8 immediately.

9 I guess my other concern is, if we look at
10 these reports, these aren't very common, and almost all
11 the children have other medications. And the ones that
12 we don't know about, the ones that we say no other
13 medications, it's just that we don't know what they
14 might be taking.

15 I kind of have a question about at what level
16 do we change the label, and I'm not quite sure where
17 that is. As a new member, I'm not quite clear about at
18 what point do we change the label to scare people who
19 may be using these medications on a regular basis. I
20 would say that probably we haven't reached that level,
21 at least in my opinion.

22 CHAIRMAN ROSENTHAL: Dr. Ward, you seem to be

1 -- you've developed a twitch during this conversation.

2 (Laughter.)

3 DR. WARD: I was checking my extrapyramidal
4 symptoms score.

5 It seems to me that the issue about at what
6 level do you reach a threshold for changing the label
7 has to do with severity and risk to the patient, as
8 opposed to simply -- I would say, as somebody mentioned,
9 if these developed we refer them to a neurologist, who's
10 going to decide is this an extrapyramidal symptom or not
11 and what is the corrective action that needs to be
12 taken, as opposed to angioedema, which is something
13 that's life-threatening, I think the recommendation to
14 place that in the label is very reasonable and a real
15 warning needs to be there.

16 But out of, what is it, 18 million
17 prescriptions, this is a pretty rare event.

18 CHAIRMAN ROSENTHAL: Thank you.

19 Can we go back to the -- are there other
20 comments? Yes, Dr. Reed?

21 DR. REED: I hate to throw a wrench in the
22 wheel here, and I'll yield to the expertise of Dr.

1 Towbin. But just as Dr. Ward mentioned the numbers
2 here, we've had a lot of discussion about extrapyramidal
3 effects. The n for suicidal ideation seems to be about
4 the same, and when you consider the relative common
5 comorbidity of depression with ADHD, should anywhere in
6 the label, should there be anything about that?

7 This is Reed again. I wasn't picking on you,
8 Dr. Towbin.

9 DR. TOWBIN: No, I don't feel picked on.

10 DR. REED: Yield to anyone else.

11 DR. TOWBIN: No, no, I don't feel picked on at
12 all. I think that, just as we've heard, comorbidities
13 in this population are the rule, not the exception, and
14 comorbidities with anxiety disorders and depression do
15 arise. Aggressive behavior is seen commonly in
16 individuals with ADHD, and so being attuned to that is
17 something that's important.

18 When one has comorbidity it's a little hard to
19 know kind of where that's coming from, which side of the
20 comorbidity? Is it the depression and anxiety that's
21 driving that? Is it the ADHD? And I think that being
22 attuned to those behavioral changes is really

1 sufficiently identified in the label as it is. I
2 wouldn't, for myself reading this, I wouldn't feel that
3 there was a need to strengthen that language or to kind
4 of attune people to it to a greater degree.

5 It sort of comes back to the earlier comment
6 about scaring people. I think that we walk a line
7 between wanting practitioners to be informed about the
8 range of possible side effects, but we also don't want
9 to be alarmist about kind of adding things or moving
10 beyond what the data suggests should be a reasonable
11 thing to be concerned about.

12 DR. TOWBIN: I concur with that. My sense
13 from the presentation is that suicidal ideation is not
14 mentioned in the label. It's an underlying -- is it?

15 DR. MURPHY: That's correct.

16 DR. TOWBIN: So it's not noted at all. But I
17 do agree about we're not here to scare anyone.

18 CHAIRMAN ROSENTHAL: Dr. Wiefling.

19 DR. WIEFLING: Speaking from a consumer's
20 perspective and looking at the label both as a
21 pediatrician and as a parent, there isn't anything --
22 that was actually one of my comments -- there isn't

1 anything really to call out suicidal ideation, nor to
2 further describe psychosis in the sense of
3 hallucinations and delusions, which some parents may not
4 understand psychosis versus hallucination and delusions.

5 Actually, I think some pediatricians might not
6 necessarily catch that piece.

7 I also noted in the label that it says -- it's
8 a little inconsistent, because it says that the
9 capsules, under warnings, depression: Focalin XR
10 extended release capsules should not be used to treat
11 severe depression. And it's our understanding that it's
12 not used to treat depression at all, and so I would
13 think that that maybe ought to be struck because I think
14 it's confusing.

15 I think some other places in the description
16 for parents could be improved, some of the symptoms
17 could be improved. But I don't know if that's the level
18 or the role of what we're supposed to be doing here.

19 CHAIRMAN ROSENTHAL: It's exactly the level,
20 yes. Thank you.

21 Are there other comments?

22 (No response.)

1 CHAIRMAN ROSENTHAL: All right. So, Dr.
2 Sachs, can you bring us back to the questions before the
3 committee?

4 (Screen.)

5 DR. SACHS: So our question to you really is
6 whether or not we should return this to routine
7 monitoring. Clearly, your comments about perhaps
8 strengthening the label in some places and removing one
9 contraindication I think have been noted.

10 CHAIRMAN ROSENTHAL: So this is another
11 complex question for a vote. Why don't we -- why don't
12 we vote on these -- well, so it looks like we could vote
13 on the first one. The second one I think we have an
14 answer, and then the third one we should perhaps vote on
15 as well. Is that how it looks to you guys on my right?

16 So why don't we take the last, the third
17 bullet, first. The question will be: Does the
18 committee concur that the FDA should return to routine
19 safety monitoring for this product? All in favor of
20 that, please raise your hands.

21 (A show of hands.)

22 CHAIRMAN ROSENTHAL: Any opposed?

1 (No response.)

2 CHAIRMAN ROSENTHAL: And any abstentions?

3 (No response.)

4 CHAIRMAN ROSENTHAL: All right. Let's go
5 around the table and please give your name and your
6 vote. Dr. White?

7 DR. WHITE: Michael White, yes.

8 DR. RAKOWSKY: Alex Rakowsky, yes.

9 DR. FELNER: Eric Felner, yes.

10 DR. WALKER: Leslie Walker, yes.

11 DR. HILLARD: Paula Hillard, yes.

12 DR. BHATIA: Jatinder Bhatia, yes.

13 DR. FRANCO: Israel Franco, yes.

14 DR. MINK: John Mink, yes.

15 DR. WIEFLING: Bridgette Wiefeling, yes.

16 DR. BAKER: Susan Baker, yes.

17 DR. KAPLAN: Shelly Kaplan, yes.

18 DR. CASTILE: Bob Castile, yes.

19 MS. EICHNER: Marilyn Eichner, yes.

20 CHAIRMAN ROSENTHAL: Dr. Kaplan, will you --

21 DR. KAPLAN: Shelly Kaplan, yes.

22 DR. WRIGHT: Joseph Wright, yes.

1 DR. KRISCHER: Jeff Krischer, yes.

2 DR. TOWBIN: Kenneth Towbin, yes.

3 DR. WAGENER: Jeff Wagener, yes.

4 DR. MOTIL: Kathleen Motil, yes.

5 DR. DRACKER: Bob Dracker, yes.

6 DR. SANTANA: Victor Santana, yes.

7 DR. REED: Michael Reed, yes.

8 CHAIRMAN ROSENTHAL: All right.

9 For bullet point number 2, which is that no
10 other labeling changes are recommended, I think we've --
11 yes, Dr. Loughren?

12 DR. LOUGHREN: Yes, this is Tom Loughren.
13 Before you vote on that question, let me remind the
14 committee again that we are in the process of looking at
15 the stimulant labeling generally and trying to bring it
16 up to date and make it better. There have been a lot of
17 useful comments made here this morning that we'll take
18 into consideration as we do that.

19 So we are going to try and make a number of
20 fixes in the label and we'll be sensitive to the
21 comments that the committee has made in doing that.

22 CHAIRMAN ROSENTHAL: So do we -- it seems like

1 we probably don't need to vote on that bullet.

2 DR. MURPHY: Unless somebody wants to make a
3 statement that they think something should be added,
4 okay, then I think that that would be the only
5 opportunity. Otherwise, I think that you could vote to
6 agree that there are no other labeling changes. So I
7 just think that there was a lot of discussion and I
8 wasn't sure.

9 It sounded like everybody was comfortable at
10 the end, but I want to give everybody an opportunity if
11 they have a recommendation that they want to make, that
12 they would make it at this point. And if they don't
13 then we could do a vote in the context that Tom has told
14 you he's heard the thoughts that you expressed.

15 CHAIRMAN ROSENTHAL: Several hands have gone
16 up. May I just ask a general question: Are the hands
17 that have gone up offering specific suggestions around
18 labeling changes? In other words, can we go around --
19 okay. So perhaps what we can do is vote on this and if
20 we vote no further labeling changes, then we won't have
21 much to add. But if we vote that we would recommend
22 further labeling changes, perhaps we can specifically

1 call them, call out what those labeling changes would
2 be.

3 Dr. Rakowsky, do you have a question?

4 DR. RAKOWSKY: Just, can we ask that the
5 division present, once you're done the revisions to the
6 label, as an informational session to come back to see
7 what changes were made? That may help in this vote to
8 see, instead of recommending, if there are things in the
9 works already.

10 I'm not sure if that's in our purview as a
11 committee, but that may help in the discussion.

12 CHAIRMAN ROSENTHAL: That may help some with
13 the organizational learning of the Pediatric Advisory
14 Committee.

15 But let's go ahead and vote on this, then.
16 All those who believe that no other labeling changes
17 should be recommended, please raise your hands.

18 (A show of hands.)

19 CHAIRMAN ROSENTHAL: All right. And all those
20 who feel that some labeling change should be
21 recommended, please raise your hand.

22 (A show of hands.)

1 CHAIRMAN ROSENTHAL: All right. And any
2 abstentions?

3 (No response.)

4 CHAIRMAN ROSENTHAL: So let's go around the
5 table and state your vote and then specifically call out
6 the labeling change or changes that you think are
7 important for the agency to focus on. Dr. Reed?

8 DR. BHATIA: Dr. Rosenthal, before you go, I
9 focused on "no other" in bullet number 1. So I withdraw
10 saying no; I'm going to say yes.

11 CHAIRMAN ROSENTHAL: Okay, noted. Thank you.

12 Okay, so let's go around the table. Dr. Reed,
13 will you get us started this time?

14 DR. REED: This is Reed. I voted no. I
15 concur with Dr. Wiefeling on cleaning up the label, and I
16 am sending a signal to our colleagues at the agency that
17 I still believe that suicidal ideation might be
18 considered for addition as a possibility on the label.

19 DR. SANTANA: This is Victor Santana. I also
20 voted no and I would support the suggestions that were
21 made across the table for suggested changes. I think it
22 would be helpful maybe if the chair or somebody could

1 summarize what those are when we finish, because I've
2 been hearing different things and I think it would be
3 helpful if at the end of this vote somebody put forth
4 the three or four suggestions that we are all agreeing
5 upon.

6 DR. DRACKER: This is Bob Dracker. I assume
7 the vote is that there are or are not labeling changes,
8 that there are labeling changes, correct? So I vote yes
9 and I think we should again reconsider the fact that the
10 majority of these medications are prescribed by
11 pediatricians and that there should be a comment made
12 with regards to the appearance and presence of
13 extrapyramidal signs and also potential risks for the
14 exacerbation of tic-like disorders, both of which should
15 recommend further evaluation.

16 Oh, I have it backwards, so let me withdraw
17 that vote. We're confusing each other.

18 So I vote no, there should be other labeling
19 changes. So let me clarify that. I apologize.

20 DR. MOTIL: Motil. I voted no for similar
21 reasons, in that I think the labeling should clarify
22 extrapyramidal movement issues and in the context of,

1 albeit small numbers, for that particular group of
2 observations I think probably the suicidal ideation
3 would qualify as another small grouping that deserves
4 review.

5 DR. WAGENER: Jeff Wagener. I voted no and I
6 voted in support of the FDA's plans for upcoming
7 changes.

8 DR. TOWBIN: Kenneth Towbin. I voted no. I
9 endorse and very much appreciate the agency's review of
10 the contraindications, particularly related to tic
11 disorders. I am on the fence about whether description
12 of muscle movement problems and spasms might be added to
13 the list. I think that the label as it currently
14 describes bipolar kinds of symptoms, which include
15 increasing depression, suicidal ideation in family
16 members, and increasing depression, is sufficient to
17 cover what we have already.

18 DR. KRISCHER: Jeff Krischer. I voted no for
19 reasons previously stated by my colleagues.

20 DR. WRIGHT: Joseph Wright. I voted no and
21 concur with the previous comments by Dr. Reed and others
22 with regard to suicidal ideation.

1 MS. EICHNER: Marilyn Eichner. I voted no.
2 I'd like to see the language strengthened a little bit
3 on the suicide. But I do agree with the pediatricians;
4 once they see abnormal tics, they'll automatically be
5 sent to the neurologist. I see that commonly happen.

6 DR. CASTILE: I'm Bob Castile. I voted no
7 because after the discussion I remain sort of
8 uncomfortable with just letting the issue of suicidal
9 ideation and extrapyramidal effects just kind of drop.
10 I suspect that they'll be looked at further going
11 forward. I guess I wonder if they shouldn't be
12 specifically targeted going forward, particularly with
13 the extrapyramidal effects. Maybe they can be better
14 defined in sort of future looks at serious adverse
15 events.

16 DR. KAPLAN: Shelly Kaplan. I voted no
17 because of all the previous comments as well, and that
18 the suicidal ideation seems to be pretty serious as
19 well, just as serious as angioedema and serious
20 hypersensitivity reaction.

21 DR. BAKER: Susan Baker. I voted no. I think
22 my other colleagues have articulated pretty clearly the

1 concerns and I concur with them.

2 DR. WIEFLING: This is Bridgette Wiefling and
3 I voted no around the depression, because I think the
4 depression wording needs to be clarified for the
5 pediatricians, the SI, hallucinations and delusions
6 should be clarified for the patient portion of the
7 information, and I would defer to Dr. Mink and Dr.
8 Towbin on the EPS.

9 I also wanted to make a general comment: As
10 you are revising in the stimulant class in general, a
11 chart of equivalent dosing would be really helpful for
12 pediatricians, given the long-acting drugs now that are
13 on the market. And what do parents do in the case of a
14 mis-dose, especially with the long-actings and the XRs?
15 And what are acceptable carriers for parents? Apple
16 sauce is the one that's been studied and if that's the
17 only choice then that should be so called out.

18 DR. MINK: John Mink. I voted no for reasons
19 already stated.

20 DR. BHATIA: Jatinder Bhatia, voted no.

21 DR. FRANCO: Israel Franco. I voted no. I
22 agree with Dr. Reed's contention that the warnings

1 should be made available regarding suicidal ideation.

2 DR. HILLARD: Paula Hillard. I voted no,
3 related to the reasons stated by my colleague.

4 DR. WALKER: Leslie Walker. I voted no in
5 relation to the previous-stated comments.

6 DR. FELNER: Eric Felner. I voted no, really
7 centering around the comorbidity of adding depression to
8 the warning.

9 DR. RAKOWSKY: Alex Rakowsky, voted no. Again
10 just to echo what Dr. Santana mentioned, we can come up
11 with maybe a list at the very end of our concerns.

12 DR. WHITE: Michael White. I voted no, and I
13 appreciate the efforts of the FDA to revise the labeling
14 for all amphetamines. Thank you.

15 CHAIRMAN ROSENTHAL: Yes?

16 DR. LOUGHREN: This is Tom Loughren. That's
17 very helpful. I must say that I'm still somewhat
18 puzzled about the focus on suicidal ideation. Again, as
19 was pointed out earlier, we did a pooled analysis of all
20 the ADHD trials looking for a signal for treatment-
21 emergent suicidal ideation and found none. There was
22 nothing coming out of the controlled trials.

1 Again, these drugs are very, very widely used
2 and what you're seeing here is a handful of reports that
3 are very difficult to interpret individually with regard
4 to causality and are always incomplete. You never
5 really know what was happening with that child. It
6 might have another comorbid disorder that wasn't
7 identified or taking other medications. Very difficult
8 to know what to do with that, and I would be very
9 reluctant to strengthen the labeling, implying that
10 there's some link to treatment-induced suicidality when
11 we see none.

12 CHAIRMAN ROSENTHAL: Dr. Goldstein?

13 DR. GOLDSTEIN: Brahm Goldstein. My concern
14 is that depression and suicidality are comorbidities
15 that are known to occur with this disease, and I don't -
16 - I haven't seen any data that suggests that adding the
17 medication either potentiates it or results in a new
18 diagnosis. So I'm wondering if -- I actually have
19 personal experience with a son who went through this,
20 and the depression and the suicidality were there prior
21 to starting therapy. So my concern is -- and actually
22 therapy made things better.

1 confusing the horse and the barn, so to speak.

2 CHAIRMAN ROSENTHAL: All right. So let's go
3 ahead and just -- we've sort of touched on the first
4 bullet, but let's go ahead and specifically vote on this
5 first bullet as well, and then we can just go through
6 the list of themes that emerge from the discussion.

7 So the FDA is recommending adding angioedema
8 and anaphylaxis to the labeling. All who support that
9 please raise your hands.

10 (A show of hands.)

11 CHAIRMAN ROSENTHAL: Any opposed?

12 (A show of hands.)

13 CHAIRMAN ROSENTHAL: Any abstentions?

14 (No response.)

15 CHAIRMAN ROSENTHAL: All right. Let's go
16 around the table and please tell us your vote, and feel
17 free to explain your vote if that would be useful. Dr.
18 White.

19 DR. WHITE: Michael White. I voted yes
20 reluctantly, because it's my impression that any drug
21 can cause angioedema and anaphylaxis, and this is a very
22 incidence that we've seen it. But it's always good to

1 have that norm.

2 DR. RAKOWSKY: Alex Rakowsky. I voted yes.
3 It looks like some of the methylphenidate labels already
4 have it in there, and there is a move on the division's
5 part to make it consistent throughout. So I think for
6 these drugs consistency is important.

7 DR. FELNER: Eric Felner. I voted -- I voted
8 no, for the same reason that Dr. White voted yes. I
9 mean, there's a low incidence of it and I think when you
10 speak of medications and anaphylaxis they go hand in
11 hand with any medicine you take.

12 DR. WALKER: Leslie Walker. I voted yes.

13 DR. HILLARD: Paula Hillard. Yes.

14 DR. FRANCO: Israel Franco. Yes.

15 DR. BHATIA: Jatinder Bhatia. Yes.

16 DR. MINK: John Mink. Yes.

17 DR. WIEFLING: Bridgette Wiefling. Yes.

18 DR. BAKER: Susan Baker. No, but I would
19 defer to the FDA. If in the review of all of these
20 drugs of this classification you thought that that was
21 an important item to add, I would defer to your
22 expertise.

1 DR. KAPLAN: Shelly Kaplan. Yes.

2 DR. CASTILE: Bob Castile. Yes.

3 MS. EICHNER: Marilyn Eichner. Yes.

4 DR. WRIGHT: Joseph Wright. Yes.

5 DR. KRISCHER: Jeff Krischer. Yes.

6 DR. TOWBIN: Kenneth Towbin. Yes, concurring
7 with Dr. Rakowsky.

8 DR. WAGENER: Jeff Wagener. Yes.

9 DR. MOTIL: Kathleen Motil. Yes.

10 DR. DRACKER: Bob Dracker. No. I think this
11 is an isolated case. I think this is a diagnosis which
12 is a significant red flag for physicians who are
13 prescribing medications, and I feel there is inadequate
14 information both clinically and with regards to the
15 evaluation of the particular patient.

16 DR. SANTANA: Victor Santana. I voted yes.

17 DR. REED: Michael Reed. Yes.

18 CHAIRMAN ROSENTHAL: All right. So rather
19 than reiterate all that's in the record, I'll just hit
20 on a few themes. It seems like there is agreement that
21 the -- agreement and support that the agency is
22 reassessing and is reconsidering some of the labeling

1 around Focalin and Focalin XR.

2 The topics that have come up, there's been
3 some discussion with mixed response regarding addition
4 of labeling to describe angioedema and anaphylaxis, but
5 it seems like there's a willingness to defer to the
6 agency's expertise around how to handle that issue.

7 Other conversations that have come up have
8 included the development, further development, and
9 detailing of the extrapyramidal symptoms section to
10 include more broadly some discussion of some of the
11 muscle movement disorders that have been observed in
12 these adverse event reports.

13 You've heard some concerns about suicidal
14 ideation and you've heard reasons why perhaps we should
15 not be so concerned about suicidal ideation in a small
16 subset of reports that we've seen. And I think you've
17 heard a request for some clarification regarding
18 hallucination and psychosis in the label.

19 Lastly, I think the committee would benefit
20 from seeing the end product of this process at some
21 point. It is difficult to make recommendations during
22 these meetings and then not -- and then not sort of

1 close the loop. So I think that would be very helpful
2 in terms of the organizational learning of the Pediatric
3 Advisory Committee.

4 DR. MURPHY: Unless we hear otherwise, when
5 you asked for that follow-up, we have a couple
6 mechanisms. One is that we simply send it to you and
7 say: This is the follow-up you've requested. That --
8 I'm taking that as what you're asking.

9 The other is that we bring it back to the
10 committee as a whole in public and present it the
11 follow-up. So if I'm misinterpreting what you're
12 asking, you need to let us know, because I interpreted
13 that you just wanted us to send it to you. Do you want
14 us to bring it back for any further comment?

15 DR. MINK: Just one question. If you send it
16 to us as follow-up information and for some reason we
17 are not happy with that, is there a mechanism to then
18 assure -- or does it require some kind of threshold of
19 disagreement to bring it back before the committee?

20 DR. MURPHY: I think what we would do is we
21 would look at the individual -- as I've said, we've done
22 this both ways. There's always the opportunity for

1 people to send us comments back. Then if it's obvious
2 that we need to bring it back, we will. Sometimes we
3 receive comments that don't require that.

4 Tom wants to add something.

5 CHAIRMAN ROSENTHAL: Dr. Loughren?

6 DR. LOUGHREN: Yes, this is Tom Loughren.

7 We'd be happy once we finish that process to come back
8 and give a brief update on where the changes are in the
9 label and the basis for them. That wouldn't be a
10 problem from our standpoint.

11 DR. MURPHY: So that's what I'm asking: Is
12 the committee comfortable with us just sending it or do
13 you prefer that you have this as an update? I mean,
14 those are the options, to publicly present it to.

15 CHAIRMAN ROSENTHAL: Quick vote: How many
16 people would be happy just receiving it as an email and
17 how many people would prefer to hear -- review the
18 changes and hear a brief rationale for why the changes
19 were made or were not made? All in favor of the email
20 approach, please raise your hands?

21 (No response.)

22 CHAIRMAN ROSENTHAL: I think you have your

1 answer.

2 (Laughter.)

3 DR. MURPHY: That was visually clear. Thank
4 you.

5 CHAIRMAN ROSENTHAL: Okay, I'll clarify for
6 the record that no hands went up for choice A. So we'll
7 ask that the agency present the new label along with
8 some very brief presentation and discussion of why
9 changes -- where changes were made and why they were,
10 and in cases where the agency felt that changes were
11 best not made, that those be explained as well.

12 Thank you very much.

13 All right, let's move forward. So, Dr. Sachs
14 will also be presenting Daytrana. Dr. Sachs.

15 DAYTRANA (METHYLPHENIDATE)

16 STANDARD REVIEW OF ADVERSE EVENTS

17 (Screen.)

18 DR. SACHS: Thank you for that discussion. So
19 we'll turn to Daytrana, where you're going to see that
20 several of these issues arise again.

21 (Screen.)

22 This outline will become very familiar.

1 (Screen.)

2 Originally approved in 2006 in patients 6 to
3 12 years of age, Daytrana's safety review was triggered
4 by a labeling change related to a PREA requirement that
5 expanded the indication to adolescents.

6 (Screen.)

7 For initial approval, efficacy in younger
8 children was based on two randomized double-blind,
9 placebo-controlled trials.

10 (Screen.)

11 One of these was a dose optimization analog
12 classroom study in 158 children and the second study was
13 an outpatient placebo- and active-controlled using
14 Concerta, or methylphenidate extended release, in 270
15 children.

16 (Screen.)

17 Similarly, in response to the PMR to evaluate
18 adolescents, the sponsor conducted a randomized, double-
19 blind, placebo-controlled outpatient flexible dose study
20 in 270 adolescents. The trial found that there was a
21 statistically significant improvement in one of the
22 validated scales used to evaluate ADHD treatment.

1 (Screen.)

2 In July of 2006, as recommended by the
3 Pediatric Advisory Committee in March of that year, the
4 warnings and precautions section of the labeling was
5 expanded to include the cardiovascular adverse events --

6 (Screen.)

7 -- as well as the psychiatric adverse events,
8 such as psychosis, mania, and aggression. The
9 information about growth was added, along with a
10 clarification that stimulants do in general lower the
11 threshold for seizures.

12 (Screen.)

13 In addition to the expanded pediatric
14 indication, labeling has been updated to include some
15 skin reactions unique to the patch, as well as a lack of
16 drug interaction between clonidine and methylphenidate
17 products.

18 (Screen.)

19 These contraindications do really look similar
20 to those of Focalin and there is a contraindication
21 regarding hypersensitivity in this labeling.
22 Anaphylaxis and angioedema is described in the post-

1 marketing section.

2 (Screen.)

3 Turning to the warnings and precautions, I'd
4 just like to draw your attention to the two warnings
5 that are somewhat unique to the patch. You can have
6 contact sensitization as well as if patients use extra
7 heat that significantly increases the absorption rate
8 and potentially systemic exposure adverse events.

9 (Screen.)

10 Once again, to put the adverse events you're
11 going to see in context, let's look at the use. You can
12 see that this product is also widely used in the
13 prescription population. About 90 percent of the
14 prescriptions are given to patients, prescription
15 patients, and a majority of these are school-age
16 children as well.

17 Once again, you can see there is about a 6.5
18 percent of off-label use in patients less than 6. And
19 if you're trying to add these numbers and have them sum
20 to 100, they won't because the kids age.

21 (Screen.)

22 This slide graphically looks at the use of all

1 the methylphenidate products, and you can see that
2 Concerta is in the top spot in 2010 and Daytrana was
3 number five.

4 (Screen.)

5 Similar to Focalin, the top prescribers are
6 the pediatricians and psychiatrists, and the top
7 diagnosis code is, unsurprisingly, ADD.

8 (Screen.)

9 So keeping these in mind, let's look at the
10 adverse events. Paralleling the use, you can see that
11 the majority of them, about half I guess, are in
12 pediatrics, and 157 of these are serious and there were
13 two fatalities.

14 (Screen.)

15 The 145 adverse events that comprise the case
16 series that we examined are derived as follows. We took
17 the 157 reports, including the two deaths, and there
18 were two reports that were excluded, and that left us
19 with 145 -- I'm sorry. There were ten reports, ten
20 duplicates that were excluded, leaving us with 145.

21 (Screen.)

22 Once again, most of these serious adverse

1 events occurred in 6 to 11-year-old males with the
2 diagnosis of ADHD. These again were mostly U.S. cases,
3 except for one, and their duration of therapy ranged
4 from one day to two years, with a median of a little
5 more than a month.

6 Looking at the fatal adverse events, one was a
7 completed suicide in a 14-year-old female who had been
8 treated with a variety of stimulants. As you've seen
9 from the previous review, suicide, although rare, is not
10 unheard of.

11 The second adverse event occurred in an 8-
12 year-old female who was treated with 10 milligrams of
13 Daytrana, had itching and redness that resolved, but
14 then died. Unfortunately, there was no clinical
15 information in this case and this report came to the
16 agency over five years after it occurred, which means we
17 couldn't really obtain any follow-up.

18 (Screen.)

19 If we look at the remaining 143 non-fatal
20 serious adverse events, you can see the breakdown.
21 Again, they are primarily neuropsych or neuromuscular.
22 17 were related to cardiovascular, 10 related to growth

1 disturbance or weight loss, and then 4 cases of
2 insomnia, and there's really a number of miscellaneous
3 events.

4 (Screen.)

5 I'll do it the same way. We'll focus mostly
6 on the unlabeled adverse events. If you look at the
7 unlabeled events again, you'll see suicidality comes up.

8 Then there is a handful of events related to
9 confusional states, paranoia or abnormal behavior.

10 (Screen.)

11 First let me look at the adverse events
12 related to suicidality. There were two patients that
13 had possible suicide attempts. One was a six-year-old
14 male, who did put a cord around his neck when a 20-
15 milligram patch was placed, and his suicidal thoughts
16 resolved when the patch was discontinued, and then they
17 recurred when it was rechallenged again at that dose,
18 but resolved when the dose was lowered.

19 Then there was a nine-year-old female who had
20 bipolar disorder, anxiety, and aggression, who did have
21 a past history of suicide attempts. A suicide attempt
22 was reported without any detail in the report.

1 (Screen.)

2 Six of the reports also do describe suicidal
3 ideation and three of them did resolve once the Daytrana
4 was discontinued. In this group of reports, all three
5 of these and the three remaining did have possible
6 confounders: family history or depression or
7 concomitant medicines also labeled for suicidality.

8 Then there was a report of a self-injury where a
9 young man cut his face with a pair of scissors, and an
10 11-year-old that was hospitalized for being a "danger to
11 herself," but she was not considered to be suicidal.

12 As you've heard, the same scenario kind of arises.
13 Even though suicide is unlabeled, the reports are
14 really rare considering the use.

15 (Screen.)

16 There were two adverse events related to
17 confusional states or disorientation. One was a six-
18 year-old male and another a ten-year-old female, and
19 both of these patients needed a visit to the emergency
20 room or urgent care clinic, with a resolution of the
21 events. Related labeling does include hallucinations as
22 well as a warning about the behavioral changes.

1 (Screen.)

2 There was a nine-year-old who developed
3 paranoia with what seems to be a fairly extremely
4 irrational fear of snakes, that persisted after Daytrana
5 was discontinued. Although paranoia is again not
6 specifically described in labeling, it is -- agitation,
7 anxiety, is one of the contraindications and
8 hallucinations is outlined in the post-marketing
9 section.

10 (Screen.)

11 Then the last two unlabeled neuropsych events
12 revolve around some abnormal behavior: one patient who
13 had some kind of funny eating behaviors, but these
14 events resolved even with continued treatment. And then
15 there was an 11-year-old who had some trichotillomania
16 some time after starting the Daytrana.

17 (Screen.)

18 So if we look at the neuromuscular adverse
19 events, the pattern seems a little bit familiar to what
20 you heard with Focalin. There were seven reports
21 related to neuromuscular events and, although tics and
22 dyskinesia are labeled, the EPS symptoms are not.

1 (Screen.)

2 Here I give you a little more details of the
3 dystonia. You can see that there was a six-year-old
4 male who did indeed have a positive challenge,
5 dechallenge, and rechallenge, but he was on olanzapine,
6 which is labeled, of course, for dystonia.

7 There was a seven-year-old male who required
8 hospitalization with dystonia, akathisia and elevated
9 blood pressure, and of course the impact of his blood
10 pressure on events is not really clear. Then
11 lastly, there was a five-year-old who had some
12 involuntary tongue protrusion.

13 (Screen.)

14 The remaining 19 neurological events are
15 labeled, 18 related to a seizure and one to a stroke.
16 The breakdown of the 17 cardiovascular events are
17 provided on this slide and you can see all of them are
18 labeled, including chest pain, syncope, tachycardia, and
19 asystole.

20 (Screen.)

21 Ten patients experienced growth disturbance or
22 weight loss and all of these are labeled events.

1 (Screen.)

2 Four patients experienced insomnia, which is
3 described in adverse reactions, but one of these
4 patients received three times the recommended dose of
5 Daytrana and the others were taking concurrent medicines
6 that are associated with insomnia.

7 (Screen.)

8 Again, the remaining adverse events fall in
9 the miscellaneous category. About half of these,
10 application site reactions and quality issues and
11 adhesive products, or problems, are unique to the patch
12 and are actually known. 31 remaining really didn't seem
13 to show a pattern and were single cases and, although
14 there were two cases of anaphylaxis, the labeling does
15 have that contraindication and a listing of anaphylaxis
16 in the post-marketing section.

17 (Screen.)

18 This concludes the pediatric safety review for
19 Daytrana. The PREA studies resulted in an expansion of
20 the indication to adolescents. We actually didn't
21 detect any new safety signals, and recommend continued
22 monitoring. We'd be interested to hear your discussion,

1 which I imagine will be very similar to the Focalin.

2 (Screen.)

3 CHAIRMAN ROSENTHAL: Thank you.

4 Comments? Dr. Towbin.

5 DR. TOWBIN: Well, I just have one question,
6 which may be a bit arcane. But some of us are very
7 interested in what happens with transdermal
8 administration devices in the MRI environment. Now,
9 Daytrana happens to be one of those that we understand
10 is safe, but I was wondering whether the agency has any
11 consideration about adding language for these kinds of
12 devices that would make clear what the safety of a patch
13 would be in an MRI environment, since some are and some
14 are not?

15 I don't know whether there's any obligation
16 about that, but it is something that comes up as a
17 safety problem. Some of the patch materials have
18 metallic fibers in them and they can heat up and cause
19 burns. So I think about this as being akin to a drug-
20 drug interaction. It just happens to be a device-device
21 interaction. I was just curious whether there was any
22 thought about adding those kinds of things to the labels

1 or if that's an issue.

2 CHAIRMAN ROSENTHAL: Dr. Loughren.

3 DR. LOUGHREN: It's something that hadn't
4 occurred to me before. I don't think there's any metal
5 in these patches, but we'll look into it.

6 DR. HAUSMAN: Ethan Hausman from FDA. There
7 was recently an FDA-DIA-sponsored transdermal patch
8 conference, I believe last September. I don't have the
9 agenda here on hand right now, but I believe that was
10 one of the discussion points at one of the breakout
11 groups. I can't comment on anything that's being done
12 about it, but please remind us to keep it on the radar.

13 DR. MURPHY: We'll follow up with our derm
14 people, because we don't have any of them here,
15 dermatology group. But it sounds like they already are
16 aware of this and already are looking into it. But
17 we'll make sure they get your comments.

18 CHAIRMAN ROSENTHAL: Doctors Santana and
19 Dracker.

20 DR. SANTANA: It's Victor Santana. I was
21 looking at the number of patients exposed and the number
22 of prescriptions for the previous product, Focalin, that

1 had 167 events. Then this product had a much smaller
2 population of people exposed to the agent, half a
3 million, with 2.8 prescriptions, but there were a
4 similar number of events.

5 Now, granted they appear to be in the same
6 profile class of events. But can you comment on the
7 limitations of my interpretation where I get a sense
8 that there's more events with this product, or are there
9 other reasons that I'm not quite understanding of why
10 this product would appear to have more events associated
11 with it?

12 DR. SACHS: The pattern, reporting pattern of
13 adverse events, is interesting and sometimes we see a
14 lot more adverse events right after a product is
15 launched. So sometimes that can account for it because
16 you're seeing the more recent. The OSE, Vicky, you can
17 correct me, but I think a lot of these also are related
18 to the patch itself.

19 DR. MURPHY: Do we have any expertise to talk
20 about whether the exposure peaks are any different in
21 any way?

22 DR. HUANG: Vicky Huang. Dr. Sachs is

1 correct. Actually, in 2011, last year, we received a
2 large influx of reports and primarily regarding the
3 application site reactions, which is an issue that the
4 agency is aware of and we're working on this issue.

5 DR. SANTANA: To follow up, so a large
6 proportion of this numerical difference is related to
7 these transdermal issues in terms of skin effects and
8 things like that? Is that what you're saying?

9 DR. HUANG: Yes. As you can see, the serious
10 pediatric reports, it's only 157 reports, whereas the
11 total is 968. So the majority of these were non-serious
12 and a large number of them were related to the patch
13 issue.

14 DR. SANTANA: But that's precisely my point,
15 that the "Serious" number column here is very similar to
16 the "Serious" number column of the previous product. So
17 it's not because of the dermatological effects that the
18 number proportionally looks different.

19 DR. HAUSMAN: That's correct.

20 DR. WARD: Bob Ward. I just want to caution
21 about trying to make the AERS quantitative. A little
22 publicity and suddenly reports come in and things, I

1 don't know, can be disproportionate.

2 DR. MURPHY: I think it's an interesting
3 question, though, is is there anything about the
4 pharmacokinetic or rate-peak curve, anything like that,
5 that would be different. I'm sure people looked at this
6 carefully. We just don't have somebody here who can
7 answer that question for you. But we will go back and
8 follow up on that.

9 CHAIRMAN ROSENTHAL: Dr. Dracker.

10 DR. DRACKER: There are two issues regarding
11 this product. First is the fact that the greatest
12 difficulty for clinicians is appliance. There is a
13 fairly significant incidence of local discomfort and
14 problems with it, and we're unsure as to whether they
15 are using the product properly.

16 The second issue is with regards to the
17 application time. We have a great deal of difficulty in
18 how long it stays on and if the parents are diligent
19 about taking it off when they're supposed to, because
20 there is additional drug in it and leaving it on for
21 extended periods of time can result in greater drug
22 delivery.

1 CHAIRMAN ROSENTHAL: Dr. Wiefling.

2 DR. WIEFLING: Not to bring it back too much
3 to the last conversation, but I did want to point out
4 two things. The paranoia is I think adequately
5 addressed in its description. It doesn't say
6 "paranoia," but -- on page 23, and I think they've done
7 a good job. And that's the kind of language that I
8 would have liked to have seen in Focalin for the
9 parents.

10 Then on page 12 for the pediatrician it has
11 "Toxic Psychosis" listed under "Nervous System" and
12 under "Psychiatric" it just says "Transient Depressed
13 Mood." I think that that might be tweaked a little
14 because I don't think that totally represents what we
15 see.

16 CHAIRMAN ROSENTHAL: Yes?

17 DR. KRISCHER: Jeff Krischer. Having
18 participated in several of these, the presentations I
19 find always interesting. But from an epidemiological,
20 statistical point of view, I do think that the
21 presentations always dwell on the numerators, don't
22 dwell on the denominators. I think that it doesn't

1 either take into account duration of exposures.

2 So I would suggest for consideration by the
3 FDA that indeed one can report these in terms of
4 incidence rates and confidence intervals and one can
5 also look at the rates relative to duration of exposure.

6 That would put all this into context, because right now
7 we're reacting to just numerators and my colleague
8 Victor and I agree, it's hard to interpret what this
9 really means.

10 Not to make it too overly complex, but one
11 could certainly, given the incidence rates, indicate
12 what we would have in terms of 95 percent confidence
13 intervals of the expected or the observed adverse
14 reactions. That is to say, one could look at this and
15 say that the rate -- we're 95 percent sure that the rate
16 is under .1 percent or some number like that, that would
17 give us some way to interpret these numerators.
18 Otherwise they're all being presented with the same
19 force of evidence in this type of presentation.

20 DR. MURPHY: From the beginning of this
21 committee, this has been the issue that we have
22 struggled with: How do you take -- provide any

1 denominator data. You have two disconnected pieces of
2 information. So I've asked Dr. McMahon, who was in our
3 Office of Epidemiology and spent the last couple years
4 trying to help us with this issue, to say what some of
5 the challenges are.

6 DR. McMAHON: Hi. This is Ann McMahon. I had
7 been in the Office of Surveillance and Epidemiology and
8 am now in the Office of Pediatric Therapeutics. Before
9 any of that, I was over in the Office of Biostatistics
10 and Epidemiology over at CBER.

11 So I've thought about and talked a lot about
12 this topic with a number of different people. I don't
13 pretend to have the answer at all, but I can tell you a
14 little bit about the kinds of conversations that I've
15 had. I think the thing about these passive surveillance
16 systems -- and this is true of the Vaccine Adverse Event
17 Reporting System and the Adverse Event Reporting System
18 -- is that the numbers are extremely imprecise, as
19 somebody was alluding to just now.

20 I think the reason that we do not in general
21 at the FDA present these kinds of information as linked
22 to duration of use and confidence intervals are several.

1 One of them is that the information in the numerator,
2 that is the number of reports themselves, is very
3 imprecise and subject to a lot of publicity, various
4 different types of -- because it's passive reporting, is
5 subject to various different types of changes that are
6 spontaneous.

7 The other is that the denominator, as Dr.
8 Murphy mentioned, is not linked to the reporting system
9 itself. So we're not really sure that the number of
10 people that we're putting in our denominator are exactly
11 those people that are relevant to the numerator.

12 So for those reasons and several more, we
13 generally don't put confidence intervals around our
14 numbers or make them incidence rates, because we don't
15 feel that they really can be called such. But that's
16 not a -- it's not the be-all and end-all answer, but
17 that is a general sense of what the discussions have
18 been at the FDA.

19 DR. MURPHY: I guess what you're hearing is
20 that people have really thought about this a lot and
21 tried to figure a better way, and we've been doing this
22 now since, I don't know, 2002 and we struggle with the

1 committee trying to give more precision to imprecision.

2 And I think we've come to the conclusion that we'd
3 rather not dress it up as something it's not, because we
4 can't.

5 Adverse event reporting, we've even gone back
6 and tried to find where that original estimate -- we get
7 a tenth maybe of the reports. Then you saw what we get
8 when we get them. So trying to make it more than it is,
9 as Dr. Ward said, is something that we're hesitant to
10 do. So that's what you're hearing from us.

11 We understand the frustration of the committee, but
12 that's why we bring a bunch of you together, to
13 basically say, this is what we think the limitations
14 are; despite all that, we still think from an informing
15 point of view it would warrant saying something
16 differently than you do, or we think, based on the
17 limitations of the data, you shouldn't do anything more
18 at the time until you get better data.

19 And you've done, the committee's done that
20 with a variety of products. We've been through the
21 SSRIs and many other analyses. We're doing that with
22 the metabolic syndrome. We look at this process as

1 signal-generating, that we then we bring to the
2 committee to have you give us your ideas. And if you
3 can be certain about something and you feel very
4 strongly, it's an opportunity to say that.

5 So yes, we wish we could come up with a better
6 metric for it.

7 CHAIRMAN ROSENTHAL: So I think the committee
8 will be -- it will be fun when we reach the point that
9 was described in Dr. Spielberg's vision, where we
10 actually are able to link some of these things more
11 directly and infer, make stronger inferences from the
12 observations that we have.

13 All right. Well, if there aren't other
14 comments, let's go ahead with this --

15 DR. MURPHY: Geof, just one other thing. I
16 think, Mitch Mathis, did you want to point out to them
17 where some of this information on the differences in the
18 pharmacokinetics are available between the patch and
19 others?

20 DR. MITCH MATHIS: Mitch Mathis. Well, it's
21 in the labels in section 12 for both of them. You can
22 see the pharmacokinetics are quite different between the

1 patch and the extended release formulation, the Focalin
2 that we just talked about. For one thing, it looks like
3 you don't get the same levels of what we would consider
4 efficacious until much later with the patch. Then, as
5 was pointed out, it's important to take the patch off
6 when it's supposed to come off because those levels stay
7 up for a while.

8 I just wanted to make the point that all that
9 information is in the labeling and if you compare the
10 two you can see those differences.

11 CHAIRMAN ROSENTHAL: Thank you, Dr. Mathis.

12 All right. Other comments before we move
13 ahead with addressing the question before us?

14 (No response.)

15 CHAIRMAN ROSENTHAL: All right. So the FDA is
16 recommending continued routine monitoring for Daytrana
17 and the question is does the committee concur. All in
18 favor, please raise your hands.

19 (A show of hands.)

20 CHAIRMAN ROSENTHAL: Thank you. Any opposed?

21 (No response.)

22 CHAIRMAN ROSENTHAL: Any abstentions?

1 (No response.)

2 CHAIRMAN ROSENTHAL: All right. Let's go
3 around the room. Dr. White, will you get us started.

4 DR. WHITE: I voted yes. I would like you to
5 take into consideration the previous comments on
6 methylphenidate, and also would you please consider,
7 reconsider, the classification of eating erasers as
8 normal developmental behavior? Dr. Rakowsky and I would
9 appreciate that.

10 DR. RAKOWSKY: Rakowsky, concur. And yes, I'm
11 a former eraser eater.

12 (Laughter.)

13 DR. FELNER: Eric Felner, yes.

14 DR. WALKER: Leslie Walker, yes.

15 DR. HILLARD: Paula Hillard, yes.

16 DR. FRANCO: Israel Franco, yes.

17 DR. BHATIA: Jatinder Bhatia, yes.

18 DR. MINK: John Mink, yes.

19 DR. WIEFLING: Bridgette Wiefling, yes.

20 DR. BAKER: Susan Baker, yes.

21 DR. KAPLAN: Shelly Kaplan, yes.

22 DR. CASTILE: Bob Castile, yes.

1 MS. EICHNER: Marilyn Eichner, yes.

2 DR. WRIGHT: Joe Wright, yes.

3 DR. KRISCHER: Jeff Krischer, yes.

4 DR. TOWBIN: Kenneth Towbin, yes.

5 DR. WAGENER: Jeff Wagener, yes.

6 DR. MOTIL: Kathleen Motil, yes.

7 DR. DRACKER: Bob Dracker, yes.

8 DR. SANTANA: Victor Santana, yes.

9 DR. REED: Michael Reed, yes.

10 CHAIRMAN ROSENTHAL: All right. Time for a
11 break. All in favor?

12 (Laughter.)

13 CHAIRMAN ROSENTHAL: Quickly before we break,
14 let's come back in 15 minutes. According to my watch,
15 it is 25 after, so let's start at 20 of, just to get a
16 jump on the second session of the morning.

17 I'd just like to remind people to please not
18 discuss the workings of the meeting or the topics of the
19 meeting on the break. We need all comments and
20 reflections entered into the record. So thank you very
21 much.

22 (Recess from 10:24 a.m. to 10:41 a.m.)

1 CHAIRMAN ROSENTHAL: Let's go ahead and get
2 started. For the late morning session, we'll be talking
3 about Seroquel, and Dr. Beth Durmowicz will be
4 presenting. She received -- and I'm just going to give
5 her a short introduction. She received her medical
6 degree from the University of Cincinnati College of
7 Medicine and completed her internship and residency at
8 the University of Colorado Health Sciences Center. Her
9 area of clinical practice is children and youth with
10 special health care needs. We're happy to have Dr.
11 Durmowicz present to us today. Thank you.

12 Thank you very much.

13 Oh, and the other thing that I need to just
14 comment or put into the record is that Dr. Franco is
15 recused from discussion of Seroquel, and it looks like
16 he's not at the table.

17 SEROQUEL (QUETIAPINE FUMARATE)

18 STANDARD REVIEW OF ADVERSE EVENTS

19 DR. DURMOWICZ: All right. Good morning.

20 (Screen.)

21 I will be presenting the pediatric focused
22 safety review for Seroquel.

1 (Screen.)

2 The presentation will follow the commonly used
3 outline that we've used in other advisory committee
4 presentations. In addition, I'll be briefly presenting
5 two of the previous safety reviews and advisory
6 committee discussions.

7 (Screen.)

8 Seroquel, quetiapine fumarate, is applied as
9 an oral tablet preparation and available in six
10 different strengths. The product is an atypical
11 antipsychotic marketed by AstraZeneca. Of note, there
12 is also an extended release formulation of quetiapine,
13 Seroquel XR, which is approved for use in adult
14 patients.

15 (Screen.)

16 This product does have PREA PMR to study
17 schizophrenia and bipolar mania and depression.
18 Although the focus of this review is the immediate
19 release formulation, the safety review covers all
20 reports for quetiapine fumarate.

21 (Screen.)

22 Seroquel is approved for the treatment of

1 schizophrenia in adult and pediatric patients 13 to 17
2 years and for the treatment of bipolar mania in adult
3 and pediatric patients 10 to 17 years. Additional
4 indications approved in adults include the treatment of
5 bipolar depression and maintenance treatment of bipolar
6 disorder.

7 A PREA post-marketing requirement is
8 outstanding for the bipolar depression indication. When
9 the data to satisfy this PREA PMR are submitted and
10 reviewed, a pediatric labeling change will occur and a
11 pediatric focused safety review and Pediatric Advisory
12 Committee presentation will occur one year after that
13 labeling change.

14 (Screen.)

15 Quetiapine was originally approved in
16 September 1997 and pediatric exclusivity was granted in
17 January 2009. The pediatric labeling changes occurred
18 in December 2009 and resulted from data submitted from
19 studies requested under BPCA as well as studies required
20 under PREA.

21 (Screen.)

22 The efficacy of Seroquel use in the treatment

1 of Seroquel use in the treatment of schizophrenia in
2 pediatric patients was established in a six-week,
3 double-blind, placebo-controlled study of two doses of
4 Seroquel. 147 patients were treated with Seroquel. As
5 you can see, the numbers were approximately equally
6 distributed between the low and high dose groups. This
7 study was requested under BPCA.

8 (Screen.)

9 The efficacy of the Seroquel in the treatment
10 of bipolar mania in pediatric patients was established
11 in a three-week study. This study was also double-
12 blind, placebo-controlled, and compared two doses of
13 schizophrenia to placebo. 193 patients were studied and
14 again the numbers were approximately split between the
15 two dosing cohorts. This study was requested under BPCA
16 and required under PREA.

17 (Screen.)

18 Safety data were collected during the two
19 efficacy studies and in an open-label, 26-week trial
20 which enrolled patients with both schizophrenia and
21 bipolar disorder. Of the 381 patients enrolled in the
22 long-term study, a little over 60 percent completed the

1 study.

2 Safety assessments included physical
3 examination, vital signs, weight, BMI, EKG, laboratory
4 evaluations, and assessments of extrapyramidal symptoms.

5 (Screen.)

6 No deaths occurred in the clinical trials and
7 the incidence of serious adverse events were deemed to
8 be similar between the quetiapine and placebo-treated
9 patients. The majority of the serious adverse events
10 were potentially related to the underlying psychiatric
11 diagnosis. With the exception of increases in pulse and
12 blood pressure, the common adverse events identified in
13 the pediatric patients were similar to those seen in the
14 adult patients.

15 (Screen.)

16 This table enumerates the incidence of
17 treatment-emergent adverse reactions that occurred
18 during the efficacy trials in 5 percent or more of
19 Seroquel-treated patients and when the incidence in the
20 Seroquel-treated patients was at least twice that of
21 placebo patients.

22 As you can see -- and I'm going to try to use

1 the mouse -- the somnolence -- Is that showing up?
2 Somnolence and dizziness were the most common adverse
3 events in both trials, and these data were added to
4 labeling.

5 (Screen.)

6 As stated earlier, the studies identified
7 increases in vital signs. The mean change analysis
8 revealed an increase in supine and standing pulse and in
9 systolic and diastolic blood pressure in the quetiapine
10 groups. This table provides an example of the data and
11 provides the pooled data of clinically important shifts
12 in supine vital signs that occurred at any time during
13 the study. As you can see, the quetiapine groups were
14 associated with a greater percentage of patients with
15 elevations in supine pulse, supine systolic blood
16 pressure, and supine diastolic blood pressure.

17 (Screen.)

18 Multiple sections of the labeling were updated
19 with pediatric information from the trials. I'm going
20 to spend a fair amount of time discussing those labeling
21 changes as important data describing the adverse events,
22 especially the metabolic adverse events, were

1 incorporated.

2 (Screen.)

3 The new indications were added. In addition,
4 subsection 1.3 also states that pediatric schizophrenia
5 and bipolar 1 disorders are serious disorders with
6 diagnostic challenges. Medication therapy should be
7 initiated only after a thorough diagnostic evaluation
8 and careful consideration to medications, and that
9 medication should be part of an overall program that
10 includes psychological, educational, and social
11 interventions. Dosage and administration was also
12 updated to provide dosing recommendations for both
13 conditions.

14 (Screen.)

15 A number of labeling changes were made in the
16 warnings and precautions section of labeling. This
17 slide provides an overview. A children and adolescents
18 subheading was added to five of the subsections and a
19 new warning regarding increased blood pressure in
20 adolescents was also added. I will discuss the changes
21 to these subsections in more detail in subsequent
22 slides.

1 The cataract warning was changed from just
2 stating that lens changes have been observed in patients
3 to state that lens changes have also been observed in
4 adults, children, and adolescents.

5 (Screen.)

6 Subsection 5.4, hyperglycemia and diabetes,
7 added a children and adolescents subheading and provides
8 the incidence of the mean change in fasting glucose
9 levels for Seroquel and placebo-treated patients.
10 Labeling notes that there was no patient with baseline
11 normal or borderline fasting glucose that had treatment-
12 emergent blood glucose levels greater or equal to 126
13 milligrams per deciliter.

14 For section 5.5, hyperlipidemia, a children
15 and adolescents subheading was also added, and a table,
16 which is shown on the next slide, provides data on the
17 lipid profiles.

18 (Screen.)

19 This is table 4 from section 5.5 of labeling,
20 with the percentage of pediatric patients with changes
21 in total cholesterol, triglycerides, LDL cholesterol,
22 and HDL cholesterol. Now, as you can see, the Seroquel-

1 treated patients consistently had elevations of their
2 lipids compared to placebo.

3 (Screen.)

4 The weight gain subsection of labeling
5 provides weight increase data from the efficacy and
6 long-term clinical studies under a children and
7 adolescents subheading. The table on this side is from
8 labeling and provides the percentage of the patients in
9 the efficacy trial with weight gains 7 percent of their
10 body weight or greater in Seroquel and treated patients.

11 As you can see, this amount of weight gain was
12 identified in 21 percent of the Seroquel-treated
13 patients with the schizophrenia indication, compared to
14 7 percent in placebo; and this weight gain occurred in
15 12 percent of patients, Seroquel-treated patients, in
16 the bipolar treated patients, versus none in the
17 placebo. The higher weight gain observed in this study
18 may be due to the longer duration of that study in
19 schizophrenia. The mean change in body weight in
20 Seroquel-treated and placebo-treated patients is also
21 provided, as well as data from the long-term study,
22 which includes mean increase in body weight and the

1 percentage of patients that gained 7 percent or more
2 body weight.

3 (Screen.)

4 Subsection 5.5 was added to labeling and
5 provides the data from the efficacy and long-term trials
6 on blood pressure changes. The incidence of increases
7 in systolic blood pressure 20 millimeters of mercury or
8 greater and increases in diastolic blood pressure of 10
9 millimeters or greater in the Seroquel-treated patients
10 in the efficacy studies is provided. The warnings and
11 precautions also stated that blood pressure should be
12 measured at the beginning and during treatment.

13 (Screen.)

14 A children and adolescents subheading was also
15 added to hypothyroidism and hyperprolactinemia warnings
16 and precautions. Labeling provides the incidence of
17 potentially important shifts in thyroid and prolactin
18 levels in the Seroquel and placebo-treated groups.

19 (Screen.)

20 Moving on to the adverse reactions section of
21 labeling, a children and adolescents subheading was
22 added in the clinical study experience subsection and

1 notes that the data provided are derived from a clinical
2 study database of 1,000 pediatric patients, of which 677
3 were exposed to Seroquel.

4 The incidence of discontinuation -- the
5 incidence of discontinuation due to adverse reactions
6 and the adverse reactions associated with
7 discontinuation for quetiapine and placebo-treated
8 patients is provided, and the incidence was higher in
9 this Seroquel-treated patients. The commonly observed
10 adverse reactions are presented in labeling and text and
11 tabular format. I will present an example of the table
12 from labeling in the next slide.

13 Adverse events potentially related to the
14 increased dose are also provided and included dizziness,
15 dry mouth, and tachycardia.

16 (Screen.)

17 This table is table 12 from labeling and it
18 provides the incidence of adverse reactions that
19 occurred during the schizophrenia trial in 5 percent or
20 more of patients treated with Seroquel and the incidence
21 in patients treated with Seroquel was at least twice the
22 incidence in placebo-treated patients. As you can see,

1 in the schizophrenia trial somnolence was the most
2 common AE, followed by dizziness and then by dry mouth
3 and tachycardia.

4 A similar table is provided with data from the
5 bipolar study. In addition to these commonly seen
6 adverse events from the schizophrenia trial, the bipolar
7 trial also had fatigue, increased appetite, nausea,
8 vomiting, and weight increased as frequent events.

9 (Screen.)

10 Results from pooled data are also provided and
11 include the adverse reactions observed again in the 5
12 percent or greater of Seroquel patients and the
13 incidence in patients treated with Seroquel was at least
14 twice the incidence in placebo. A table provides the
15 incidence of approximately 25 adverse reactions for
16 which the incidence in patients treated with quetiapine
17 was 1 percent or greater than the incidence in patients
18 treated with placebo.

19 (Screen.)

20 Data regarding extrapyramidal symptoms are
21 also included in section 6.1, with data from the
22 controlled efficacy trials. The aggregated incidence of

1 EPS is provided and was increased in both studies. In
2 addition, adverse experience potentially associated with
3 EPS are provided in tabular format for both efficacy
4 studies, as you'll see in the next slide.

5 (Screen.)

6 This is table 15 from labeling, which provides
7 the adverse experiences potentially associated with EPS
8 in the schizophrenia efficacy trial. A similar table
9 provides data from the bipolar efficacy trial and, as
10 you can see, there was not a dose response identified in
11 either trial.

12 (Screen.)

13 The adverse reactions reported from the long-
14 term open label trial also provided -- these are
15 provided in labeling text. However, I presented the
16 data in tabular form on this slide. These are reactions
17 that occurred in 5 percent or more of Seroquel-treated
18 patients.

19 (Screen.)

20 Section 6.2, vital signs and laboratory
21 values, states that increases in blood pressure have
22 been reported with quetiapine use in children. Vital

1 sign data from the pediatric efficacy trials are
2 provided under a children and adolescents subheading.
3 For both the short-term efficacy studies, the incidence
4 of potentially clinically significant increases in heart
5 rate and the mean increase in heart rate are provided
6 for both doses of Seroquel and placebo.

7 (Screen.)

8 The pediatric use subsection previously just
9 stated that safety and efficacy were not established in
10 pediatric patients. Information was added to labeling
11 on the general adverse reactions in the pediatric
12 clinical trials compared to adult trials. The approved
13 and unapproved indications are identified with a brief
14 description of the trials supporting approval, and
15 differences in the PK in pediatric patients are noted.

16 (Screen.)

17 The children and adolescents subheading was
18 also added as section 12.3, pharmacokinetics, and
19 pediatric PK is described and compared to adult data.
20 The children and adolescents subheading was also added
21 to section 14.1 and 14.2 and these sections provide a
22 brief description of the clinical studies.

1 (Screen.)

2 Increased blood pressure in pediatric patients
3 was added to the patient counseling information and the
4 medication guide. In addition, potential side effects
5 with Seroquel use in pediatric patients is provided in
6 the medication guide. These were the most common
7 adverse events that we've discussed.

8 (Screen.)

9 Additional labeling that's relevant to the
10 safety review includes a boxed warning. Quetiapine has
11 a boxed warning stating the increased risk of suicidal
12 thinking and behavior in pediatric patients and young
13 adults taking anti-depressants for psychiatric
14 disorders.

15 (Screen.)

16 The product has 23 warnings and precautions.
17 Relevant warnings and precautions not previously
18 described are provided on this slide and the following
19 slide. The suicide warnings and neurologic,
20 hematologic, cardiac, and gastrointestinal warnings are
21 all relevant to findings from the safety review.

22 (Screen.)

1 Additional relevant safety data are provided
2 in the pregnancy subsection, overdose, patient
3 counseling, and medication guide.

4 (Screen.)

5 Moving on to our denominator, our drug
6 utilization review, an analysis of quetiapine use in the
7 outpatient retail setting was performed. During the 20-
8 month period from December 2009 through July 2011, over
9 20 million quetiapine prescriptions were dispensed to
10 over 3 million patients. Over 1.5 million prescriptions
11 were dispensed over 260,000 pediatric patients. Looking
12 at total market share, the Seroquel immediate release
13 tablets represent a little more than 80 percent of the
14 market share.

15 (Screen.)

16 This table provides estimated number of
17 patients who received a dispensed prescription for
18 quetiapine products stratified by patient age. So of
19 the over 3 million total patients, as you can see 8
20 percent were in the pediatric age group. Use in the
21 unapproved age group for Seroquel was 1.2 percent and
22 for Seroquel XR was less than 1 percent.

1 The top prescribing specialties for quetiapine
2 prescriptions are psychiatry and general practice-family
3 medicine. Pediatricians accounted for 1 percent of
4 Seroquel and less than 1 percent of Seroquel XR
5 prescriptions. Affective psychoses was the top
6 diagnosis code in pediatric patients for Seroquel in the
7 unapproved and approved age range, and bipolar affective
8 was the top diagnosis code in pediatric patients 10 to
9 17 years for Seroquel XR.

10 (Screen.)

11 Moving on to the pediatric safety reviews.

12 (Screen.)

13 Quetiapine approval for use in pediatric
14 patients was discussed at the Psychopharmacological
15 Drugs AC in June 2009. A review of the pediatric post-
16 marketing data for quetiapine since product approval was
17 performed and the safety profile of the pediatric
18 population was determined to be similar to that in
19 adults. No new safety signals were identified.

20 (Screen.)

21 For the Pediatric Advisory Committee in 2009,
22 to assess for a differential risk between drugs or age

1 groups a pediatric-focused safety review of
2 extrapyramidal symptoms, hyperprolactinemia, metabolic
3 effects, and precocious puberty of five atypical
4 antipsychotics, including quetiapine, was performed. An
5 increased report for metabolic effects in association
6 with olanzapine and quetiapine was identified in the
7 disproportionality analysis.

8 (Screen.)

9 In preparation for this advisory committee,
10 the AERS database was searched for adverse events
11 reports associated with quetiapine over the 20-month
12 period December 2009 through July 2011. The main focus
13 of the review was pediatric deaths and pediatric reports
14 of serious unlabeled adverse events. Serious adverse
15 events of interest included central nervous system,
16 metabolic, cardiac, and hematologic events.

17 As noted in the table, there are approximately
18 300 -- there we go -- 300 total pediatric reports,
19 approximately 220 of the reports were coded as serious,
20 and there were 37 reports of death.

21 (Screen.)

22 Looking more at the case selection, after

1 removing duplicate reports, reconciling null age death
2 values, 176 serious pediatric cases associated with
3 quetiapine use were identified. These included 19
4 deaths and 157 non-fatal serious post-marketing cases.

5 Looking at the characteristics of the events,
6 the adverse events were approximately equally split by
7 gender. Approximately 75 percent of reports in patients
8 within the 2 to 16-year age group were from patients in
9 the 12 to 16-year age group. The median daily dose
10 reported was 50 milligrams and the median duration of
11 therapy was 202 days.

12 (Screen.)

13 An outcome of death was reported in 19 cases
14 over the 20-month search period. Ten reports were
15 related to self-harm or drug misuse. Three reports were
16 related to cardiac adverse events and the causes of
17 death in the six fatal cases remaining were varied.

18 (Screen.)

19 In this slide and the following slides, just
20 as Hari did, I will underline the adverse events that
21 are not included in labeling. Looking more carefully at
22 the death cases, five reports of completed suicides were

1 identified. There were four in teenagers and one in a
2 seven-year-old. Three of the five suicide cases
3 reported autopsy results of drug poisoning with
4 quetiapine and-or other medications. One case reported
5 suicide by hanging and one report by coiling a shower
6 hose around the neck. All of these reports were
7 confounded by concomitant medications labeled for
8 suicidality and underlying disease. In addition,
9 labeling notes that underlying disorders are considered
10 the strongest predictors of suicide.

11 (Screen.)

12 Three cases were reported as toxicity to
13 various agents: a 15-year-old with a reported drug
14 poisoning with quetiapine resulting in cardiopulmonary
15 arrest; a report of quetiapine toxicity in a 13-year-
16 old, resulting in seizure, coma, and death; and a drug
17 poisoning with multiple medications in a 10-year-old
18 resulting in cardiopulmonary arrest.

19 (Screen.)

20 Two reports of overdose were identified: one
21 in a 12-year old who stopped breathing; and one in a 4-
22 year old. The reports did not specify which medications

1 were involved in the overdose.

2 (Screen.)

3 Three cases reported a cause of death related
4 to cardiac adverse events. The first case was that of a
5 cardiomyopathy in a 13-year-old that developed
6 subsequent to cessation of quetiapine. The second was a
7 heart attack in a 16-year-old; and the third was a
8 reported cardiac arrest at six weeks gestation secondary
9 to prenatal exposure.

10 (Screen.)

11 Of the remaining six death reports, two death
12 cases reported an unknown cause: a four-month-old
13 infant with a toxicology screen for quetiapine and
14 atropine; and an eight-year-old with ketoacidosis,
15 diabetes, and pancreatitis. There were also single case
16 reports for a patient with hepatic failure, multi-organ
17 system failure, neuroleptic malignant syndrome and QT
18 prolongation, and shock due to pancreatitis and diabetic
19 ketoacidosis.

20 (Screen.)

21 This slide presents a summary of the non-fatal
22 serious adverse events. As we mentioned, the OSE review

1 focused on neuromuscular, neuropsychiatric, metabolic,
2 and cardiovascular and hematologic events. As you can
3 see, the greatest number of reports were in the central
4 nervous system and metabolic categories.

5 (Screen.)

6 44 CNS events were identified. 24 of these
7 reports were reported as neuropsychiatric. Half of
8 these were suicidality and there were also four reports
9 of aggression and three reports of self-injurious
10 behavior ideation and two reports of hallucination.

11 Three unlabeled events, with one case each, were for
12 abnormal behavior, drug abuse, and obsessive-compulsive
13 disorder.

14 14 of the CNS events were reported as
15 neuromuscular, with four reports of a neuroleptic
16 malignant syndrome or a neuroleptic malignant syndrome-
17 like reaction, two reports of tardive dyskinesia.

18 Of the eight remaining single case reports,
19 there is one case with an unlabeled event. It was a
20 patient with muscle twitching, tic, and headache. Five
21 of these cases were confounded with associated
22 comorbidities and concomitant medications.

1 (Screen.)

2 Of the remaining six CNS reports, there were
3 three reports of loss of consciousness and one case each
4 of labeled events. Five of these six reports were
5 considered confounded.

6 (Screen.)

7 Moving on to the metabolic adverse events,
8 there were 44 cases of metabolic adverse events in the
9 pediatric patients associated with quetiapine use.
10 There were 29 cases of diabetes-associated
11 complications. 25 of 29 of these cases were complicated
12 with comorbidities and concomitant medications. There
13 were also weight changes identified in 12 of the cases.

14 One report identified a weight loss in a patient
15 receiving concomitant dextroamphetamine-amphetamine, but
16 the other reports identified weight gain. The median
17 time to weight gain was 202 days; the range of weight
18 gain, as you'll see on the next slide, was from 10 to
19 greater than 100 pounds; and eight reports identified a
20 concomitant medication labeled for weight gain.

21 (Screen.)

22 This is the table from the safety review which

1 provides the data on the reports of weight changes. As
2 you can see, the patient that was treated -- this is
3 kind of the fourth patient here -- with stimulants had a
4 43-pound weight loss in approximately one year, but
5 otherwise the weight gain really ranged from about 13.2
6 pounds in 7 weeks, 15.4 pounds over 2 months. It's
7 appearing the largest weight gain was over 100 pounds,
8 during May 2009.

9 (Screen.)

10 The three remaining metabolic serious adverse
11 events were two reports of hypoglycemia and a report of
12 hyperlipidemia. Hypoglycemia is an unlabeled event.
13 The first report was a 13-year-old who was diagnosed
14 with hypoglycemia in the emergency room with a post-
15 prandial glucose level of 62. That patient was
16 discharged from the emergency department and quetiapine
17 was continued.

18 The second patient was a 16-year-old with
19 depression who was hospitalized with depression and
20 hypoglycemia and decreased appetite.

21 The report of dyslipidemia was in a 15-year-
22 old taking 15 milligrams, 50, 5-0, of quetiapine, who

1 experienced markedly elevated lipid levels. The levels
2 were reported to normalize after discontinuation of
3 quetiapine.

4 (Screen.)

5 Nine reports of cardiac events were
6 identified. Eight of these cases were confounded by
7 comorbidities and-or medications labeled for cardiac
8 adverse events. Unlabeled events included cardiac
9 arrest, ventricular fibrillation, and ventricular
10 extrasystole.

11 Nine hematologic events were identified, each
12 of which had confounding findings. Unlabeled events
13 included one report each of methemoglobinuria and PT
14 time decreased.

15 (Screen.)

16 Of the other serious miscellaneous events,
17 there were seven gastrointestinal reports: six cases of
18 pancreatitis and one case of esophageal spasm in a
19 patient with cerebral palsy and a feeding tube. There
20 were five serious adverse events reports classified as
21 an injury, poisoning, or procedural complication. These
22 were two accidental ingestions and two intentional

1 overdoses. The general category identified two reports
2 of drug ineffective and unlabeled event.

3 (Screen.)

4 Other serious adverse event reports included
5 two endocrine cases, one of Cushing syndrome and one of
6 hypothyroidism. There were two reports of cataracts
7 identified and two reports of infection.

8 (Screen.)

9 So in summary, based on the pediatric clinical
10 trial data FDA has made extensive changes in the
11 quetiapine labeling. Labeling provides pediatric data
12 regarding the adverse metabolic effects of quetiapine
13 compared to placebo. We are continuing to review
14 additional data from clinical trials regarding pediatric
15 adverse events related to atypical antipsychotic use.
16 We recommend continuing routine, ongoing post-marketing
17 safety monitoring, and would be interested in your
18 discussion.

19 (Screen.)

20 I'd like to thank the following people for
21 their help with the presentation.

22 CHAIRMAN ROSENTHAL: Thank you, Dr. Durmowicz.

1 Any comments, questions? Dr. Wagener.

2 DR. WAGENER: I just had one question. As far
3 as pregnancy warnings, I assume that the 29 adverse
4 events in less than one-month-olds where the mother was
5 on the drug at the time. It seems like a fairly high
6 number of reported cases. I just wanted to make sure
7 that within the package insert there was some warning
8 about perinatal events on the fetus.

9 DR. HAUSMAN: Ethan Hausman. You are correct.
10 Those are transplacental events. I'll have to go back
11 and doublecheck the label about your second part of your
12 comment.

13 CHAIRMAN ROSENTHAL: Other comments, other
14 questions?

15 (No response.)

16 CHAIRMAN ROSENTHAL: Thank you, Dr. Felner. I
17 was discouraged because usually it's not a quiet
18 committee. So thank you.

19 DR. FELNER: Eric Felner. I was just going to
20 make a comment on some of the metabolic endocrine
21 issues. At least for a lot of those that were strung
22 together, at least listed initially, I think the

1 hyperglycemia and diabetes mellitus along with
2 hypothyroidism and hyperprolactinemia and weight gain, I
3 think we probably could -- we'll ask a cardiologist, but
4 I think we could probably lump some blood pressure in
5 there, too.

6 But so much of those are really related to
7 weight gain. If you look at -- not the
8 hyperprolactinemia obviously; that's obviously related
9 to the drug and its effect on dopamine. But when you
10 gain a significant amount of weight -- we see a lot of
11 obese kids that have abnormal TSH levels, but normal T4
12 or free T4 levels, and they are called hypothyroidism,
13 but they probably don't have hypothyroidism or need to
14 be treated.

15 The abnormal glucose tolerance, again for kids
16 that are already on the borderline of weight, they get
17 put on this medication and all of a sudden gain
18 excessive weight or have a tendency to -- or a family
19 history suggestive of getting type 2 diabetes. That's
20 where a lot of that plays in.

21 There was a mixture at some point about type 1
22 and type 2 diabetes, and I think those were all patients

1 that were already established. But that would be
2 something to clarify, if those were newly diagnosed
3 after being started or those were patients who were on
4 it and developed hyperglycemia for some point.

5 Then the last thing on this hypoglycemia
6 issue, it doesn't make a lot of sense, why is somebody
7 checking a fasting sugar of 85 that day and then getting
8 62? I mean, most likely the clonidine probably made the
9 patient pass out and fall down, and who knows if they
10 ate in the last 24 hours, and their sugar was just
11 dipping down.

12 But I think some of those things look very
13 scary for somebody who doesn't see these patients pretty
14 regularly. I don't know if you had some clarifying
15 information on those histories.

16 DR. DURMOWICZ: For the hypoglycemia case, I
17 don't know. Tracy, do we have additional -- oh, Tracy's
18 at the table.

19 Did you want the diabetes cases or the
20 glycemia case? I don't --

21 DR. FELNER: I was going to say, the
22 hypoglycemia, at least it looks -- for me it doesn't

1 look very worrisome because we see this all the time.
2 But I don't know what the non-endocrinologists think
3 about this, because I know we get called for
4 hypoglycemia all the time in the office and half the
5 time it's not even hypoglycemia; it's somebody feels
6 shaky and low, and they didn't eat enough or who knows
7 what other medicine they're taking.

8 But that, I wanted to make sure that that
9 didn't even get looked at as a concern, because that to
10 me looks more worrisome than those that are, at least to
11 the non-pediatrician or non-endocrinologist looking at
12 that --

13 CHAIRMAN ROSENTHAL: Dr. Dracker.

14 DR. DRACKER: I think a concern is any time we
15 see hypoglycemia, whether they're on drugs or not, we
16 are concerned whether it represents a pre-diabetic
17 condition. So sometimes we do a modified glucose
18 tolerance test, which is contentious. The
19 endocrinologists don't necessarily feel it's necessary
20 or appropriate. But we do evaluate them to make sure
21 that, unrelated to the medication they're on, that they
22 don't have a prediabetic predisposition.

1 CHAIRMAN ROSENTHAL: Dr. Hillard.

2 DR. HILLARD: So my question was related to
3 the hyperprolactinemia, which can result in menstrual
4 irregularities. So this is something that in
5 transmitting information to patients, families, and
6 clinicians might be useful information in terms of
7 monitoring. So I didn't see the numbers with
8 hyperprolactinemia, but if that were something that was
9 relatively common, at least it was reported, then adding
10 the information that that can result in menstrual
11 irregularities might be useful.

12 CHAIRMAN ROSENTHAL: Dr. Mink.

13 DR. MURPHY: One minute, before we go to Dr.
14 Mink. I think OSE did have some information about the
15 hypoglycemia.

16 DR. SALAAM: Hi. This is Tracy Salaam. I'm a
17 CQ evaluator in the Office of Surveillance and
18 Epidemiology, and I just wanted to give you additional
19 information since you asked about that particular case
20 with the hypoglycemia.

21 This was the case of the 13-year-old female
22 taking quetiapine for approximately 2 years to treat

1 bipolar disorder and mood change, who passed out and
2 fell in the shower. Three months prior to the event,
3 she had a fasting blood glucose of 85. The units were
4 not reported. Six days prior to the event, her post-
5 prandial blood glucose was 62. Her quetiapine dose at
6 the time of the event was 300 milligrams daily.

7 She was seen in an urgent care center, where
8 she was found to be hypoglycemic at the time. The
9 physician reported the patient had been, quote, "eating
10 a lot of sugar and behaving lethargic for a while, so
11 she might have been hypoglycemic for some time,"
12 unquote.

13 The patient was not hospitalized and no action
14 was taken with quetiapine. She recovered from the
15 events on an unspecified date, and the concomitant
16 medication again was trazodone and clonidine. I agree
17 with you in that the clonidine may have contributed as
18 well to the fall in the shower.

19 Thank you.

20 CHAIRMAN ROSENTHAL: Thank you for clarifying.

21 Dr. Mink.

22 DR. MINK: Two areas where I wanted to

1 comment. One was, reading the packet, the labeling, it
2 seems to be quite reassuring that hyperglycemia is not a
3 risk. Based on short-term studies, there were no cases
4 of what seemed to be pre-diabetes or diabetes. At least
5 it wasn't higher than placebo. Yet it seems that with
6 chronic use that's much more of a concern.

7 I'm just wondering, in terms of practicality.

8 Looking over the label, I find it falsely reassuring in
9 the setting of this longer term information.

10 The other that I'm struck by, and I was struck
11 by this when we reviewed a different antipsychotic last
12 meeting, was how many of the serious adverse events
13 occur in patients that are getting this for off-label
14 use? I know that it's not our charge to do anything
15 about that, but again I'm really struck by someone who's
16 getting this for somnambulism, for example, having a
17 fatal response, whether it was due to the medicine or
18 not. Still, looking at the use, I'm really struck by
19 that.

20 DR. MURPHY: We would have to have the
21 diagnoses for which -- do you have some of that for us?

22 Thank you.

1 DR. SALAAM: Hi. Tracy Salaam again. The
2 indications for 125 out of the 176 reports regarding the
3 primary indication that was listed in the report, there
4 were 33 reports indicated for bipolar disorder, 14 for
5 depression, 11 for psychosis and psychotic disorders, 11
6 for sleep disturbances, which includes your
7 somnambulance, 10 for schizophrenia and schizoaffective
8 disorder, 6 were affective disorder, 6 for ADHD, 5 for
9 abnormal behavior, 5 drug exposure during pregnancy, 3
10 for aggression, 3 for anxiety, 3 for autism. Two
11 indicated for hallucinations, two indicated for mood
12 disorders, two indicated for obsessive compulsive
13 disorder, and then one each of the following:
14 adjustment disorder, basal ganglion degeneration,
15 convulsion prophylaxis, impulsive behavior, intermittent
16 explosive disorder, mental retardation, oppositional
17 defiant disorder, pain, and psychotherapy.

18 Thank you.

19 CHAIRMAN ROSENTHAL: Dr. Bhatia.

20 DR. BHATIA: Coming from a different
21 perspective, that hypoglycemia, maybe we don't need to
22 be as concerned as we are making it out to be. Those

1 are not cause and effect. They were temporal
2 relationships across time, and there were two patients.

3 So we need to take that into consideration before
4 making hypoglycemia a true, true cause and effect,
5 because of the way that this has been portrayed.

6 CHAIRMAN ROSENTHAL: Are there other comments?

7 Dr. Towbin.

8 DR. TOWBIN: This is Dr. Towbin. I just
9 wanted to say one thing about Dr. Mink's comments and
10 then to make a comment about the indications that we
11 just heard. Of course, when these drugs were reviewed
12 for pediatric use we did talk extensively about how the
13 constellation of severe irritability and aggressive
14 behavior in the context of ADHD sometimes gets labeled
15 bipolar disorder, and the way in which practitioners
16 often think about this class of second generation
17 antipsychotics as being all alike, and so if you might
18 offer something like risperidone or aripiprazole to
19 somebody with an autism spectrum disorder, you might as
20 well just give them quetiapine. There is a lot of off-
21 label use.

22 I guess my summary comment is that I looked

1 closely at the label and I really appreciated the way in
2 which the agency has worked to make clear what the
3 trials showed. They didn't go beyond what the trials
4 showed. So all of this data in children and adolescents
5 is six-week and three-week studies, and that the data
6 about the long-term use of these drugs is really quite
7 unknown.

8 We know in the community -- and I bet
9 everybody here around the table who sees patients knows
10 -- that it is a very rare child indeed who gets these
11 drugs for six weeks or less. In fact, it's months and
12 months and months and in many cases years of being on
13 them. I don't think that the label can control
14 practice, but I do think it's wonderful that the label
15 makes clear that we have no data and that the safety and
16 efficacy of these agents for long-term continuous use is
17 not known.

18 CHAIRMAN ROSENTHAL: Dr. Durmowicz, can you
19 put the questions up before the committee?

20 (Screen.)

21 DR. MURPHY: I just want to say, in response
22 to your comment, you know as we tried to look at these

1 metabolic side effects and we worked with AHRQ and
2 others, the problems we're finding in trying to look at
3 these long-term effects relate a lot to what Dr.
4 Spielberg said. You know, after a whole lot of work and
5 really precise work, we actually ended up we think not
6 being that much further ahead with being able to advise
7 people any better about how to deal with some of these
8 metabolic side effects.

9 Ann, did you have anything else you wanted to
10 add to that about any of the work that may be still
11 going on with this?

12 CHAIRMAN ROSENTHAL: Dr. McMahon has just come
13 to the table.

14 DR. McMAHON: This is Ann McMahon, Office of
15 Pediatric Therapeutics. I think suffice it to say that
16 there is ongoing work trying to look at observational
17 data sets for pediatric -- for pediatric antipsychotic
18 use, and particularly metabolic effects. So the design
19 of such studies is still ongoing and so there's not a
20 lot of detail, but suffice it to say that it is being
21 looked at.

22 DR. MURPHY: If we had more we'd bring it to

1 you. So we're continuing. It is not a subject that is
2 done with, I guess is what I want to say. People are
3 continuing to look at it. So thank you.

4 CHAIRMAN ROSENTHAL: So the question before us
5 is whether the committee concurs that the agency should
6 continue routine ongoing post-marketing safety
7 monitoring. All in favor of that, please raise your
8 hands?

9 (A show of hands.)

10 CHAIRMAN ROSENTHAL: Thank you.

11 Any opposed?

12 (No response.)

13 DR. WAGENER: Clarification.

14 CHAIRMAN ROSENTHAL: Yes?

15 DR. WAGENER: This is Wagener. I would just
16 ask a clarification from Dr. Murphy, and that is for
17 continued routine ongoing post-marketing safety
18 monitoring, how long would it be before there would be a
19 similar presentation such as this at the next pediatric
20 review?

21 DR. MURPHY: Dr. Loughren will tell you that
22 it seems like we always have some product that is coming

1 back where we use the opportunity. But fundamentally
2 the things that trigger these reviews or that a product
3 is studied in children and labeled, which now the law
4 says even for negative studies it will get labeled,
5 because we know it's used off label.

6 I haven't looked to see if we have Seroquel
7 specifically --

8 DR. DURMOWICZ: There's a PREA PMR
9 outstanding. There is a PREA PMR outstanding for
10 bipolar depression for Seroquel.

11 DR. MURPHY: So we do have one, that when it
12 comes -- what they're telling you is we have a post-
13 marketing requirement study, and so when that study
14 comes in that would trigger another review. So that's
15 one mechanism.

16 The other mechanism is that something comes
17 up. OSE or the division brings up an issue and they
18 would like to bring it back either to a committee for
19 that drug specifically, because there's something more
20 than safety, or that it's a safety issue that they just
21 want to reinform this committee about.

22 Tom, did you want to add anything to that?

1 DR. LOUGHREN: This is Tom Loughren. Just to
2 add that as some of these additional studies, like the
3 one that Ann talked about, are completed, it would be
4 appropriate for us to bring the findings of that to the
5 committee, and we surely would want to do that as well.

6 DR. MURPHY: We just don't know the timing on
7 those other studies. As you saw last time, we tried to
8 bring you some follow-up as to where they were with it
9 when it goes on for years and years. We try to bring
10 some follow-up on that.

11 DR. WAGENER: So just to clarify -- this is
12 Wagener again -- if there were no red flags that came up
13 and if there was no PMR, would this come back in five
14 years, or it wouldn't come back at all unless one of
15 those things happened?

16 DR. MURPHY: It would not come back.

17 CHAIRMAN ROSENTHAL: I can't see whose mike is
18 red over on the left, but is there a question or
19 comment?

20 (No response.)

21 CHAIRMAN ROSENTHAL: All right. So thank you
22 for that clarification.

1 Does the committee -- I guess we should revote
2 since you've clarified things, Dr. Wagener. So let's
3 just once again raise your hands if you concur that the
4 FDA should continue routine ongoing post-marketing
5 safety monitoring for this product.

6 (Screen.)

7 CHAIRMAN ROSENTHAL: All right. Any nays?

8 (No response.)

9 CHAIRMAN ROSENTHAL: Any abstentions?

10 (No response.)

11 CHAIRMAN ROSENTHAL: So it looks like a
12 unanimous vote.

13 Dr. White, can you get us started.

14 DR. WHITE: Yes.

15 DR. RAKOWSKY: Alex Rakowsky, concur.

16 DR. FELNER: Eric Felner, yes.

17 DR. WALKER: Leslie Walker, yes.

18 DR. HILLARD: Paula Hillard, yes.

19 DR. BHATIA: Jatinder Bhatia, yes.

20 DR. MINK: John Mink, yes.

21 DR. WIEFLING: Bridgette Wiefling, yes.

22 DR. BAKER: Susan Baker, yes.

1 DR. KAPLAN: Shelly Kaplan, yes.

2 DR. CASTILE: Bob Castile, yes.

3 MS. EICHNER: Marilyn Eichner, yes.

4 DR. WRIGHT: Joseph Wright, yes.

5 DR. KRISCHER: Jeff Krischer, yes.

6 DR. TOWBIN: Kenneth Towbin, yes.

7 DR. WAGENER: Jeff Wagener, yes, recognizing
8 that the FDA has said there's a PMR that will be coming
9 back within the next few years.

10 DR. MOTIL: Kathleen Motil, yes.

11 DR. DRACKER: Bob Dracker, yes.

12 DR. SANTANA: Victor Santana, yes.

13 DR. REED: Michael Reed, yes.

14 CHAIRMAN ROSENTHAL: All right. Dr.
15 Durmowicz, thank you very much for your presentation.

16 The next presentation will be Dr. Amy Taylor,
17 who will be presenting Xolair for us. Dr. Taylor has
18 served as a medical officer with the Pediatric and
19 Maternal Health Staff for four years. Prior to joining
20 the FDA, Dr. Taylor was the deputy director and then the
21 acting director of the Division of Clinical Quality in
22 the Health Resources and Services Administration,

1 implementing the quality improvement strategy for
2 community health centers.

3 Dr. Taylor served as a pediatrician in the
4 United States Army for nine years and was an urgent care
5 physician with Egleston Children's Health Care System in
6 Atlanta for two years. Dr. Taylor received her medical
7 degree from Howard University and completed her
8 residency in pediatrics at Madigan Army Center, at
9 Madigan Army Medical Center in Tacoma, Washington. She
10 received a master's of health science in health policy
11 at the Johns Hopkins University Bloomberg School of
12 Public Health.

13 We have some new people at the table for FDA.
14 Could you please introduce yourselves.

15 DR. STARKE: I'm Dr. Peter Starke, a
16 pediatrician by training. I'm a medical officer in the
17 Division of Pulmonary, Allergy, and Rheumatology
18 Products.

19 DR. KALRA: Dipti Kalra, safety evaluator,
20 OSE.

21 CHAIRMAN ROSENTHAL: Thank you.

22 Dr. Taylor.

1 XOLAIR (OMALIZUMAB)

2 DR. TAYLOR: Yes, thank you.

3 (Screen.)

4 I will be presenting the pediatric focused
5 safety review for Xolair, or omalizumab.

6 (Screen.)

7 This is an outline of the topics I will be
8 covering.

9 (Screen.)

10 Xolair is marketed as an injectable
11 formulation for subcutaneous administration for moderate
12 to severe persistent asthma in patients with a positive
13 skin test or an in vitro reactivity to a perennial
14 aeroallergen and symptoms that were inadequately
15 controlled with inhaled corticosteroids.

16 Of note, there are limitations of use included
17 in the labeling. This product is not indicated for
18 other allergic conditions, acute bronchospasm, or status
19 asthmaticus, or in pediatric patients less than 12
20 years.

21 (Screen.)

22 This recombinant DNA-derived humanized IgG

1 kappa monoclonal antibody selectively binds to human
2 immunoglobulin, IgE, was labeled originally -- excuse
3 me. It was originally approved for marketing on June
4 20, 2003. PREA labeling changes leading to this safety
5 review were made on January 4, 2010.

6 (Screen.)

7 Adolescents 12 and older were evaluated along
8 with adults in clinical studies which were part of their
9 original approval in 2003. We did not require studies
10 in patients zero to five years because of the safety
11 concerns of anaphylaxis and malignancy associated with
12 the use of Xolair in adults and adolescents.

13 (Screen.)

14 Studies were conducted in pediatric patients 6
15 years to less than 12 years. Safety and effectiveness
16 was evaluated in two clinical studies in 926 pediatric
17 asthma patients age 6 to less than 12 years, a
18 randomized, double blind, placebo-controlled trial and a
19 seven-month safety study with an evaluation of efficacy
20 as a secondary outcome.

21 The randomized controlled trial demonstrated
22 statistically significant reduction in the rate of

1 exacerbations. Important secondary efficacy measures --
2 nocturnal symptom scores, beta-agonist use, and measures
3 of air flow -- were not statistically different in
4 Xolair -- in the Xolair group compared to the placebo
5 group.

6 (Screen.)

7 There were no new or unusual safety trends
8 noted in the clinical studies. There were no deaths and
9 no cases of associated anaphylaxis. There were two
10 cases of malignancy in two patients treated with
11 placebo. Small numerical differences in asthma
12 hospitalizations between the groups in favor of Xolair,
13 there were, which had no statistical difference.

14 (Screen.)

15 FDA presented this information to an advisory
16 committee on November 18, 2009. The majority of the
17 committee members did not feel that the safety and
18 efficacy data provided substantial and convincing
19 evidence to support approval of Xolair for the treatment
20 of asthma in patients 6 to 11 years of age.

21 (Screen.)

22 The following was added to the labeling: "For

1 patients 6 to less than 12 years, due to the risk of
2 anaphylaxis and malignancy seen in adults and adolescent
3 patients treated with Xolair and the modest efficacy of
4 Xolair seen in the randomized controlled trial in the 6
5 to less than 12-year-old patients, the risk-benefit
6 assessment does not support the use of Xolair in this
7 age group."

8 However, Xolair was approved in the European
9 Union for patients 6 to less than 12 years in September
10 2009.

11 (Screen.)

12 The next few slides cover the relevant safety
13 labeling for Xolair. There is a boxed warning for
14 anaphylaxis, which you see here.

15 (Screen.)

16 There are warnings and precautions for
17 anaphylaxis, malignancy, acute asthma symptoms --

18 (Screen.)

19 -- corticosteroid reductions, eosinophilic
20 conditions, and symptoms similar to serum sickness.

21 (Screen.)

22 In adult and adolescent patients 12 years or

1 older, anaphylaxis was reported in 3 of the 3,507
2 patients, and malignancy was seen in .5 percent of
3 patients treated with Xolair versus .2 percent in the
4 control group.

5 (Screen.)

6 The table you see here lists the adverse
7 reactions in adults and adolescents 12 years and older
8 which occurred at a rate of 1 percent or greater.

9 (Screen.)

10 We'll now talk a little bit about the use
11 information. Over the cumulative time period from
12 August 2008 through July 2011, allergy specialists and
13 pediatricians were the top prescribing specialties.
14 Asthma was not otherwise -- asthma not otherwise
15 specified was the top diagnosis for patients age 6 to 11
16 and 12 to 17.

17 (Screen.)

18 Over the cumulative time period from August
19 2008 through July 2011, around 18,703 patients had a
20 prescription claim for Xolair from a sample of U.S. mail
21 order specialty pharmacies. Of these patients,
22 approximately 9 percent of total patients with a

1 prescription claim were age 12 to 17 years.
2 Approximately 2.5 percent of patients with a
3 prescription claim were age 6 to 11 years, and less than
4 1 percent of total patients with a prescription claim
5 were age zero to 5 years.

6 (Screen.)

7 The next three slides present data on the
8 number of adverse event reports submitted to the agency.

9 From June 2003 to January 2010, there were a total of
10 261 prescription reports, of which 183 were serious,
11 including 6 deaths. The table also breaks down the data
12 by age, zero to 11 years and 12 to 16 years.

13 (Screen.)

14 This table provides information on the
15 pediatric reports from June 2003 to January 2010 for
16 selected adverse events. These include death,
17 infection, neoplasms, and anaphylaxis. The data are
18 provided by age group zero to 11 years and 12 to 16
19 years.

20 (Screen.)

21 Then this table provides information on the
22 pediatric reports from January 2010 to July 2011. These

1 are the cases provided -- the basis for our review
2 today.

3 In selecting the cases to review, we begin
4 with a crude count of 98 cases. This is 96 serious
5 pediatric cases and 2 serious cases with null age.
6 There were 6 duplicate reports, leaving 92 unduplicated
7 reports, including 5 deaths. 11 reports were excluded
8 because an adverse event was not reported, and that was
9 3 of the cases; 2 cases where the event occurred prior
10 to administration of Xolair; and 2 cases in which the
11 age was then found to be greater than 16; and 4 cases
12 where the event was due to underlying causes.

13 This left us with 81 serious cases, including
14 death cases.

15 (Screen.)

16 Three of the cases with a fatal outcome were
17 in utero exposures. One case, the patient had -- it was
18 a 37-week gestation and the patient was found to have
19 trisomy 18 or 19. One died in utero at 15 weeks
20 gestation and one was stillborn.

21 Xolair is categorized as a pregnancy category
22 B.

1 (Screen.)

2 There were two cases with a fatal outcome in
3 which there was direct exposure of Xolair. The first
4 case is a ten-year-old male receiving monthly Xolair for
5 asthma for three months, who experienced gastroenteritis
6 followed by necrotizing colitis after treatment with
7 steroids was interrupted. Medical history is
8 significant for Wolff-Parkinson-White syndrome and
9 adrenal insufficiency. Autopsy report listed the cause
10 of death as adrenal cortical insufficiency and
11 necrotizing enterocolitis.

12 The second --

13 (Screen.)

14 I'm sorry.

15 (Screen.)

16 The second case involves a 16-year-old male
17 with an unknown past medical history who was receiving
18 Xolair for an unknown indication. His last dose was one
19 week prior to the event. He presented with temperature,
20 upper respiratory tract infection and presumed
21 sinusitis. The patient was already receiving
22 intravenous antibiotics.

1 Within 24 hours he developed possible septic
2 shock and died. Concomitant medications include
3 piperacillin and tazobactam, budesonide, formoterol
4 fumarate, pirbuterol acetate, and an unspecified nasal
5 spray.

6 (Screen.)

7 This slide provides information on the age,
8 gender, and country of occurrence for the serious
9 pediatric cases.

10 (Screen.)

11 In the next few slides I will provide
12 information on the serious non-fatal adverse events.
13 There were 33 hypersensitivity reactions, including
14 anaphylaxis, serum sickness, drug-induced lupus,
15 shortness of breath, cardiovascular and adverse events
16 suggestive of allergic or hypersensitivity reaction, and
17 other serious allergic reactions.

18 (Screen.)

19 There were ten cases of respiratory or asthma
20 exacerbation, eight cases of infection, and seven
21 neuropsychiatric cases.

22 (Screen.)

1 There were three cases with syncope, two cases
2 with weight gain, two with gastrointestinal adverse
3 events, and two with nephrotic syndrome.

4 (Screen.)

5 There were two cases with blurred vision, one
6 with immunothrombocytopenia, and one case of arthralgia
7 and myalgia. There were five cases of adverse events
8 associated with in utero exposure.

9 (Screen.)

10 In summary, this concludes the pediatric-
11 focused safety review, in which no new pediatric safety
12 signals were identified. FDA recommends returning to
13 routine monitoring. We ask whether the committee
14 concurs.

15 (Screen.)

16 I want to thank the following folks for their
17 help with this presentation.

18 CHAIRMAN ROSENTHAL: Thank you, Dr. Taylor.

19 Dr. Rakowsky.

20 DR. RAKOWSKY: This isn't a safety question,
21 but more of a logistics question. So two years ago the
22 label specifically mentioned that this drug is not

1 approved for use in kids less than 12 years of age. In
2 that use data that you presented for 2008 on, have we
3 seen a trend of use going down? Has it stayed the same?
4 has that label change made any difference in regards to
5 use of this medication in that age group?

6 (Screen.)

7 DR. TAYLOR: You're talking about --

8 DR. MURPHY: We're going to have our use OSE
9 group that generates that data come to the table.

10 DR. GOVERNALE: Our review only looked at the
11 cumulative time period, so we didn't look at any trends,
12 so we could take -- the issue with looking at trends
13 with these kinds of data is that Xolair is mainly
14 distributed through specialty pharmacies and we don't
15 have a nationally projected use of specialty pharmacies
16 in the country. Therefore, when we're looking at use
17 over time the number of data providers are coming in and
18 out of the system. So therefore we can't really get a
19 good sense of trending for these kinds of drugs that are
20 distributed through specialty pharmacies.

21 That's one of the reasons why we looked at the
22 cumulative time period.

1 CHAIRMAN ROSENTHAL: Thank you. Can you
2 please introduce yourself for the record?

3 DR. GOVERNALE: Laura Governale, OSE.

4 DR. MURPHY: We actually, if we see something
5 like that where we know a product has a new warning or
6 we know it wasn't approved, we usually ask if we think
7 we can get relevant information, for the use people to
8 track that for us. But I think you heard what our issue
9 is here.

10 CHAIRMAN ROSENTHAL: Dr. Ward and then Dr.
11 Kaplan.

12 DR. WARD: Dr. Ward. I have two or three
13 questions. The first has to do with your slide 12,
14 where you show the frequency of I believe it was
15 anaphylaxis, .2 and .5 percent. Are those actually
16 significantly different or are those really the same?

17 DR. TAYLOR: I think that's why -- well, I'll
18 let actually maybe Peter would be better to answer that.

19 DR. WARD: I'm sorry. With respect to
20 malignancy.

21 DR. TAYLOR: I think the reason that it's
22 numerically higher is that it was not -- but again, Dr.

1 Starke might be able to answer that better.

2 CHAIRMAN ROSENTHAL: Dr. Ward is referring
3 specifically to bullet number -- the second bullet
4 point.

5 DR. TAYLOR: The second one.

6 CHAIRMAN ROSENTHAL: On slide 12.

7 DR. STARKE: Yes. This is Dr. Starke. I
8 think you're talking about malignancy; is that right?

9 DR. WARD: Yes.

10 DR. STARKE: All I can say is that that is
11 what was found in the clinical trials that were
12 initially performed for this product.

13 DR. WARD: Could you clarify what you mean by
14 that? Those don't look different, .5 and .2, with this
15 kind of a denominator; is that correct?

16 DR. STARKE: I can't comment on whether
17 there's a statistical difference between the two.

18 DR. WARD: Okay.

19 The other is I have a concern about the
20 efficacy issues here. The frequency of exacerbations
21 was reduced, yet the pulmonary function tests did not
22 appear to be different. It's very challenging to get

1 accurate pulmonary function tests in young children and
2 frequently the problem with asthmatic exacerbations is
3 very important to families and children. So I'm not
4 convinced that this isn't an effective drug for these
5 children.

6 DR. MURPHY: Again, Bob, comments are welcome,
7 but you don't get the packet that looks at the full
8 approval process. Then I guess the only other thing to
9 say to that is that the primary end point is usually
10 negotiated, has to be validated, has to pass a certain
11 standard, and then there are others that people want to
12 look at for just the reasons you stated. But you've got
13 to make it on the primary end point.

14 CHAIRMAN ROSENTHAL: Dr. Kaplan, then Dr.
15 Goldstein, then Dr. Dracker.

16 DR. KAPLAN: I was interested in the nephrotic
17 syndrome adverse events. There were two, if I recall,
18 and it didn't seem like there were that many kids who've
19 received this drug over the last year and a half or so
20 or two years. I know it's fraught with error to come up
21 with incidence figures, but just looking at this in a
22 textbook, I think nephrotic syndrome is present in one

1 in 100,000 kids and this was 2 in maybe 2,000 kids.

2 Do you have any more data on those two
3 patients?

4 DR. KALRA: Dipti Kalra, FDA. One of the
5 cases is of an 11-year-old male with severe persistent
6 asthma, who is treated with Xolair. He developed
7 nephrotic syndrome and was hospitalized for eight days.
8 Symptoms improved with diuretics and prednisone, but
9 the patient experienced two relapses of his nephrotic
10 syndrome. He was treated with prednisone and
11 cyclosporin and the outcome of the event was not
12 provided. He had a history of allergic rhinitis,
13 Morbus-Cushing, and Gilbert's Disease.

14 The other case was of a 14-year-old male who
15 received Xolair for three years, presented with
16 nephrotic syndrome, and was hospitalized. The action
17 taken with Xolair was not reported and the report had
18 insufficient clinical information to assess causality.

19 In both cases the patients were receiving
20 Xolair for three years before experiencing the adverse
21 event.

22 CHAIRMAN ROSENTHAL: Dr. Starke, you had

1 something to add?

2 DR. STARKE: Yes. We can come back to it,
3 though, if you want to finish the nephrotic syndrome.
4 It was to discuss the efficacy issue.

5 CHAIRMAN ROSENTHAL: Okay.

6 Further discussion on nephrotic syndrome?

7 (No response.)

8 CHAIRMAN ROSENTHAL: Dr. Starke.

9 DR. STARKE: Thank you. I just wanted to
10 mention, in response to the issue of efficacy, is that
11 this was a pediatric supplement that was brought to the
12 agency for the 6 to 11-year-olds. It was presented at
13 an advisory committee. At the advisory committee I
14 actually was the presenter for the agency.

15 We agreed with the sponsor that, based on the
16 primary evaluation, there was modest efficacy shown.
17 But all of the secondary efficacy end points were not
18 also showing the similar response. When you looked at
19 the primary efficacy end point, which was the same as
20 what was used in adults, which was reduction in
21 exacerbations, and you changed it over to a number
22 needed to treat -- I can give you those figures -- it

1 was actually quite, really quite modest.

2 We're talking about during the 24-week fixed
3 inhaled corticosteroid use period -- there was a 52-week
4 double-blind, placebo-controlled period, but during the
5 first 24 weeks it was 2.34 was the number needed to
6 treat, meaning you had to treat patients for 2.34 years
7 to see one exacerbation reduction, which an exacerbation
8 reduction was the need for oral corticosteroids for at
9 least three days, based on the investigator's decision
10 to use corticosteroids.

11 Based on that, we did not feel that the risk-
12 benefit was appropriate to use in this patient
13 population.

14 CHAIRMAN ROSENTHAL: Dr. Goldstein.

15 DR. GOLDSTEIN: My question had to do with the
16 comment that the drug is approved for use in the EU in
17 children between 6 and 11. This maybe is toward Dianne
18 mostly. In addition to sharing information about
19 clinical trial design and approval processes, is there
20 an exchange of information with the EMA in terms of
21 post-marketing surveillance and safety data on approved
22 drugs?

1 I'm just wondering. There's only a few
2 hundred children who received this drug off label in the
3 U.S., but nonetheless they are receiving it, and I was
4 wondering if there might be safety data that could also
5 be combined on the other end of the process.

6 DR. MURPHY: Yes, it can be. Every month
7 we're running around 20 PIPs, which is the pediatric
8 investigational plan that is sent to Europe. So every
9 month they have to pick. This is again in the pre, when
10 they're designing the trials. They'll pick the issues
11 that they want to talk about with those PIPs, because we
12 don't talk about all of them.

13 In that situation, a product of a similar
14 class, that's one way it might come up, because you've
15 got post-marketing safety data or you have pre-clinical
16 data on another moiety of similar mechanism of action.
17 Or if we or they are going to take some sort of action
18 or are in the process of looking at something, it may be
19 put on the agenda to discuss. But it is not routinely
20 put on the agenda that we would follow up with them on
21 all the post-marketing safety that we do, because, as
22 you know, we're doing around 15 for each of these

1 meetings. So we're not putting it on as a routine,
2 unless there's an issue.

3 DR. TAYLOR: I just wanted to add too that
4 when we do look at the cases within AERS we include
5 those cases from the U.S. as well as from international
6 reports.

7 CHAIRMAN ROSENTHAL: Dr. Dracker.

8 DR. DRACKER: In consideration of the
9 infection-malignancy issue, is there any consideration
10 of a requirement of a pre-treatment serum IgE level?
11 Many of these children present with clinical
12 manifestations that could be considered to be consistent
13 with Job-like syndromes, with hyper-IgE syndrome,
14 reactive airway disease, and eczematous-like rash, which
15 would predispose them to infection and also to
16 malignancy.

17 CHAIRMAN ROSENTHAL: Dr. Starke?

18 DR. STARKE: This is Dr. Starke again. So the
19 dosing schedule for Xolair is based on weight and
20 baseline IgE. So physicians generally have to have an
21 IgE in order to be able to decide on the dosing
22 schedule. This is both for adults and adolescents, and

1 it was also the way it was studied in the pediatric
2 population 6 to 11 years of age.

3 DR. DRACKER: But if you had data that was
4 suggestive of something more than just an elevated IgE,
5 which would suggest perhaps an atopic-like -- if you had
6 IgE's, let's say, of 4,000 or 6,000, even higher, which
7 I've seen, is that something that should be considered
8 to be perhaps increased concern?

9 DR. STARKE: Not being an allergist, I'm not
10 sure if I can answer your question directly. Perhaps
11 someone who is can.

12 CHAIRMAN ROSENTHAL: Dr. Wagener.

13 DR. WAGENER: This is Jeff Wagener. There is
14 an upper IgE level in dosing that says it's not to be --
15 it's not supposed to be used for patients with IgEs, I
16 believe it's around 700 or something.

17 DR. STARKE: That's correct.

18 CHAIRMAN ROSENTHAL: Thank you.

19 DR. DRACKER: I know for a fact it is used for
20 patients in excess of 700.

21 DR. WAGENER: That would be considered off
22 label. Certainly physicians can do that. I think the

1 package insert is pretty clear, though, that it has a
2 specific range of IgE and, as mentioned, the dose is
3 calculated based on the IgE and the body weight.

4 CHAIRMAN ROSENTHAL: Other comments or
5 questions about Xolair?

6 (No response.)

7 CHAIRMAN ROSENTHAL: Dr. Taylor, can you take
8 us back to the slide that has the voting question,
9 please?

10 (Screen.)

11 CHAIRMAN ROSENTHAL: The proposal at hand is
12 that the FDA would return Xolair to routine safety
13 monitoring. Does the committee concur with this
14 recommendation? All in favor?

15 (Screen.)

16 CHAIRMAN ROSENTHAL: All opposed?

17 (No response.)

18 CHAIRMAN ROSENTHAL: Any abstentions?

19 DR. KAPLAN: Could I ask for a clarification?

20 CHAIRMAN ROSENTHAL: Yes, Dr. Kaplan.

21 DR. KAPLAN: If I thought there was a safety
22 signal that was identified, how does that affect the

1 routine monitoring?

2 DR. MURPHY: I'll ask Dr. Hausman to describe
3 to you what routine monitoring is. We probably should
4 have done that for our new members.

5 DR. HAUSMAN: When we decide to go back to
6 routine monitoring, it isn't that we put a drug in a
7 black box and don't look at it. We have regular
8 portfolio monitoring across 10 or 12 teams. Each safety
9 -- I'm sorry. Each safety evaluator has a portfolio of
10 drugs they regularly look at. They get, I don't know,
11 it's anywhere between 3 to 10 or 12 drugs per safety
12 evaluator. Their box, their computer in box, gets
13 populated approximately a couple times a week to once a
14 week, and then they go through it.

15 So it's not that it's put off into the back
16 and nobody looks at it again. If we actually find
17 ticklers for any particular safety signal, we look at a
18 review and we say we're not going to do another
19 comprehensive safety evaluation on this particular issue
20 right now; we don't consign that issue to the dust bin.

21 The safety evaluators regularly re-look at things and
22 we do data mining, a number of tools, and we actually

1 pull cases from time to time to see if the signals are
2 getting any stronger.

3 So if the committee actually finds a
4 particular signal, you can discuss it and make
5 recommendations to us and we'll take it back and we can
6 continue investigating, even though it's technically in
7 routine monitoring.

8 DR. MURPHY: I think the differentiation to
9 know is that -- well, two things. One, it doesn't go
10 into a black box, so they're always looking, okay. But
11 if there's a particular pediatric signal -- because
12 remember they're looking at numbers, and you know what
13 happens with kids. So it's a lower amount of reporting.

14 So if there's a specific issue that the committee was
15 concerned about, we can ask that we focus on that.

16 But outside of that, otherwise it would go
17 back to the routine monitoring.

18 CHAIRMAN ROSENTHAL: Dr. Starke.

19 DR. STARKE: I just wanted to add, as a
20 medical officer and a primary reviewer in a review
21 division, we get those safety reports just as OSE does
22 and we look at them. I see them all the time.

1 I also wanted to mention that there is a
2 pregnancy registry that is an ongoing evaluation of the
3 potential for any effect on pregnancies with this
4 particular product.

5 CHAIRMAN ROSENTHAL: Okay, thank you.

6 Dr. Kaplan, are you okay with just going ahead
7 with calling out the vote?

8 DR. KAPLAN: I'm okay with calling out the
9 vote.

10 CHAIRMAN ROSENTHAL: Thanks. So, Dr. Reed,
11 will you get us started.

12 DR. REED: Michael Reed votes yes.

13 DR. SANTANA: Victor Santana votes yes.

14 DR. DRACKER: Bob Dracker, yes.

15 DR. MOTIL: Kathleen Motil, yes.

16 DR. WAGENER: Jeff Wagener, abstain.

17 DR. TOWBIN: Kenneth Towbin, concur.

18 DR. KRISCHER: Jeff Krischer, yes.

19 DR. WRIGHT: Joe Wright, yes.

20 MS. EICHNER: Marilyn Eichner, yes.

21 DR. CASTILE: Bob Castile, yes.

22 DR. KAPLAN: Shelly Kaplan. Yes, I agree with

1 the returning to routine monitoring. I'm not sure that
2 a safety signal hasn't been identified here, though.

3 DR. BAKER: Susan Baker, yes.

4 DR. WIEFLING: Bridgette Wiefling, yes.

5 DR. MINK: John Mink, yes.

6 DR. FRANCO: Israel Franco, yes.

7 DR. HILLARD: Paula Hillard, yes.

8 DR. WALKER: Leslie Walker, yes.

9 DR. FELNER: Eric Felner, yes.

10 DR. RAKOWSKY: Alex Rakowsky, yes.

11 DR. WHITE: Michael White, yes.

12 CHAIRMAN ROSENTHAL: Dr. Starke.

13 DR. STARKE: I'd just like to ask what safety
14 signal are you concerned about so we can at least
15 consider it?

16 DR. KAPLAN: Shelly Kaplan. The nephrotic
17 syndrome issue. There were the two cases in maybe 2100
18 patients. Again, I realize that determining a numerator
19 and a denominator is difficult, but it seems like that's
20 a lot higher than what one would expect in 2,000 kids.

21 DR. MURPHY: We already passed it on. So it
22 will be looked at.

1 DR. CASTILE: Bob Castile. Is there a way to
2 flag that in particular in your routine monitoring?
3 Because I thought it was an astute pickup. I don't
4 carry those numbers in my head. But I mean, it seems
5 like an uncommon occurrence. I think both of them were
6 in long-term treated patients, so it sort of makes
7 physiologic sense.

8 So I guess my question for this and even for
9 the other drugs is, in your routine monitoring could you
10 flag for this one nephrotic syndrome and for drugs
11 earlier this morning some of the other issues that we
12 were concerned about? I mean, do they get flagged?

13 DR. HAUSMAN: It has just been flagged by the
14 committee. I don't say that to make light of it. It's
15 just been flagged. Part of what we do is -- well, all
16 of what we do is we look at cases. When people ask
17 about numerators and denominators, they're certainly
18 exceptionally important from an epidemiological
19 standpoint. On the pharmacovigilance side, when the
20 safety evaluators do the reviews they actually look at
21 numbers. But they also concentrate on the quality of
22 the cases.

1 You hear us say a lot about confounders and
2 insufficient clinical information. I pulled the reports
3 with the safety evaluators for these particular cases
4 because they tickled my interest, too, and there really
5 isn't a lot of data there. So we're tickled. We don't
6 -- when we say there's not enough to go on, again we
7 don't consign it to the dust heap. We can take the
8 issue back within the division and discuss how we want
9 to follow up, and then we can get back through Dianne to
10 the committee if necessary.

11 DR. CASTILE: Bob Castile again. So being new
12 to the committee, are there -- it appears that there are
13 other options other than yes or no. One is to flag the
14 drug and I think probably there's another, which is to
15 investigate further and come back with more information,
16 on issues where we're not sure that we want to vote yes
17 or no. Am I getting it?

18 DR. MURPHY: You're getting it. We usually
19 give you FDA's recommendation. Again, because we do
20 have a large number of people who aren't routinely on
21 the committee, we could have probably spelled it out
22 better for you, that if you have a concern, yet you

1 don't want us to bring that product specifically back
2 within a certain period of time or after a certain
3 metric, you can say that, I'm concerned and would like
4 additional follow-up. And we'll take that back.

5 CHAIRMAN ROSENTHAL: Just to point out that,
6 although the votes are sort of a dramatic moment in the
7 proceedings of the committee, what the agency seems to
8 really process and mull over for months to years -- I've
9 seen this happen over periods of years -- are the
10 comments that are made, the discussions that happen
11 around this table.

12 So if you do have reflections, if you do have
13 comments, never be shy about bringing them up. That's
14 what matters much more so than the voting, in my
15 opinion.

16 DR. MURPHY: I wanted to second that. We go
17 back -- we get into internal discussions: Oh, that's
18 not what they said. We'll pull the transcripts and
19 we'll go back. Oh, that is what they said. So if you
20 have an issue, this is -- that's why you're here, to
21 bring it up. And maybe nobody will agree with you, but
22 that's okay.

1 CHAIRMAN ROSENTHAL: Actually, I'll one-up you
2 on that, Dr. Murphy. I think sometimes the dissenting
3 view ends up being the view that really has a new
4 kernel, a new reflection that should be considered by
5 the agency. So I would encourage people, if 14 people
6 raise their hands and you don't feel like that's the
7 right thing to do, then don't raise your hand and
8 explain why. That's the best -- that's the best you can
9 do for this public health effort.

10 All right. Dr. White, I've seen your hand up
11 a couple times down there. Did you still have a
12 comment?

13 DR. WHITE: Just a very quick one. I've been
14 sitting on the IRB. We see lots of antibodies,
15 conjugated antibodies, and it seems like nephrotic
16 syndrome is not that unusual. Is there a way to compare
17 this particular antibody-based drug to others, to see if
18 there's an increased incidence for nephrotic syndrome?
19 Or that might be one way to monitor it.

20 DR. HAUSMAN: I'd actually have to go back and
21 talk to our experts, because it sounds like a bit more
22 of a complicated question on its face and I wouldn't

1 want to misspeak right now.

2 DR. WHITE: Okay. Thank you.

3 CHAIRMAN ROSENTHAL: All right. Well, thank
4 you, Dr. Taylor. Dr. Taylor's going to come back for a
5 return visit this afternoon.

6 But right now we get to break for lunch. Dr.
7 Ellenberg's telling me that there are some small rooms
8 set aside over in the restaurant for the committee
9 members. Please don't talk about the proceedings during
10 lunch, and we'll see you back at 1:00, at 1:00 o'clock,
11 for the open public forum.

12 Thank you.

13 DR. MURPHY: Particularly for the new members,
14 it may be very tempting to talk amongst yourselves. But
15 that really is something we ask you not to do. We've
16 gotten into trouble previously. So thank you.

17 (Whereupon, at 12:04 p.m., the meeting was
18 recessed, to reconvene the same day at 1:00 p.m.)

19

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21

22

1 For example, this financial information may
2 include the payment of your travel, lodging, or other
3 expenses in connection with your attendance at this
4 meeting.

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

11 All right. That having been said, we have two
12 speakers for the open public forum. The first is Lydia
13 Stuckey, who's going to be speaking on behalf of
14 Reproductive Health Technologies Project.

15 Each of the speakers will have five minutes
16 and, just to orient you to the room, there's a light,
17 which I don't have my glasses on, so I can't see it, but
18 there's a light right there, which will give you some
19 cues about your timing.

20 Thank you.

21 STATEMENT OF LYDIA STUCKEY

22 MS. STUCKEY: I appreciate this opportunity to

1 speak with you today. I am Lydia Stuckey, a senior
2 associate for programs and policy at the Reproductive
3 Health Technologies Project, and I am reading comments
4 on behalf of Kirsten Moore, our president and CEO.

5 RHTP is a national not-for-profit advocacy
6 organization with a mission to advance the ability of
7 every woman to achieve full reproductive freedom with
8 access to the safest, most effective, appropriate, and
9 acceptable technologies for ensuring her health and
10 controlling her fertility. RHTP does not receive any
11 funding from pharmaceutical companies.

12 For more than a decade, RHTP has worked to
13 expand access to and awareness of emergency
14 contraception, a safe, effective backup birth control
15 method. RHTP has long believed that the full potential
16 of this product will not be achieved until it is on the
17 shelf within easy reach of all consumers who need it.

18 We hope the committee today will send a strong
19 and unambiguous statement that all available information
20 provides reassuring evidence that Plan B One-Step,
21 levonorgestrel emergency contraception product, can
22 safely be used by anyone at risk of an unintended

1 pregnancy, including adolescents, and should be made as
2 easily available as possible in hopes of reducing the
3 rates of unintended pregnancy.

4 Teenage pregnancy is a real public health
5 concern. According to the latest statistics, there were
6 approximately 750,000 pregnancies among teens 15 to 19.

7 82 percent of teen pregnancies are unplanned and teens
8 account for about one-fifth of all unintended
9 pregnancies annually.

10 Nearly one in five teens at risk for
11 unintended pregnancy were not using any contraception
12 method at last intercourse. The need among adolescents
13 for a backup contraception method is clear.

14 Plan B One-Step, as I'm sure everyone here is
15 aware, is a birth control method that can prevent
16 pregnancy up to 72 hours after unprotected sex or
17 contraceptive failure. Extensive data, including the
18 reports from the FDA in the briefing books in front of
19 you, show there is no evidence of pediatric safety
20 signals for Plan B One-Step. Any side effects are minor
21 and temporary.

22 More important, the risks posed by these --

1 the risk posed by these side effects is slight when
2 compared to the potential risks posed by unplanned
3 pregnancy, especially among adolescent and young
4 adolescents females. It's not easy to think about a
5 teenage couple having sex, but if they are it's
6 important they have access to safe options that can
7 reduce the risk of an unwanted pregnancy.

8 Plan B One-Step is more effective the sooner
9 it's used. Keeping the product on prescription for
10 adolescents 16 years and younger and behind the counter
11 for all leads to unnecessary delays and detours to
12 accessing this safe product. We should help teens who
13 are facing the risk of unintended pregnancy take quick
14 action to protect themselves, not put more barriers in
15 their way.

16 Another reason that emergency contraception
17 should be available over the counter is that, given the
18 limitations to access of health care services today,
19 this safe and effective product does not need to be a
20 further burden on health care providers' time unless
21 there are real questions by patients about the product.

22 Data shows teens can easily understand the instructions

1 for use and take the product as directed.

2 With all the positive data on levonorgestrel
3 emergency contraception out there, it is perplexing that
4 the Department of Health and Human Services has allowed
5 politics to trump science time and again over the last
6 decade. Most recently, in December HHS Secretary
7 Kathleen Sebelius overruled the thorough review of
8 experts at the FDA who approved Plan B One-Step for
9 over-the-counter access. With its remarkable and well
10 documented safety profile, there is no reason to hold
11 Plan B One-Step to a different standard, kept on
12 prescription and held behind the pharmacy counter.

13 For more specific information about how Plan B
14 One-Step is safe and meets the criteria for over-the-
15 counter use, it is documented in your packet through
16 letters by the American College of Obstetricians and
17 Gynecologists, researchers Doctors Tina Raine and Dr.
18 Cynthia Harper, and a joint letter from women's
19 advocates submitted by the Reproductive Health
20 Technologies Project.

21 In sum, there is no evidence to suggest a need
22 to relabel Plan B One-Step based on its safety profile,

1 but there is copious evidence to support relabeling it
2 for over-the-counter use. We hope you confirm this
3 today.

4 Thank you.

5 CHAIRMAN ROSENTHAL: Thank you, Ms. Stuckey.

6 Our next speaker will be -- our next speaker
7 will be Kate Ryan from the National Women's Health
8 Network.

9 STATEMENT OF KATE RYAN

10 MS. RYAN: Hello. My name is Kate Ryan. I'm
11 with the National Women's Health Network. It's a
12 nonprofit advocacy organization that works to improve
13 the health of all women, and we bring the voices of
14 women consumers to policy and regulatory decisionmaking
15 bodies. We're supported by our members and do not take
16 financial contributions from drug companies, medical
17 device manufacturers, insurance companies, or any other
18 entity with a financial stake in women's health
19 decisionmaking.

20 My comments today will focus on the pediatric
21 safety of three reproductive health products that the
22 committee is discussing today and tomorrow: Plan B,

1 Mirena, and Cervarix. As advocates for women's health
2 and for appropriate safety surveillance, we're pleased
3 the FDA continues to monitor the safety and efficacy of
4 contraceptives and other products like the HPV vaccine
5 that women rely on for reproductive health.

6 Extensive research over many years shows that
7 it's very safe to use levonorgestrel, the drug contained
8 in Plan B and Plan B One-Step, as a backup birth control
9 method to prevent pregnancy after unprotected sex or
10 contraceptive failure. Given the depth of this evidence
11 base, we're unsurprised the FDA's post-marketing
12 evaluation safety review found no evidence of pediatric
13 safety concerns with Plan B or Plan B One-Step.

14 In fact, as I'm sure you're all aware and as
15 Lydia just mentioned, the agency recently evaluated all
16 available data for pediatric use of Plan B from
17 scientific evidence to clinical information and found
18 that not only are there no pediatric-specific safety
19 concerns, but that levonorgestrel-based emergency
20 contraceptive products meet the FDA's standard for over-
21 the-counter products for women of all reproductive ages.

22 The agency concluded that Plan B One-Step is safe and

1 simple enough for anyone to use without a learned
2 intermediary.

3 We're deeply disappointed that the FDA's
4 scientific determination was overturned by HHS Secretary
5 Kathleen Sebelius and, though we understand this
6 advisory committee is not tasked with deciding whether
7 Plan B One-Step should be an over-the-counter product,
8 we hope the committee will make a strong and unambiguous
9 statement that all available evidence demonstrates Plan
10 B One-Step can be safely used by teens.

11 With a safety track record this strong, there
12 should be no doubt in anyone's mind that regulatory
13 barriers to access this product serve only to make it
14 more difficult to prevent unintended pregnancy.

15 With regard to Mirena, the levonorgestrel-
16 release IUD, we're pleased to see the agency's safety
17 review found no evidence of pediatric safety concerns.
18 Although Mirena also has a strong safety track record,
19 the history of IUDs in the U.S. continues to cast a
20 shadow over public perceptions of the method, which we
21 hope FDA's safety reviews, such as this one, can help to
22 dispel.

1 Although pediatric use of Mirena accounts for
2 less than one percent of the patient population, it is
3 important to examine the safety and efficacy of this
4 product in women of all reproductive ages.

5 Finally, we're also pleased to see the FDA
6 review found no safety issues for Cervarix, the vaccine
7 for prevention of strains of HPV. This safety finding
8 is particularly important and timely, given the baseless
9 charges recently leveled against the HPV vaccine by some
10 political candidates. This review adds to the base of
11 evidence that supports making the HPV vaccine available
12 and can help stem the spread of misinformation and
13 scientifically debunk claims that serve only to
14 undermine the public health.

15 A strong statement from this committee and
16 from the FDA providing a positive evaluation of
17 Cervarix's safety will reassure parents and provide
18 advocates with further evidence to push back against
19 these claims based on ideological opposition to the
20 product rather than science.

21 In conclusion, we strongly support the FDA's
22 determination that there is no evidence of pediatric

1 safety concerns for any of the three reproductive health
2 products considered by the committee, Plan B, Mirena, or
3 Cervarix, and consequently no changes to their label are
4 necessary.

5 Nevertheless, we support the FDA's
6 recommendation that post-market safety surveillance of
7 these products continues in accordance with the
8 standards established by BPCA and PREA for all similar
9 products in pediatric use. This position reflects two
10 deeply held principles that guide the NWHN's advocacy.
11 Since its inception, we have recognized the need for
12 long-term evaluation of safety and effectiveness of
13 medical products so that women have evidence-based
14 information on which to base their health care
15 decisions, and we believe that political considerations
16 should not lead the agency to hold reproductive health
17 products to a different standard than other products.

18 Thank you for your time.

19 CHAIRMAN ROSENTHAL: Thank you.

20 Now we have a few written comments that have
21 been submitted, and Dr. Ellenberg and I will tag-team in
22 the reading of these. I will read first a letter that

1 was sent to the agency by Cynthia Harper, Ph.D.,
2 Associate Professor, Department of Obstetrics,
3 Gynecology, and Reproductive Sciences at the University
4 of California-San Francisco. The letter is:

5 "Regarding comments for the U.S. FDA Pediatric
6 Advisory Committee on Plan B One-Step, levonorgestrel.
7 Data from numerous studies we have conducted in
8 pediatric and adolescent populations demonstrate that
9 young females who take levonorgestrel emergency
10 contraception exhibit similar pharmacokinetics and side
11 effect profiles as adults. They also demonstrate that
12 they are able to correctly use levonorgestrel emergency
13 contraception and that they do not have increased risk
14 behaviors as a result of increased access to the
15 medication.

16 "Our most recent study, submitted as actual
17 use data to the FDA, assessed appropriate self-selection
18 based on reading the product label and correct use of
19 Plan B One-Step without consultation with a health care
20 provider. The study results provide a high level of
21 support for the ability of young females under age 17 to
22 appropriately select and correctly use levonorgestrel

1 1.5 milligram single tablet in a manner consistent with
2 over-the-counter access.

3 "Females aged 11 to 17 years requesting
4 emergency contraception at teen reproductive health
5 clinics were eligible to participate. At the request of
6 the FDA, the original protocol incorporated a goal to
7 enroll a minimum of 25 participants of each age group
8 from 11 to 17 years. However, based on information from
9 published literature on age of menarche and age of
10 sexual initiation in the United States, as well as study
11 experience over a two-year period showing that very low
12 numbers of females 13 years and under actually present
13 to clinics requesting emergency contraception, the FDA
14 eliminated the requirement for 25 participants in each
15 group from age 11 to 13 years.

16 "Over a two-year period, three participants
17 under age 13 were enrolled in our study, 35 aged 14, 100
18 age 15, 141 age 16, 66 age 17. No females under age 13
19 were screened or enrolled.

20 "After reading the label, 91.5 percent
21 appropriately made the decision whether to use the
22 product or not. There were no differences in

1 appropriate selection after reading the label by age.
2 Among participants in the correct use analysis, 92.9
3 percent correctly used it less than 72 hours after
4 unprotected sex. There were no significant differences
5 in age in the correct use analysis. No unusual adverse
6 events were observed among participants who used the
7 product.

8 "In our studies conducted in 2004 to 2006 on
9 the tolerability and pharmacokinetics of levonorgestrel,
10 female 13 to 16-year-olds had similar pharmacokinetics
11 and side effect profiles as did adults. We also
12 conducted large behavioral studies that showed that
13 adolescents under age 16 behaved no differently than
14 older adolescents or young adults, and those with
15 increased access to the product used emergency
16 contraception more frequently if needed, but did not
17 show any difference in sexual risk behaviors, including
18 unprotected intercourse, consistent condom use, STI
19 acquisition, pressure for sex, or increase in number of
20 sexual partners.

21 "Adolescents with increased access to
22 emergency contraception also reported higher convenience

1 and inconvenience was a frequent reason for non-use
2 after unprotected intercourse.

3 "Teenage pregnancy is a serious health problem
4 in the United States, but is not prevalent among
5 preteens. The argument that we have insufficient data
6 on how 11-year-olds use emergency contraception is a
7 distraction from the truth. In the United States, few
8 have reached menarche, less than 10 percent, and far
9 fewer, only 7 out of 1,000, have had sex. Keeping
10 emergency contraception prescription-only for females
11 under 17 has the largest impact on 15 to 16-year-olds,
12 who are 280 times more likely to be sexually active than
13 adolescents under age 13.

14 "Figure 1" -- there's a figure in this that
15 I'll describe in a second. "Figure 1 from our ongoing
16 research shows the steep age curve for emergency
17 contraception use, with the first significant provision
18 of the medication occurring among 15 to 16-year-olds.
19 By restricting access to emergency contraception, we're
20 not providing prompt treatment for the largest group of
21 teens in need."

22 Figure 1, the title is "Female Family PACT

1 Clients Provided Emergency Contraception in 2009 By
2 Age," and there is a skewed frequency distribution.
3 number of clients is on the Y axis, goes from zero to a
4 peak of 36,000 or 37,000. The age distribution is such
5 that the median looks like it's about at age 20.

6 "Thank you for your thorough review and
7 consideration of the pediatric and adolescent data on
8 levonorgestrel emergency contraception." Signed,
9 "Cynthia Harper, Ph.D."

10 DR. ELLENBERG: I'm going to read the next
11 comment, which was submitted by Lisa Smith Goldstein on
12 behalf of the American College of Obstetricians and
13 Gynecologists:

14 "The American College of Obstetricians and
15 Gynecologists ("the college"), a national medical
16 organization representing over 56,000 members who
17 provide health care for women, thank the U.S. Food and
18 Drug Administration for holding the Pediatric Advisory
19 Committee meeting and for the opportunity to comment on
20 the safety of Mirena, Plan B One-Step, and Cervarix for
21 adolescents.

22 "The American College of Obstetricians and

1 Gynecologists supports the use of levonorgestrel
2 intrauterine system emergency contraception and human
3 papilloma virus vaccine by adolescents and urges the
4 committee to do the same. Adolescents are a unique
5 subset of the pediatric population. Adolescence is a
6 time of psychosocial, cognitive, and physical
7 development as young people make the transition from
8 childhood to adulthood. This transition includes sexual
9 development and often may entail behaviors that put
10 young women at risk for pregnancy and sexually
11 transmitted infections.

12 "Access to needed reproductive health care can
13 greatly facilitate young people's healthy transition to
14 adulthood. Given the importance of the appropriate
15 reproductive health care for this population, the
16 college thought it especially important to provide
17 support regarding the safety of these three products.

18 "Intrauterine contraception. Data support the
19 safety of intrauterine contraception for most women,
20 including adolescents. The complications of
21 intrauterine contraception differ little between
22 adolescents and older women. As such, the college

1 supports the use of intrauterine contraception for
2 adolescent females.

3 "The Centers for Disease Control and
4 Prevention's 2010 medical eligibility criteria for
5 contraceptive use, endorsed by the college, supports the
6 use of intrauterine contraception in women from menarche
7 to age 20 years, stating that 'The benefits of
8 intrauterine contraception generally outweigh the
9 risks.'" Over 40 percent of 15 to 19-year-old girls have
10 ever had sex" -- excuse me -- "have ever had sexual
11 intercourse.

12 "Because adolescents contribute
13 disproportionately to the epidemic of unintended
14 pregnancy in this country, top tier methods of
15 contraception, including levonorgestrel intrauterine
16 system, should be considered as a first-line choice for
17 both nulliparous and parous adolescents.

18 "Correct and consistent use of the
19 contraception is an integral part of the prevention of
20 adolescent pregnancy, and intrauterine devices are a
21 long-term safe, highly effective, and non-user-dependent
22 method of contraception. That may be a particular

1 benefit to adolescents, who are less adherent to daily
2 contraceptive regimens and less likely to use
3 contraception consistently.

4 "The levonorgestrel intrauterine system may
5 also alleviate bleeding concerns, decreasing days missed
6 from school or work.

7 "Emergency contraception. Since 2001 the
8 college has been on record in strong support of making
9 emergency contraception available over the counter with
10 no age restriction. The college thanks the FDA for its
11 recent evidence-based conclusion that Plan B One-Step is
12 safe and effective and should be approved for non-
13 prescription use for all females of childbearing
14 potential. The overwhelming scientific evidence
15 demonstrates that the emergency contraception is both
16 safe and effective in preventing an unintended
17 pregnancy.

18 "Emergency contraception provides a post-
19 coital method of contraception that may be particularly
20 useful for adolescents who rely on condoms or who have
21 had unprotected intercourse and have had high rates of
22 unintended pregnancy.

1 "The Centers for Disease Control and
2 Prevention's 2010 medical eligibility criteria for
3 contraceptive use, endorsed by the college, include no
4 conditions in which the risk of emergency contraception
5 use outweighs the benefits."

6 "Human papilloma virus vaccination. Human
7 papilloma virus ("HPV") is the most common sexually
8 acquired infection in the world. Numerous natural
9 history studies have demonstrated that as many as 50
10 percent of sexually active young women in the United
11 States will have positive test results for HPV within 36
12 months of the onset of sexual activity.

13 "Recurrent infections are also common.
14 Consequently, prevalence data indicate that up to 57
15 percent of sexually active female adolescents in the
16 United States at any one point in time are infected with
17 HPV. The college therefore recommends HPV vaccination
18 with either the bivalent or quadrivalent vaccine of
19 females age 9 to 26, with receipt of the first dose
20 ideally at 11 to 12 years of age. Both HPV vaccines are
21 the most effective if given before the exposure to the
22 HPV infection. However, sexually active girls and women

1 can receive some benefit from the vaccination because
2 pre-treatment exposure to all HPV types prevented by the
3 vaccines is unlikely in females age 13 years through 26
4 years.

5 "Summary and recommendations. The college
6 supports the FDA's efforts to ensure the safety of
7 Mirena levonorgestrel-release intrauterine system, Plan
8 B One-Step, and Cervarix for adolescents. It is the
9 opinion of the college that all three are safe for use
10 by adolescents and serve a vital role in preventing
11 unintended pregnancy and sexually transmitted
12 infections. We encourage the Pediatric Advisory
13 Committee to concur with this opinion.

14 "For more information, please contact Lisa
15 Goldstein, senior director, adolescent health care."
16 And she provided her email address and her phone number.

17 CHAIRMAN ROSENTHAL: These are being read into
18 the record, but the actual paper versions will be
19 included in the docket for the meeting as well.

20 So this is the last comment. It is from a
21 person who identifies themselves as "Gene Public." The
22 topic of this email is, it says, "Public Comment on

1 Federal Register: Pediatricians have a conflict of
2 interest in promoting vaccines. The money and greed of
3 it all."

4 The content, the body of this note is as
5 follows: "This is a complaint about this agency
6 advocating 70, 7-0, doses of vaccines for little tiny
7 children, which represents an assault on a small
8 developing body. The growth factor in cells is
9 negatively influenced by all of these vaccines. They're
10 given too early in life, not spaced well. Who knows how
11 biosecure they really are?

12 "Nobody investigates where the chickens live
13 that produce the eggs. Nobody knows what the eggs look
14 like and how clean are their surroundings. We all know
15 a million eggs were recalled for salmonella. You could
16 be injecting" -- expletive deleted -- "into kids. You
17 don't really know, and you don't really seem to care,
18 either."

19 And that's the end of that comment.

20 All right. Well, at this point we move from
21 the open public meeting to the next presentation by Dr.
22 Taylor, for Plan B One-Step, levonorgestrel.

1 PLAN B ONE-STEP (LEVONORGESTREL)

2 STANDARD REVIEW OF ADVERSE EVENTS

3 DR. TAYLOR: This is the pediatric focused
4 safety review for Plan B One-Step levonorgestrel.

5 (Screen.)

6 Thank you.

7 This is an outline of the topics I will cover.

8 (Screen.)

9 (Screen.)

10 Plan B One-Step is marketed as 1.5 milligram
11 oral tablets by Duramed Pharmaceuticals, Incorporated.
12 This progestin-only emergency contraception is indicated
13 for the prevention of pregnancy following unprotected
14 intercourse or a known or suspected contraceptive
15 failure. It is available by prescription for women
16 younger than age 17 years and available over the counter
17 for women 17 years and older.

18 (Screen.)

19 Plan B One-Step was originally approved for
20 marketing on July 10, 2009, the same date of the PREA
21 labeling changes. There are two related products, Plan
22 B and Next Choice, which contain 0.75 milligrams of

1 levonorgestrel and are dosed at one tablet very 12 hours
2 for a total of 2 doses.

3 (Screen.)

4 The pivotal clinical study leading to approval
5 was a double-blind, randomized, multi-center,
6 multinational study of 2,381 healthy women who needed
7 emergency contraception within 72 hours of unprotected
8 intercourse. The patients were randomly allocated to
9 receive either a single dose of 1.5 milligrams or two
10 doses of 0.75 milligrams.

11 The women who took Plan B One-Step had 84
12 percent of expected pregnancies prevented and those who
13 took Plan B had 79 percent of expected pregnancies
14 prevented.

15 (Screen.)

16 The labeling states that safety and efficacy
17 are expected to be the same for post-pubertal
18 adolescents less than 17 years and for users 17 years
19 and older.

20 (Screen.)

21 The next few slides discuss the safety
22 labeling, both prescription and over-the-counter. The

1 prescription labeling contraindicates use in the case of
2 known or suspected pregnancy. The labeling provides
3 warning for ectopic pregnancy, lack of effectiveness in
4 termination of an existing pregnancy, alteration of
5 expected menses, and lack of protection against STIs or
6 HIV.

7 (Screen.)

8 The labeling also provides a warning that a
9 rapid return of fertility is likely following treatment
10 with Plan B.

11 (Screen.)

12 This table lists the adverse events seen in
13 greater than 4 percent of women studied, with heavier
14 menstrual bleeding being the most common.

15 (Screen.)

16 The drug facts label contains similar warnings
17 and precautions as the prescription labeling. The label
18 lists common adverse events, as you see here.

19 (Screen.)

20 On to some information about use.

21 (Screen.)

22 From year 2002 to year 2010, the number of

1 packages sold for over-the-counter and prescription Plan
2 B, Plan B One-Step, and Next Choice increased from
3 129,000 packages to 7.2 million. During year 2010, Next
4 Choice accounted for the highest proportion of the total
5 sales market with 65 percent, followed by Plan B One-
6 Step with 35 of total sales, and Plan B with less than 1
7 percent.

8 (Screen.)

9 This figure reiterates the same data discussed
10 in the previous slide.

11 (Screen.)

12 The number of patients receiving dispensed
13 prescriptions for oral single-ingredient levonorgestrel
14 products as a whole increased from 64,400 in year 2002
15 to 484,000 in year 2006. It then decreased to 190,000
16 in year 2010.

17 (Screen.)

18 Oh, I'm sorry. Excuse me.

19 (Screen.)

20 During year 2010, 106,000 patients received
21 prescription for Next Choice, 85,500 patients received
22 prescriptions for Plan B One-Step, and 3,800 patients

1 received prescriptions for Plan B.

2 (Screen.)

3 This figure shows that the majority of
4 patients receiving dispensed prescriptions for oral
5 single-ingredient levonorgestrel products throughout the
6 time period examined was age 18 years and older.
7 Pediatric patients age 17 years and younger accounted
8 for a small proportion of total patients.

9 (Screen.)

10 This table again shows that the majority of
11 patients receiving dispensed prescriptions for
12 individual product Plan B, Plan B One-Step, and Next
13 Choice in year 2010 was 18 years and older. Pediatric
14 patients age 17 years or younger accounted for around 10
15 percent of patients receiving dispensed prescriptions
16 for each product. The trend is similar for other years.

17 (Screen.)

18 Over the cumulative time period from 2002 to
19 year 2010, gynecologist was the top prescribing
20 specialty for Plan B. The top prescribing specialty for
21 Next Choice and Plan B One-Step was unspecified,
22 followed by gynecologist. Over the same time period,

1 contraception management was the top diagnosis for Plan
2 B for all age groups and for Next Choice for adults age
3 18 years and older.

4 (Screen.)

5 I will now review the post-marketing adverse
6 events reports received by the agency. There were a
7 total of 19 pediatric reports, of which 18 were coded as
8 serious and included one death.

9 (Screen.)

10 This slide illustrates the process for case
11 selection of the serious adverse events. We start with
12 a crude count of 18 serious pediatric reports. There
13 were no duplicate reports. We excluded three reports,
14 one with a fatality in a premature infant and two
15 premature births. We were left with 15 cases, none of
16 which were fatal.

17 (Screen.)

18 All of the cases were in females. The ages
19 range from 15 to 17 years. The majority of the cases
20 involved the two-dose regimen.

21 (Screen.)

22 This slide provides a breakdown of the cases

1 by adverse event. Three adverse events -- hematemesis,
2 loss of consciousness, and syncope -- are unlabeled
3 events. There were four cases of hematemesis.

4 (Screen.)

5 The first case involved a 15-year-old who took
6 Plan B and experienced dizziness, non-menses-like
7 stomach pain, and poor appetite two to three days later.

8 The next day the patient experienced one episode of
9 vomiting blood.

10 The second case involves a 16-year-old who
11 took Plan B One-Step. 14 days later, the patient
12 vomited blood for an unknown duration. A home urine
13 pregnancy test conducted the same day was positive.

14 (Screen.)

15 In the third case, a 16-year-old took a single
16 dose of Plan B and experienced nausea and intermittent
17 vomiting that same day. Two days later, the patient
18 experienced hematemesis and went to an emergency room
19 for evaluation. The patient's stomach was pumped and
20 she was discharged home. Three days later, the nausea
21 and vomiting continued, but no further hematemesis. In
22 addition, the patient experienced vaginal bleeding which

1 was later than her normal menses.

2 The last case involves a 17-year-old who took
3 Plan B. The next day the patient experienced vaginal
4 bleeding heavier than her normal period for one day.

5 Two days after taking Plan B, the patient experienced
6 one episode of vomiting with a small amount of blood.

7 (Screen.)

8 There were four cases involving loss of
9 consciousness or syncope. The first is a 16-year-old
10 who took Plan B two tablets as a single dose and then
11 another two tablets as a single dose one day later. The
12 next day after the second dose, she stood up from a
13 seated position and lost consciousness for approximately
14 five seconds. The patient did not seek medical
15 treatment.

16 The next case is a 16-year-old who took Plan
17 B. The next day the patient experienced severe
18 abdominal pain, which caused her to faint and hit her
19 chin, resulting in a laceration. She was transported to
20 the emergency room, where it was thought that the
21 abdominal pain caused a drop in blood pressure. She was
22 treated and released five hours later. The abdominal

1 pain resolved the next day.

2 (Screen.)

3 The third case is a 17-year-old who took Plan
4 B and experienced a nosebleed and menstrual-like
5 cramping the next day. That same day, the patient
6 passed out while at school for an unknown duration. She
7 was seen by the school nurse, who released her after an
8 hour. The nosebleed resolved the same day, but the
9 cramping persisted for an unknown length of time.

10 In the last case, we have a 16-year-old who
11 took Plan B and experienced dizziness and fainting that
12 same day while in the heat and watching her boyfriend
13 feed a mouse to a snake. The dizziness and fainting
14 resolved the next day -- the same day.

15 (Screen.)

16 In summary, this concludes the pediatric
17 focused safety review. There were no new pediatric
18 safety signals identified. FDA recommends returning to
19 routine monitoring. Does the committee concur?

20 (Screen.)

21 I'd like to thank the people here for their
22 help with this presentation.

1 CHAIRMAN ROSENTHAL: Thank you, Dr. Taylor.

2 All right. What discussion shall we have
3 about Plan B One-Step?

4 DR. MURPHY: We are not here to discuss the
5 efficacy. Remember, that's for all products, please.
6 We're to discuss the safety. We will take safety and
7 any other remarks and consider the whole picture, but
8 today we're focusing on the safety, please.

9 CHAIRMAN ROSENTHAL: Dr. Wagener.

10 DR. WAGENER: I just have a question. It has
11 to do with the use data you have, because between 2006
12 and 2007 it went OTC. Do you have any data on the OTC
13 use, because I think you gave us just the prescription
14 use.

15 DR. TAYLOR: Is Tracy Pham here? Can you deal
16 with it?

17 Is there a particular slide that I can show,
18 or is this separate?

19 DR. WAGENER: You can go to slide 14, I
20 suppose would work.

21 (Screen.)

22 DR. PHAM: Hi. This is Tracy Pham. I'm a

1 drug use analyst from OSE.

2 We look at the sales data. If you go back a
3 couple of slides --

4 (Screen.)

5 Okay. So we look at the sales data from the
6 year 2002 to year 2010. So that covers all of the
7 single-ingredient levonorgestrel products, including
8 Next Choice, Plan B, and Plan B One-Step. We did look
9 at the OTC database that specifically looked at the
10 households, number of households that purchased these
11 products, and we weren't able to find a good number of
12 households that purchases these over-the-counter
13 products. So that's why we didn't include it in the
14 review, because it was not -- the number was very low
15 and it didn't support -- it didn't show any supportive
16 result for these products. So that's why we didn't
17 include it in the review.

18 Instead of looking at that, we looked at the
19 number of dispensed prescriptions for these products
20 instead.

21 CHAIRMAN ROSENTHAL: Other questions or
22 statements? Yes, Dr. Dracker.

1 DR. DRACKER: This is a tough one to comment
2 on, but the question I have is, you know, seeing quite a
3 few children between the ages of 13 and until they leave
4 me at 22, the concern I have is the use of a product,
5 especially if it were over-the-counter, not just on an
6 emergency basis the way it was originally intended, but
7 using it as a form of delayed onset birth control when
8 they've missed their period, much, much later.

9 You know, we commonly see children, and I
10 would say it probably occurs five to ten times a year,
11 who come in from abdominal pain, for abdominal pain, and
12 we find that they are three, four, or five months
13 pregnant, whether they were aware of it or not, whether
14 they want to discuss it or not.

15 The concern I have is to use that as a form of
16 birth control in a way that it was never intended to be
17 used when the use of other forms of birth control in
18 adolescents isn't even considered, despite the fact that
19 it's readily available. It's just a concern I have, not
20 personally, but really as a physician taking care of
21 these young women.

22 CHAIRMAN ROSENTHAL: Other comments or

1 responses to that observation or statement?

2 DR. MURPHY: I think that we're interested in
3 any concerns the members want to express as it relates
4 to the safety of the product. So we note your concern.

5 CHAIRMAN ROSENTHAL: Dr. Hillard.

6 DR. HILLARD: A couple of things. One, to
7 respond to the previous comment, I think that it's
8 pretty clear that this product does not have an effect
9 of interrupting a preexisting pregnancy. It just
10 doesn't work. And there are not data to indicate risks
11 in that situation. So it's not going to work, but I'm
12 not concerned about the safety in that situation.

13 I think the data as we have heard, and we've
14 heard from ACOG and gynecologists and the FDA, this is a
15 very safe product. It is so safe that it is outrageous
16 that it is not available for women of all ages over the
17 counter. So that is my statement. Thank you.

18 CHAIRMAN ROSENTHAL: Yes, Dr. Walker.

19 DR. WALKER: I agree fully with what Paula
20 just said. The other thing about that, too, is if a
21 woman of any age chooses to use it repeatedly that's
22 kind of their choice. It is safe. In practice, I don't

1 normally see that because it takes time. One, if you
2 actually have to go to the doctor and get it over and
3 over again, that takes time. And if you have to pay for
4 it, adolescents don't tend to have the money to pay for
5 things over and over anyway. More likely, people don't
6 use anything.

7 But I think that is a discomfort someone may
8 have, but yet it's the woman's choice.

9 CHAIRMAN ROSENTHAL: Dr. White.

10 DR. WHITE: If I put on my hat as an ethicist,
11 I have a lot of concerns about the discussion that we
12 can't have. But as a discussion of safety, if we look
13 at the safety issue, and that's all we're going to
14 address here, then I think we can say that the safety
15 issue is that it's fine for anyone that chooses to take
16 it. And if that's the case and we can't discuss any of
17 the ethical concerns, then I'd kind of like to move
18 forward and vote in favor of all this safety data
19 supporting the use in women over-the-counter.

20 CHAIRMAN ROSENTHAL: Other comments? Yes.

21 DR. WIEFLING: This is Bridgette Wiefling and
22 I have a few things I'd like to add to the packaging,

1 regardless of the age, especially if you're going to be
2 dealing with children under 17, is the medications that
3 concurrently can cause a problem and interfere. I think
4 the disease that's being treated by that medication
5 should be located adjacent to the medication in case
6 they're not -- like for instance the seizures and things
7 like that; I think the disease should be located next to
8 the medication, because it is the scientific medication
9 name that's being used and not necessarily the brand
10 name, which they may be familiar with, might be on their
11 bottle.

12 I think the packaging does not do a good job
13 of explaining what to do if you're on birth control
14 pills and you take the plan B and then you need to
15 restart your birth control pills. It's not explicitly
16 laid out, like do you resume your birth control pills
17 that very same next day, do you seek advice from your
18 physician. So I think that that should be laid out.

19 CHAIRMAN ROSENTHAL: Thank you.

20 Other? Yes, Dr. Wagener.

21 DR. WAGENER: I have just a question to the
22 FDA. Two things that showed up and I believe you

1 underlined them, suggesting they're not on the package
2 insert, was the hematemesis and the syncope. Is there a
3 reason why you felt they should not be added to the
4 package insert or to the information packet given to the
5 individual purchasing the product?

6 DR. ROTHSTEIN: This is Adrienne Rothstein
7 with the Office of Surveillance and Epidemiology.
8 There's substantial use of this product and there's just
9 a handful of reports. It's something that we are
10 monitoring, but there is very little information in
11 these reports to directly link this to the product. So
12 in the syncope, there was the episode where the mouse
13 was being fed to the snake. There are some other
14 alternative explanations.

15 But it is something we are monitoring. We
16 continue to review the safety of the product, and in the
17 future if we think that it should be added to the
18 labeling we would do so.

19 DR. MURPHY: Dr. Wagener, I would just add to
20 that that there was a fair amount of discussion about
21 this issue. Some would say it could make sense from a
22 bleeding point of view. So I think that what you --

1 when you see this recommendation where we're not
2 suggesting anything in the way of labeling, it usually
3 will indicate, as said, there's large use, small, few
4 reports, mostly explanations in some way, but could make
5 sense.

6 So I think it's reassuring to know at least
7 that they will continue monitoring for that.

8 DR. WAGENER: Do you see a similar number of
9 reports in the adult population? Just because somebody
10 was feeding a mouse to a snake doesn't mean that it
11 wasn't drug-related.

12 DR. MILLER: This is Mark Miller. I'm a
13 safety evaluator with the FDA. We looked at all ages
14 and there's 23 total reports of hematemesis. There are
15 reports of loss of consciousness and syncope with other
16 ages as well.

17 DR. MURPHY: We actually do look at the
18 adults. Part of our mandate is to try to look -- unless
19 there's huge numbers. Then we'll try to break that out,
20 what part of the adult population we might look at.

21 DR. WAGENER: But it sounds like it's probably
22 evenly distributed in the age groups or whatever. At

1 least the reporting, as best we can tell, is coming from
2 both?

3 DR. MILLER: That's correct. The reporting is
4 mostly consumer reports, so it's very difficult. We
5 can't go back and actually follow up with these reports.
6 So that's -- I would say the majority of all the
7 reports are consumer reports.

8 CHAIRMAN ROSENTHAL: Dr. Cope.

9 DR. COPE: I just wanted to highlight, I think
10 almost all these reports were voluntary reports,
11 consumer reports. The other difficulty was -- we went
12 very carefully over all these cases. So if you look, we
13 actually took the adverse event review up to age 18 for
14 this. So we wanted -- sometimes we'll stop at the 16th
15 birthday or go through 16, and we wanted to look at
16 older adolescents.

17 DR. ROTHSTEIN: This is Adrienne Rothstein. I
18 want to correct something. We actually went up to age
19 17. I want to correct that.

20 Then, although there were consumer reports,
21 when they're reported to the sponsor the sponsor is then
22 obligated to report it to the agency. So I just wanted

1 to clarify that. Thank you.

2 CHAIRMAN ROSENTHAL: Dr. Hausman, did you have
3 your hand up?

4 DR. HAUSMAN: No.

5 CHAIRMAN ROSENTHAL: No, okay.

6 Dr. White, did you?

7 DR. WHITE: You brought up an interesting
8 point and one that I don't quite understand how you can
9 get the data, which is if this is an over-the-counter
10 drug what is the reporting system that would give you
11 access to reports, other than if somebody happened to
12 call the sponsor or the manufacturer and say, I've got a
13 problem? Is there an adverse event reporting system
14 that captures over-the-counter drug risks?

15 DR. MURPHY: Anybody can call in to MedWatch
16 and report for over-the-counter, for prescription. So
17 that system accepts not just the sponsor reports, but
18 public reports for whatever they've taken.

19 DR. WHITE: Is it widely used?

20 DR. MURPHY: That's where we get our one in
21 ten estimate of expected adverse events that are
22 actually reported. So the question is to how widely

1 it's used is we don't -- we don't have an accurate
2 estimate of that. Various people have tried to address
3 that, and I don't think we could break it out, unless
4 the OSE people would tell me something, for over-the-
5 counter versus prescription.

6 Certainly we know that this reporting is
7 influenced, as you've heard today a couple of times, by
8 many things, be it public information, a new product,
9 lawsuits, all those things. Sometimes the most reports
10 we get on a product are from a lawyer.

11 CHAIRMAN ROSENTHAL: May I just? May I ask a
12 naive question? I'm trying to think, and I haven't come
13 up with anything, about whether there are other products
14 that are over-the-counter for adults and prescription
15 medications in kids. If someone can help me understand
16 that, that would be useful.

17 But then also, for this particular product is
18 the rationale one that's based on safety and efficacy or
19 is -- and I don't mean to be sort of opening up a
20 difficult discussion, other than I just want to be clear
21 if there is a scientific basis that's not obvious to the
22 committee.

1 DR. MURPHY: We'll have the representative
2 from the division address maybe some of the thinking
3 there. And we can think if there are any other
4 products.

5 CHAIRMAN ROSENTHAL: The only thing I could
6 come up with was ethanol, and I don't know if you can
7 prescribe that to kids.

8 DR. MURPHY: Yes, yes.

9 DR. WHITE: In Louisiana we use that all the
10 time.

11 DR. FURLONG: My name is Leslie Furlong. I'm
12 from the Over-the-Counter Division. As far as we know,
13 there aren't any products, besides the Plan B and Plan B
14 One-Step and the generic versions, that are labeled
15 differently for children and adults in terms of
16 prescription and over-the-counter access. We do have
17 other contraceptives over the counter, condoms and
18 spermicides, that are not restricted by any particular
19 chronologic age.

20 CHAIRMAN ROSENTHAL: The next part of my
21 question was can you help me understand whether that
22 difference is based on safety and efficacy differences

1 that are age specific or whether it's based on things
2 other than what we might consider a scientific basis?

3 DR. FURLONG: I can't tell you the thinking
4 that went into that decision. However, I can tell you
5 that since about 1959 or so when the first birth control
6 pill was approved by the agency, we have, except for the
7 Plan B, the levonorgestrel-only products, we have
8 assumed as an agency that all women of reproductive age
9 are covered by the safety and efficacy trials for
10 contraceptives.

11 So Plan B is quite unique among oral
12 contraceptives in its labeling.

13 DR. MURPHY: The only other thing somebody
14 wanted me to point out was -- and this isn't quite what
15 you asked, but if you look at a number of products like
16 TPIS and some of the other over-the-counter products,
17 they'll be over-the-counter for a certain dosing level
18 and then prescription for another dosing level. So
19 that's not at all uncommon.

20 CHAIRMAN ROSENTHAL: Okay. Dr. Wiefling and
21 then Dr. Dracker.

22 DR. WIEFLING: I bring up all the easy stuff.

1 So on the last page of the Plan B, where you have the
2 phone numbers for STD education, you need to have a web
3 site, because less than 17, they're more likely going to
4 be using a web site rather than a phone number. Thank
5 you.

6 DR. DRACKER: This is almost like a ridiculous
7 comment to make, but I would submit that collecting your
8 data or getting demographics on the use of this product
9 in adolescents below 18 years of age is almost
10 impossible, because, much like alcohol, many of these
11 products may be obtained by friends or associates above
12 the age of 18.

13 I see it all the time, not necessarily with
14 this product, but other products, whether it's diversion
15 of ADHD drugs or obtaining of alcohol or cigarettes.
16 It's routine, especially in a young girl who finds
17 herself in a difficult situation and will find another
18 source to get the medication.

19 DR. MURPHY: I do know that people did bring
20 that issue up in the discussion.

21 CHAIRMAN ROSENTHAL: Dr. White.

22 DR. WHITE: I know I'm treading on thin ice.

1 The ethics of this really bother me, because I think it
2 does deserve discussion and I don't know what the
3 appropriate forum is. So I'm going to ask this question
4 anyway: What do you do about emancipated adults?
5 They're under the age of 18 and legally adults. Are
6 they allowed to buy this over-the-counter?

7 DR. MURPHY: I'm going to defer. But before I
8 defer, I will say that I know -- and Dr. Nelson, Skip
9 Nelson, may want to address some of this -- that the way
10 we look at a number of like trials, where you have to
11 decide whether they're adults, emancipated adults, or
12 not, it's whatever the state determines is the --
13 whether you get an emancipated adult in the trial.

14 I don't know, Skip. Is there anything else to
15 add to that?

16 The label says 17 and above. But I'm just
17 saying, what do we do? He's asking what do we do about
18 emancipated adults.

19 DR. NELSON: It's emancipated minors. An
20 emancipated minor --

21 DR. WHITE: I apologize. You're correct.

22 DR. NELSON: An emancipated minor is an adult

1 in the eyes of the law, depending on the jurisdictions
2 within which that minor lives. Having said that --
3 which would give them the perfect legal right to have
4 access to this. But procedurally, I could imagine it
5 would be difficult because I think most states don't
6 carry emancipated minor cards, as opposed to their
7 driver's license, which has their age on it. So
8 whatever proof they would need to give at the local
9 level, it could be problematic to them.

10 DR. WHITE: So do we have any data to suggest
11 they're at greater risk for problems with this drug than
12 those that are not emancipated minors?

13 DR. NELSON: No, not that I'm aware of.

14 DR. WHITE: Thank you.

15 CHAIRMAN ROSENTHAL: Just to be clear, that's
16 Dr. Skip Nelson. He's a pediatric ethicist for the FDA.

17 Other comments or questions regarding -- yes,
18 Ms. Eichner?

19 MS. EICHNER: Yes. Marilyn Eichner. I'm just
20 wondering, given the population that's going to be
21 targeted, will the language in the label change?

22 CHAIRMAN ROSENTHAL: Can you be more clear?

1 DR. MURPHY: Yes, I'm not sure what you're
2 asking.

3 MS. EICHNER: I'm just -- I'm looking at the
4 label and I know it's geared toward 17 and above. If a
5 13-year-old is going to buy this drug, I'm looking at
6 some of the terminology that I don't think they would
7 understand. I'm just wondering, is the language going
8 to be made more simpler?

9 DR. MURPHY: So you're saying, if we were
10 going to make it --

11 MS. EICHNER: Yes.

12 DR. MURPHY: -- available over-the-counter,
13 would we consider making the language more appropriate?

14 MS. EICHNER: Exactly.

15 DR. MURPHY: I think in general I would say
16 any time we try to make the label as understandable as
17 possible. I don't know that we would -- this has been
18 such a different topic. I don't know that I can use any
19 precedent to say what we would or wouldn't do. I think
20 it would have to be discussed internally and certainly
21 considered that if you're going to be trying to provide
22 information for that population, do you need to change

1 the language in the label.

2 CHAIRMAN ROSENTHAL: Dr. Hausman, did you have
3 a question?

4 DR. HAUSMAN: I was actually going to ask the
5 same clarification that Dr. Murphy did.

6 CHAIRMAN ROSENTHAL: Thank you.

7 Dr. Baker.

8 DR. BAKER: This is Susan Baker. I just
9 wanted to repeat something that you said in the letter
10 that you read from the gynecologists and that I believe
11 was in the briefing materials. That's that you have
12 studies that show that women under 17 down to age 13
13 could understand the labeling, could use the medication
14 correctly, and didn't have any problems with it.

15 So I don't know. I'm interested in why
16 someone might want to consider changing it when you have
17 data that suggests it's good, it works.

18 DR. MURPHY: I think the question was if you
19 were going to do any younger than that. That's the way
20 I took it.

21 DR. BAKER: Younger than 13?

22 DR. MURPHY: Yes. That's the way I understood

1 the question.

2 CHAIRMAN ROSENTHAL: Yes, Dr. Castile.

3 DR. CASTILE: Recognizing we may be nearing
4 voting -- this is Bob Castile -- I just want to make
5 sure I understand the implications of the vote. I'm not
6 actually sure. In patients 17 and under, is this
7 currently a prescription drug, a behind-the-counter
8 drug, or an on-the-shelf drug?

9 And if we vote, are we voting for it becoming
10 a behind-the-counter drug or an on-the-shelf drug? Or
11 what are the implications of the vote, safety issues
12 aside? I personally don't seem to have any concerns
13 with the minor safety issues.

14 CHAIRMAN ROSENTHAL: I think the question
15 before us pertains only to the safety issues. We've not
16 been asked to consider whether the prescription status
17 of this should be changed.

18 DR. CASTILE: So the vote has nothing to do
19 with the accessibility of this drug for 17-year-olds and
20 less; is that right?

21 CHAIRMAN ROSENTHAL: The vote doesn't. The
22 conversation may inform that topic.

1 Would you like to -- would you like to speak
2 to that?

3 DR. CASTILE: I'm not sure, if the vote has
4 nothing to do with it.

5 I guess the other question that comes up in my
6 mind is this issue of the FDA's recommendation
7 previously being overruled by Health and Human Services.

8 I just need a little bit more understanding of what
9 that recommendation was and what was overruled and what
10 the implications were. I'm not sure I understand that
11 entirely.

12 DR. MURPHY: I think what we tried to do today
13 is to bring this product to you in as emotionless state
14 as possible, so that it looked at what we would
15 regularly look at for this product, which is any product
16 studied in children comes to this committee to look at
17 the safety signals that might have occurred post-
18 marketing, and we wanted to do that. We wanted to make
19 sure that that happened.

20 So we have brought you our review and we've
21 done as thorough a job as we usually do and have brought
22 that to you. What you are voting on is is there any

1 information or any better way that we could provide
2 information in the labeling about safety from the data
3 that you've seen. That's what you're voting on.

4 DR. CASTILE: So whether it's prescription or
5 behind-the-counter or on the shelf is to be decided
6 elsewhere?

7 CHAIRMAN ROSENTHAL: Has been decided
8 elsewhere.

9 DR. CASTILE: Has been decided elsewhere,
10 okay.

11 CHAIRMAN ROSENTHAL: Yes. So the question
12 before us --

13 DR. CASTILE: And that's the answer to my
14 question about the overruling by Health and Human
15 Services. It was decided elsewhere. Got it.

16 DR. MURPHY: We have a factual clarification
17 about use, is that correct?

18 DR. GOVERNALE: Yes.

19 DR. MURPHY: We like to go back to facts
20 whenever we can.

21 CHAIRMAN ROSENTHAL: Yes.

22 DR. GOVERNALE: Laura Governale, FDA Office of

1 Surveillance and Epidemiology. The previous question
2 was regarding the sales information. I don't know if
3 you can go back to slide number 13 --

4 DR. TAYLOR: 13.

5 (Screen.)

6 DR. GOVERNALE: Yes. So that slide shows both
7 over-the-counter and prescription sales distribution
8 from the manufacturers. I just wanted to make that
9 clear. The other slides were looking at the
10 prescription use just to get the age information.

11 CHAIRMAN ROSENTHAL: Thank you for that
12 clarification.

13 Other points? Other questions? Any other
14 questions pertaining to the safety of this product or
15 the usage?

16 (No response.)

17 CHAIRMAN ROSENTHAL: All right. Can we go
18 back to the voting question.

19 (Screen.)

20 CHAIRMAN ROSENTHAL: This is one of our usual
21 voting questions. It's the FDA is recommending
22 returning to routine monitoring. As we've heard this

1 morning, routine monitoring is an active process. It's
2 not passive. It implies a high level of vigilance and
3 integrated thinking.

4 So the question before the committee is, do we
5 concur with the recommendation to have the safety
6 profile for Plan B One-Step return to that usual
7 process?

8 Dr. White, are you voting yes or --

9 DR. WHITE: I have a question. I have a
10 question.

11 CHAIRMAN ROSENTHAL: A question, yes.

12 DR. WHITE: I apologize again. The
13 recommendation of the FDA as it exists, are we voting to
14 say that we found no routine safety problems with this
15 drug, or have we found that we have uncovered no new
16 safety issues related to this drug as an over-the-
17 counter drug, as demonstrated in everyone over the age
18 of 18, that there's no difference?

19 If we're not really paying attention to the
20 regulation of this drug, is the safety -- do we need to
21 specify or can we specify that it's just as safe over-
22 the-counter as it is as a prescriptive as part of our

1 vote?

2 CHAIRMAN ROSENTHAL: Dr. White, I think that
3 we should be focused on issues of safety as they pertain
4 specifically to the pediatric population.

5 DR. WHITE: And currently in use, as currently
6 used?

7 CHAIRMAN ROSENTHAL: As reflected in the data
8 that have been presented to us.

9 DR. MURPHY: Again, as has been said for other
10 products, you can say at this time: We don't see
11 anything; we're concerned about hematemesis and we want
12 you to come back. As you heard, we can do that. That's
13 -- it doesn't have to be just this if there is a concern
14 that you have about safety.

15 CHAIRMAN ROSENTHAL: Again, the discussion is
16 where the money is in these. So if one is comfortable
17 with the FDA returning to its routine monitoring, with
18 the understanding I think that the FDA has, Dr.
19 Hausman's term, that the hematemesis has tickled the
20 eyes -- I'm mixing metaphors. But anyway, the idea is
21 that the attention is already drawn to this issue of
22 hematemesis for this product.

1 So if one feels that routine monitoring is
2 reasonable, then one should vote yes. If one feels that
3 some additional monitoring or other actions to better
4 assure safety based on what's been presented is
5 reasonable, then you should vote no and indicate in your
6 answer why you feel that something additional is needed,
7 and in the descriptions of what else is needed a lot of
8 information that's useful for the agency comes from
9 these discussions.

10 Is there further discussion? Dr. Motil.

11 DR. MOTIL: As the pediatric
12 gastroenterologist of the group, I guess the word
13 "hematemesis" is sort of a blase word for me. While
14 hematemesis has the implication of a large amount of
15 blood being vomited, we see the description of
16 hematemesis and in the eyes of the beholder any bit of
17 blood is a lot of blood. Very often it's a kid who
18 gaggles in the back of the throat and then bleeds, has a
19 nosebleed along the way, bleeds a little bit, maybe has
20 a Mallory-Weiss tear because they did vomit a little bit
21 more forcefully.

22 But it's rare for me to truly see the

1 hematemesis child, unless they have known liver disease
2 or some of these other issues. So I guess the word
3 "hematemesis" does not frighten me in the context of one
4 report, and really it's just a very low blip on my radar
5 and doesn't cause me angst. But that's my biased eye
6 from what I see in the clinical world.

7 CHAIRMAN ROSENTHAL: Well, actually, Dr.
8 Motil, I'd say that your biased eye is actually the eye
9 of a subspecialist in the area, so I think your
10 observations are both of interest and are relevant.

11 Dr. Hausman.

12 DR. HAUSMAN: Just a comment about the reports
13 that we got. The terms that we get are a combination of
14 how things are coded by the sponsor or the reporter, if
15 it's a consumer report, and the database entry folks who
16 enter the report information into AERS. Having gone
17 over these reports with Mark Miller, there isn't any
18 indication that, hypothetically, somebody came in and
19 had exuberant retching, had a Mallory-Weiss tear and
20 bled five units.

21 I say that specifically because we do look for
22 things like that. We also have no idea whether somebody

1 bit their lip. The characterization of the reports in
2 your background package is substantially verbatim what
3 we receive. There are some extra tidbits of information
4 that we didn't feel were significant enough to actually
5 put in the review.

6 So I'm glad the subject came up one more time
7 so we could get to the committee the impression that we
8 really did take a very, very careful look at these
9 reports, and whether or not any of us would have used
10 the word "hematemesis" from our clinical background may
11 not necessarily relate to how the reports come in.

12 Thank you.

13 CHAIRMAN ROSENTHAL: Yes, Dr. Bhatia.

14 DR. BHATIA: Not to belabor the point, ethics
15 aside, pragmatically we're talking about 15 cases with a
16 denominator we do not even know. All we know is so much
17 was sold wholesale. So unless there's smoke there's no
18 fire at this point in time. And the recipients at the
19 other end of this, 13-year-olds having children -- 17 is
20 considered old primigravida nowadays. So prevention is
21 needed.

22 Thank you.

1 CHAIRMAN ROSENTHAL: Other comments? Thank
2 you. Other comments or discussion?

3 (No response.)

4 CHAIRMAN ROSENTHAL: All right. Who's in
5 favor of having the FDA return to routine safety
6 monitoring for this agent, for Plan B One-Step?

7 (A show of hands.)

8 CHAIRMAN ROSENTHAL: Who is not in favor?

9 (No response.)

10 CHAIRMAN ROSENTHAL: And who has abstained?

11 (One hand raised.)

12 CHAIRMAN ROSENTHAL: So we've got no nays, one
13 abstention, and the others are affirmative.

14 Dr. Reed, will you tell us your vote and why,
15 if that's relevant?

16 DR. REED: Michael Reed. I vote yes. I
17 suspect there's relevance to my vote, why I decided.

18 (Laughter.)

19 CHAIRMAN ROSENTHAL: I'm sorry, Dr. Reed. I'm
20 sorry. I take it back.

21 DR. REED: I was awake.

22 CHAIRMAN ROSENTHAL: I take it back, I take it

1 back, I take it back.

2 DR. REED: I feel that going forward with
3 routine monitoring as it has been, and particularly as
4 we've been enlightened today that this is not a passive
5 process, I feel very comfortable moving forward with
6 continued routine monitoring.

7 CHAIRMAN ROSENTHAL: Thank you very much for
8 that explanation.

9 Dr. Santana.

10 DR. SANTANA: Victor Santana, abstain. No
11 further comment.

12 DR. DRACKER: Bob Dracker. I voted yes
13 despite the fact that you thought I would vote no. But
14 I just want to make a comment that I think obtaining
15 accurate information with regards to safety monitoring
16 for this age group is going to be very difficult.

17 DR. MOTIL: Kathleen Motil, yes.

18 DR. WAGENER: Jeff Wagener, yes. And I would
19 add that, with only 15 serious events over 9 years, that
20 safety in children is clearly shown. I would encourage
21 the FDA in your future deliberations to not discriminate
22 against children in their access to this.

1 DR. TOWBIN: Kenneth Towbin. I concur. I
2 wanted to express my appreciation to the FDA for
3 sticking close to the scientific data and remaining calm
4 and cool in the face of the review, and the way in which
5 they have continued to be consistent in making
6 recommendations based on the science.

7 Thank you.

8 DR. KRISCHER: Jeff Krischer, vote yes.

9 DR. WRIGHT: Joe Wright, yes.

10 MS. EICHNER: Marilyn Eichner, yes.

11 DR. CASTILE: Bob Castile. I voted yes. I
12 apologize for my naivete, and I agree fully with my
13 fellow pediatric pulmonologist Jeff Wagener.

14 DR. KAPLAN: Shelly Kaplan. Yes.

15 DR. BAKER: Susan Baker, yes.

16 DR. WIEFLING: Bridgette Wiefling, yes, and I
17 just hope you'll take into consideration the
18 clarifications on the packaging.

19 DR. MINK: John Mink, yes.

20 DR. BHATIA: Jatinder Bhatia, yes.

21 DR. FRANCO: Israel Franco, yes.

22 DR. HILLARD: Paula Hillard. I think the data

1 indicate very clearly that this product is equally safe
2 in women of all ages and, unfortunately, the requirement
3 that it be limited to adolescents to prescription only
4 severely limits access to a population that desperately
5 needs it.

6 I also thank the FDA for their response in all
7 of this.

8 DR. WALKER: Leslie Walker and I vote yes and,
9 although we were not speaking of it being over-the-
10 counter, I do want to make note that I look forward to
11 the day that there is no discrimination and anybody, any
12 woman who feels she needs it of any age, can get it over
13 the counter.

14 DR. FELNER: Eric Felner, yes.

15 DR. RAKOWSKY: Alex Rakowsky, yes.

16 DR. WHITE: Michael White, yes, and I would
17 like to support the comments of Dr. Hillard and -- I'm
18 sorry. Thank you.

19 CHAIRMAN ROSENTHAL: That concludes our
20 discussion about Plan B One-Step and so now we'll
21 transition to a discussion about Flomax, and Dr. Alyson
22 Karesh will be talking, will be presenting for us. Dr.

1 Karesh received her medical degree from the Medical
2 College of Virginia and completed her internship and
3 residency at the Children's Hospital of Pittsburgh.
4 Prior to joining the Pediatric and Maternal Health Staff
5 in the summer of 2008, she worked as a pediatric
6 hospitalist at Inova Fairfax Hospital in Fairfax,
7 Virginia. Additionally, she's worked as a pediatrician
8 for Kaiser Permanente.

9 Thank you for presenting today.

10 FLOMAX (TAMSULOSIN HYDROCHLORIDE)

11 (Screen.)

12 DR. KARESH: Good afternoon. This afternoon
13 I'm going to talk to you about Flomax.

14 (Screen.)

15 By now you're familiar with this outline.

16 (Screen.)

17 Flomax capsules are approved in adults for the
18 treatment of the signs and symptoms of benign prostatic
19 hyperplasia. Flomax is not approved for use in
20 pediatrics.

21 (Screen.)

22 Flomax was originally approved April 1997 and

1 pediatric exclusivity was granted September 2009. The
2 BPCA labeling changes that we're focusing on today
3 occurred on December 22, 2009.

4 (Screen.)

5 There were two pediatric Flomax studies done
6 to gain exclusivity. The studies were in patients 2 to
7 16 years of age with elevated detrusor leak point
8 pressure associated with a known neurological disorder.

9 (Screen.)

10 One of these two studies was a 14-week
11 randomized, double-blind, placebo-controlled, PK, safety
12 and efficacy study in 161 patients. The end point was a
13 reduction in detrusor leak point pressure below 40
14 centimeters of water. No statistically significant
15 difference was seen between the groups.

16 The other study was a 12-month, open-label,
17 safety study in 87 patients who received tamsulosin.

18 (Screen.)

19 This slide lists the most frequently reported
20 adverse events from these two pediatric studies. As you
21 can see, the most common adverse events included UTI, as
22 well as symptoms suggestive of infection, such as

1 pyrexia and pharyngitis, and GI complaints.

2 (Screen.)

3 In the pediatric studies there was one
4 fatality. A seven-year-old male with a complex medical
5 history, including unrepaired myelomeningocele and
6 hydrocephalus with a shunt, was found unresponsive 15
7 days after beginning tamsulosin treatment.

8 (Screen.)

9 The patient had uneventful clinical
10 evaluations 8 and 14 days after he started tamsulosin.
11 After he died, his parents declined post-mortem
12 evaluations and the primary investigator concluded that
13 the patient's cause of death was indeterminate.

14 (Screen.)

15 As a result of these two pediatric clinical
16 trials, labeling continues to state that Flomax was not
17 indicated for pediatric use, but now also describes the
18 two pediatric studies.

19 (Screen.)

20 The clinical pharmacology section of labeling
21 states that urologic pharmacodynamic effects have been
22 evaluated in neurologically impaired pediatric patients

1 and that Flomax is not indicated for pediatric use.

2 (Screen.)

3 On the last two slides we discuss pediatric
4 labeling changes. This and the next slide discusses
5 relevant Flomax safety labeling. Flomax labeling states
6 that Flomax is contraindicated if known to be
7 hypersensitive to tamsulosin or any component of Flomax,
8 and that reactions have included skin problems,
9 angioedema, and respiratory symptoms.

10 (Screen.)

11 Relevant warnings and precautions are
12 orthostasis and priapism.

13 (Screen.)

14 Now that we've discussed the pediatric studies
15 and labeling changes along with relevant safety
16 labeling, we'll turn our attention to Flomax use. The
17 total number of dispensed prescriptions nearly doubled
18 between 2002 and 2010, from approximately 6.5 million to
19 approximately 12.6 million prescriptions. Approximately
20 92.1 million prescriptions were dispensed between
21 January 2002 and June 2011.

22 (Screen.)

1 Those approximately 92.1 million prescriptions
2 were received by approximately 11.3 million patients,
3 99.8 percent of whom were adults.

4 (Screen.)

5 Although pediatric use was very low, we were
6 able to estimate the breakdown of pediatric use of
7 different benign prostatic hyperplasia medications,
8 including tamsulosin, between 2002 and 2010. Tamsulosin
9 is represented by the blue bar and was the most common
10 benign prostatic hyperplasia medication prescribed to
11 pediatric patients over this time frame.

12 (Screen.)

13 This table lists the diagnoses associated with
14 pediatric outpatient use of tamsulosin. Note that the
15 largest share were in patients with calculus of the
16 kidney, but please remember, as we discussed earlier,
17 the overall use in pediatrics was very low.

18 (Screen.)

19 Overall, between January 2002 and June 2011
20 males accounted for a majority of use. This finding was
21 expected since Flomax is approved for treatment of the
22 signs and symptoms of benign prostatic hyperplasia in

1 adults. Among pediatric patients, nearly 40 percent of
2 use was in females, which is consistent with the gender-
3 neutral conditions of use in pediatrics we just
4 reviewed.

5 (Screen.)

6 The most common prescribing specialty was
7 urology. Pediatric providers accounted for less than 1
8 percent.

9 (Screen.)

10 Now that we've established the foundation of
11 Flomax use, we'll discuss the safety review results.
12 Between April 1997 and July 2011 there were 13 total
13 pediatric reports. On the next few slides I will
14 provide further information about those reports.

15 (Screen.)

16 Of the 13 pediatric reports, 8 were serious
17 and none were fatalities. None of these 13 reports were
18 duplicates, but 2 were actually in adult patients. One
19 was a patient who was not actually receiving Flomax, one
20 concerned a patient exposed in utero. That left us with
21 nine pediatric cases, four of which were serious, none
22 were fatal.

1 (Screen.)

2 Of the four serious cases, three concerned
3 accidental exposure and one bradycardia, hypertension
4 and lethargy. On the following slides I will provide
5 more information about these four cases.

6 (Screen.)

7 The three accidental exposure cases are listed
8 here. One patient, a 21-month old female who ingested
9 approximately 1.6 milligrams of Flomax, experienced
10 diarrhea and decreased urine output. A two-year-old
11 female did not have adverse events. And the third
12 report, which was about a three-year-old female who
13 ingested approximately 0.2 milligrams of Flomax,
14 experienced hypotension. Diarrhea and hypotension are
15 labeled adverse events. Please note the report
16 concerning the three-year-old female, as we'll return to
17 it in a few moments.

18 (Screen.)

19 The fourth serious pediatric case was about a
20 four-year-old male who experienced bradycardia,
21 hypertension and lethargy. These are unlabeled events.
22 The patient received 200 micrograms for one day and

1 then 400 micrograms for one week. The patient's weight
2 was not specified in the report and therefore how the
3 dose relates to his weight is not known. As a point of
4 reference, I'll mention that the average four-year-old
5 male, per the CDC growth chart, weighs approximately 16
6 kilograms. In a pediatric study a 16-kilogram patient
7 would have received between 25 and 100 micrograms.

8 (Screen.)

9 In addition to the safety review I just
10 described, FDA also did an analysis focused on potential
11 hypotension events. Of the 163 hypotension-related
12 reports identified, only one was a pediatric report.
13 That case was a three-year-old female who ingested
14 approximately 0.2 milligrams of Flomax that we discussed
15 a few moments ago. Her blood pressure was reported as
16 64 over 31 and responded to IV fluids. The report did
17 not contain the patient's height, but for comparison
18 purposes the 50th blood pressure for a three-year-old
19 girl at the 50th percentile of height is 89 over 49, per
20 the Fourth Report on the Diagnosis, Evaluation, and
21 Treatment of High Blood Pressure in Children and
22 Adolescents.

1 (Screen.)

2 In addition to the general pediatric safety
3 review and the hypotension review, because three of the
4 four pediatric serious adverse events concerned
5 accidental exposure FDA also conducted a medication
6 errors post-marketing review. This review found six
7 accidental pediatric exposure cases, three of which
8 we've already discussed and three of which were
9 additional cases, which I will describe on the next
10 slide.

11 (Screen.)

12 Two of the three cases were two-year-old males
13 and one was a female whose age was not specified. Each
14 ingested approximately one Flomax capsule. No specifics
15 on the outcome was reported for any of the three cases.

16 (Screen.)

17 Because how tamsulosin was obtained by the
18 child was only described in one of the six accidental
19 exposure cases and Flomax is packaged in high-density
20 polyethylene bottles with child-resistant closures, the
21 Division of Medication Errors and Prevention Analysis
22 did not recommend changes.

1 (Screen.)

2 So this concludes the pediatric focused safety
3 review. No new pediatric safety signals were identified
4 and FDA recommends returning to routine monitoring.

5 Does the Pediatric Advisory Committee concur?

6 (Screen.)

7 I would like to acknowledge the folks listed
8 on this slide.

9 Thank you.

10 CHAIRMAN ROSENTHAL: Thank you for your
11 presentation.

12 Discussion about Flomax, safety specifically?

13 Yes, Dr. Franco.

14 DR. FRANCO: I'd like to make a couple of
15 comments. One is that, as a user of the medication,
16 it's always a big problem because the medication is
17 labeled only for females, and every time we go to order
18 it we have to argue incessantly with the insurance
19 companies that the medication can be used in females.
20 So I would ask the FDA to consider, especially since the
21 Flomax study and the other studies that have been done
22 in alpha blockers have all included females, that it is

1 safe in females and it can be used in females.

2 We use it primarily for bladder neck
3 dysfunction, the vast majority of our patients, and we
4 use it for our spina bifida and spinal dysraphism
5 patients in an attempt to lower leak point pressures.
6 So it becomes exceedingly difficult to get the
7 medication to the patients, and in many cases it's been
8 rejected by the insurance companies because it's, quote
9 unquote, "not approved in females." So we need to try
10 to see and fix that problem.

11 The orthostasis problem is probably not
12 related at all to the medication itself. If you look at
13 some of the data from the original studies that were
14 done utilizing Hytrin, there was no connection.
15 Actually, in our experience using the alpha blockers we
16 found in a series of 300 patients that came in to our
17 office who had voiding dysfunction that those 300
18 patients when asked specifically whether they had a
19 history of orthostasis, dizziness, 25 of them had it.
20 Those were the patients that had a tendency to respond
21 quite excessively when alpha blockers were introduced to
22 their treatment regimen. So it may be that these

1 patients have an underlying autonomic dysfunction to
2 begin with and that's why they have bladder neck
3 dysfunction, and then subsequently when you add an alpha
4 blocker to them it aggravates the autonomic dysfunction.

5 So I would recommend that probably putting in
6 what we do, and these patients will tolerate it once
7 they've been introduced to the medication slowly, and
8 that is to increase fluid intake, increase salt intake,
9 prior to starting treatment with the Flomax or any of
10 the alpha blockers.

11 The other thing is is that orthostasis has
12 nothing to do with the size of the patient. In our
13 experience, I've used alpha blockers in one-year-olds to
14 treat -- to lower bladder pressures and stop uninhibited
15 bladder contractions, and I can give a one-year-old one
16 milligram of Hytrin without any difficulty with
17 terazosin. So again it really has to do -- and I can
18 give a 250-pound football player .4 of Flomax and
19 they'll get dizzy.

20 So it basically appears not to have any
21 correlation with the dose, at least at low doses.

22 CHAIRMAN ROSENTHAL: Thank you.

1 Dr. Goldstein.

2 DR. GOLDSTEIN: I have this question for Dr.
3 Franco actually, or there may be other people on the
4 committee who may know. Unless there was some
5 supplemental data that I didn't see or didn't have a
6 chance to review, the data that was presented suggests
7 that there is a lack of efficacy, which pertains to how
8 one would view the safety signal.

9 So my question is -- and I know that there's
10 a lot of off-label use of different types of drugs that
11 don't necessarily have efficacy signals that are
12 approved in children. So I was just wondering from a
13 practical standpoint if you could give me some
14 background information on how the drug is used, even
15 though the efficacy study was not positive?

16 DR. FRANCO: Israel Franco. Actually the
17 problem with the study itself that was conducted, that
18 and the other study that was conducted with Sanofi with
19 Alfuzosin, is that they picked the leak point pressure
20 as the primary end point to the study. Now, they
21 arbitrarily picked 40 or they picked 40 centimeters of
22 water pressure as the level.

1 As a safety measure, historically we have felt
2 that 40 cm's is safety; it protects the upper tracts.
3 But when you try to -- many of these children would have
4 leak point pressures in excess of 80. Now, to expect a
5 child who has a leak point pressure of 80 and to expect
6 him to drop his leak point pressure below 40 is quite a
7 big drop, when you may have another child who has a leak
8 point pressure of 55 and he may drop below 40.

9 So that was one of the problems with the
10 study, that it was arbitrarily decided that you had to
11 drop below 40. So if you enrolled a large number of
12 patients that were in the study with exceedingly high
13 leak point pressures, the likelihood that you would
14 achieve success would be quite low.

15 So besides that, probably Flomax, which is a
16 selective alpha 1A receptor blocker, is probably not as
17 good at lowering pressures as compared to some other
18 non-selective alpha blockers, the terazosin and others,
19 which are selective -- non-selective 1A and 1D
20 receptors.

21 So we seem to see much greater improvements in
22 bladder capacity in some of these patients along with a

1 drop in leak point pressure. As far as -- for us it's
2 critical to be able to use the medication for our
3 dysfunctional voiders. This would give us an ability to
4 treat these patients who have primary bladder neck
5 dysfunction with a, medication that at least we know has
6 been safety tested and to sort of eliminate it would
7 make it very difficult for us to be able to continue
8 this treatment. And we know in the primary bladder neck
9 dysfunction patients that it works very, very well.

10 CHAIRMAN ROSENTHAL: Other questions or
11 comments regarding Flomax?

12 (No response.)

13 CHAIRMAN ROSENTHAL: All right. Are people
14 comfortable with the FDA returning to routine safety
15 monitoring for this product?

16 (No response.)

17 CHAIRMAN ROSENTHAL: All in favor, please
18 raise your hands.

19 (A show of hands.)

20 CHAIRMAN ROSENTHAL: Any opposed?

21 (No response.)

22 CHAIRMAN ROSENTHAL: Any abstentions?

1 (No response.)

2 CHAIRMAN ROSENTHAL: That looks like a
3 unanimous vote. Dr. White?

4 DR. WHITE: I concur.

5 DR. RAKOWSKY: Alex Rakowsky, concur.

6 DR. FELNER: Eric Felner, yes.

7 DR. WALKER: Leslie Walker, yes.

8 DR. HILLARD: Paula Hillard, yes.

9 DR. FRANCO: Israel Franco, yes.

10 DR. BHATIA: Jatinder Bhatia, yes.

11 DR. MINK: John Mink, yes.

12 DR. WIEFLING: Bridgette Wiefeling, yes.

13 DR. BAKER: Susan Baker, yes.

14 DR. KAPLAN: Shelly Kaplan, yes.

15 DR. CASTILE: Bob Castile, yes.

16 MS. EICHNER: Marilyn Eichner, yes.

17 DR. WRIGHT: Joseph Wright, yes.

18 DR. KRISCHER: Jeff Krischer, yes.

19 DR. TOWBIN: Kenneth Towbin, yes.

20 DR. WAGENER: Jeff Wagener, yes.

21 DR. MOTIL: Kathleen Motil, yes.

22 DR. DRACKER: Bob Dracker, yes.

1 DR. SANTANA: Victor Santana, yes.

2 DR. REED: Michael Reed, yes.

3 CHAIRMAN ROSENTHAL: That concludes the
4 discussion about Flomax.

5 DR. MURPHY: I just want to, now that we've
6 voted, I just wanted to say -- and we're not supposed to
7 talk about approval -- that one of the things we do do,
8 though, is we try to look at failed pediatric studies
9 and we try to figure out -- we've done this for
10 hypertension, we've done it for migraines -- we try to
11 figure out if a redesign of the study is necessary, a
12 different end point, a different population subset,
13 timing, whatever.

14 So I think again this meeting is not to
15 redesign the trials, but if you have feedback for the
16 division about these trials for children and if there's
17 a better way to design them, then obviously we're
18 interested that you communicate that, because we do try
19 to learn from failed trials. Are they failed because
20 they really don't work or are they failed because for
21 kids we need an end point that's slightly different?

22 DR. FRANCO: I would say that you should

1 probably look at some of the data from the Alfuzosin
2 study, where bladder volume was increased. It seemed to
3 work more in achieving that than actually lowering
4 bladder pressures. From our perspective as pediatric
5 urologists, we'd rather see an increase in bladder
6 capacity in a child who has spina bifida, who does
7 intermittent catheterization, than necessarily lowering
8 their outlet resistance, which is going to make them
9 incontinent and wet all the time.

10 So I'd rather have an increase in bladder
11 capacity. So I think that was one of the problems, was
12 the original assumption that we were just dropping
13 bladder pressure. So I'd be more than happy to discuss
14 that with you.

15 CHAIRMAN ROSENTHAL: Thank you.

16 Dr. Rakowsky, did you have a comment?

17 DR. RAKOWSKY: Dr. Franco brings up an
18 interesting comment, and this has come up I think a few
19 times in the past. I've been on the committee for
20 almost four years now. We have had drugs where it would
21 be almost impossible to get a pediatric indication, but
22 there is a small subset of patients for which there

1 appears to be a use. And yet, again speaking as a
2 clinician, you're fighting the insurance and you're
3 fighting the label.

4 I mean, this label specifically says for
5 benign prostatic. The MedGuide says not to be used in
6 children, not to be used in females. Has there been
7 thought about having a "other potential use" sort of
8 statement in there? It doesn't give you an indication
9 per se, but -- this has come up as to rare drugs, but
10 this is one where I can see where Dr. Franco's issue is,
11 and then you spend hours just trying to get the thing
12 approved.

13 I can't see this ever -- some of these drugs
14 have such a small population; how do you actually get
15 that indication in there?

16 DR. MURPHY: Well, you know, recently we had a
17 meeting on how to do trials in small populations, trying
18 to use information, where you can extrapolate, where you
19 can't extrapolate. I mean, the bottom line is can you
20 find a convincing set of data that would allow the
21 agency to label it, because, as you know, Alex, anything
22 that goes in the label can be marketed. So that's the

1 quandary.

2 I don't know, Lisa; did you want to add
3 anything to that?

4 DR. LISA MATHIS: No, other than this is a
5 common problem that we face in pediatrics, because if
6 the population is small you can't possibly do a large
7 enough study to demonstrate safety and efficacy in order
8 to support a second indication.

9 So in cases like this, it's always helpful if
10 we have a scientific rationale for extrapolation of
11 efficacy, that we can take down the numbers that we need
12 to support efficacy. But obviously we still need the
13 safety. So without that scientific evidence to support
14 extrapolation of efficacy, we're in a bit of a bind.

15 CHAIRMAN ROSENTHAL: Dr. White.

16 DR. WHITE: Is there any way to set up a
17 category similar to the humanitarian device exemption,
18 where you prove safety and suspected efficacy? With an
19 HDE you don't have to prove efficacy. All you have to
20 do is that it's safe and maybe it works.

21 In the circumstance where you have a small
22 population, it's just like the humanitarian use

1 exemption for devices, so is that something we should
2 explore?

3 DR. MURPHY: I think the issue with HDEs,
4 because pediatric devices have not been developed, okay.

5 As you know, with pediatric therapeutics, drugs
6 particularly, the way that we've been able to get this
7 field moving is to incentivize it for marketing. With
8 HDEs, they have a prohibition on profit-making. So
9 that's something that's also being looked at.

10 But the way that they tried to move that field
11 forward for children was to lift that prohibition for
12 profit-making. But even so, you're not talking about
13 huge numbers. So I think the issue of small population,
14 though, is clearly one that the agency's trying to be
15 innovative in figuring out ways to gather science and
16 data that they believe in.

17 I guess -- I don't know about Lisa. I'm sort
18 of hesitant right now to take children back to a level
19 where we're not going to require efficacy. We published
20 a paper on almost ten years, I don't think it was quite
21 ten years, of trials where we tried to look at where we
22 could extrapolate and where we couldn't, and we've

1 changed our mind over time.

2 Most of them we're pretty good at, but over
3 time we changed our minds. Where we felt we could, we
4 could not; we found that we really can't; and other
5 places where we now feel confident enough that we can.
6 But I think it's that kind of base you want to build.
7 You want to build that information. You don't want to
8 just say: Let's not do it.

9 CHAIRMAN ROSENTHAL: Other comments? Yes, Dr.
10 Mathis.

11 DR. LISA MATHIS: I just wanted to add that it
12 is that fine balance. We have the atypical
13 antipsychotics where we see a lot of off-label use and
14 we want to figure out ways to discourage it. So we're
15 right in the middle here, right where -- is there some
16 way to get the off-label use on the labels so people can
17 use it?

18 I think that it's probably better if we demand
19 a certain level of evidence prior to granting an
20 indication, knowing of course that we don't regulate
21 medical practice and that off-label use is always
22 allowed when a physician is dealing with a particular

1 patient.

2 That doesn't get to answering the question
3 about access to the medication and I know that it can be
4 very difficult trying to negotiate with an insurance
5 company to pay for a product that's not labeled for use
6 in a given population. But I think it is really
7 important for us to remember that part of what BPCA and
8 PREA have done for us is to allow us to have evidence-
9 based treatment of children and we really don't want to
10 drop the bar for children at this point.

11 So while I appreciate the position, I'm not
12 sure it's the best place to go.

13 CHAIRMAN ROSENTHAL: Dr. Franco, yes.

14 DR. FRANCO: I just want to make one more
15 comment regarding the studies of these patients. The
16 vast majority of all these antimuscarinics and alpha
17 blockers that are being tested in children are being
18 tested in a very small, select group, which are the
19 children with spinal dysraphism and neurogenic bladders,
20 which makes it very difficult to recruit, and you have
21 to rely completely on urodynamic data in many cases to
22 come up with results.

1 There is tremendous variability in the
2 performance of urodynamics from one location to the
3 next, so there is inhomogeneity of the data that we get.

4 That invariably can sort of doom a study. And after
5 being one of the reviewers reviewing urodynamics on one
6 study, it's clear that one site will do it very
7 differently.

8 Since we're locked in to only selecting this
9 one group of patients to be able to study these groups
10 of drugs, we're in a quandary that we're never going to
11 be able to get any of these drugs approved for these
12 children.

13 CHAIRMAN ROSENTHAL: Dr. Towbin and then Dr.
14 Dracker.

15 DR. TOWBIN: I just wanted to add a comment
16 related to working in this area of off-label use. I do
17 recognize, having spent some time being interested in
18 what are rare disorders and applications of agents that
19 would be off-label for rare disorders and the problems
20 that families have getting medications, sometimes quite
21 expensive medication -- some of the newer, second
22 generation antipsychotics, for example; paying for those

1 out of pocket can be exceedingly expensive. When we
2 were using them in some occasions for individuals with
3 Tourette's disorder, it's very expensive for those
4 families.

5 On the other hand, I am very keenly aware and
6 really concerned about the downward translation of data
7 to younger and younger populations, and particularly for
8 some of the medicines that I deal with day to day,
9 beginning to see use in preschoolers of very serious
10 agents.

11 So I'm really glad that we're staying with
12 safety and efficacy. I think the example that Dr.
13 Mathis raises of the SGAs is a great example and why I'm
14 really pleased that we're thinking about what the public
15 policy implications are, but that we're staying close to
16 what safety and efficacy data we've got and not lowering
17 the bar for children.

18 DR. DRACKER: Just a quick comment. All
19 physicians have participated in off-label use, even if
20 they don't realize it, which is probably usually the
21 case. Regardless, I think you can collect some very
22 valuable information if there was a feasible way to

1 encourage data collection from physicians who are using
2 drugs and products with the intent of trying to help
3 their patients.

4 So almost getting to the friendly FDA approach
5 of working with physicians in clinical practice and say,
6 if you're using a medication in an off-label use
7 application, we're interested in knowing why you're
8 using it, the indication for it, and how the patient
9 does, and if there's any adverse outcome, because I
10 think it would be invaluable.

11 DR. MURPHY: Funny you should suggest that,
12 because it is one of the things that we are trying to
13 do. We commiserate with the committee on the
14 information we have to use to make these decisions, and
15 we've been trying to get better decisions -- better
16 data. So one -- not better decisions, sorry. Better
17 data. And one of the things that we're trying to do,
18 and we did present this to the committee, is use our
19 network that is actually existing in CDRH. It's called
20 MedCenter KidNet. They actually train people in
21 hospitals for devices and how to report them, and they
22 QC them, and they get better reports.

1 So we're actually piloting using their KidNet,
2 so it's hospitals that are involved in KidNet and
3 actually some hospitals that aren't, that we're trying
4 to get to join KidNet, to see if we can get better data
5 when we have either somebody trained in the hospital or
6 we have these communications going back and forth, so
7 that we can have them know what we need in the way of
8 information and they can alert us to signals.

9 We've actually taken a question the committee
10 has submitted, now years ago, on -- there's so much use
11 of PPIs in the nurseries and children in hospitals that
12 we now are trying to pilot looking at why, what are the
13 indications -- we all think we know, but what are they -
14 - and how is it being used?

15 So we're trying to do that type of better data
16 collection. But that relates back to the problem we
17 said earlier, is that we're now finding that with the
18 electronic records, you need to go find a real record,
19 okay. So actually you need to have somebody in the
20 hospital who knows where to get the real data, versus
21 the electronic database, because we've tried pharmacy
22 data.

1 It's a good point and that's a long-winded way
2 of saying we are trying to build those kind of reporting
3 activities back to the agency.

4 CHAIRMAN ROSENTHAL: Yes, Dr. Ward, and then
5 Dr. Wiefling.

6 DR. WARD: I just want to make a couple of
7 observations for Dr. Franco. One is that under 2007
8 BPCA well-done studies can be included in the label if
9 they provide new important data about the effectiveness
10 or safety of the medication. I've seen clinical trials,
11 I've designed clinical trials, like what you described,
12 that failed because of the end point.

13 If you in the clinical arena, however, have
14 experience at using the medications with measurable
15 outcomes, such as reduction in bladder neck pressure, I
16 think that it needs to be carefully done, described, and
17 published, and that then gives the pediatricians and the
18 FDA the opportunity to try to put it in the label.

19 DR. WIEFLING: This is Bridgette Wiefling.
20 Actually, the federally qualified health system has a
21 pretty strong reporting system already through HRSA.
22 Every year we do something called the UDS report and it

1 may be worth a conversation between the FDA and HRSA
2 around the kinds of data that might -- that federally
3 qualifieds could provide to the FDA around specifically
4 utilization of medications, to create some kind of a
5 database, because, like I said, it is the one thing that
6 we have to do, is all kind of data collection. So it
7 would be just one more field to fill out. And we all
8 have to have an electronic medical record. So just a
9 suggestion.

10 DR. MURPHY: We actually have been -- our OSE
11 people have a group that does contracting out with
12 different groups for data like that. So AHRQ, HRSA --
13 I'm not the expert on that, but they are.

14 CHAIRMAN ROSENTHAL: All right. Well, it's
15 time to take a break. So a 15-minute break puts us back
16 at, why don't we say 5 after 3:00. And we will be -- at
17 that point we will be 40 minutes ahead of schedule. So
18 we're moving along this afternoon. So 5 after 3:00.

19 I'd like to remind the people on the committee
20 to please not talk about the topics being discussed in
21 the committee during the break, and I'll see you all
22 back in a few minutes.

1 (Recess from 2:50 p.m. to 3:07 p.m.)

2 CHAIRMAN ROSENTHAL: All right. For the two
3 angiotensin receptor blockers that we'll be discussing
4 next, Dr. Nadia Hejazi, who is a pediatric neurologist,
5 will be presenting these findings for us. She received
6 her medical degree from King Abdulaziz University in
7 Jeddah, Saudi Arabia. Dr. Hejazi received additional
8 training in neuropathology and pediatric EEG at the
9 University of Washington in Seattle and at UT-
10 Southwestern in Dallas.

11 As a research fellow in cellular
12 electrophysiology at the National Institute on Alcohol
13 Abuse and Alcoholism, she studied the role of glycine
14 receptor in hyper --

15 DR. HEJAZI: -- ekplexia.

16 CHAIRMAN ROSENTHAL: There's a typo on this.
17 -- and cannabinoid function.

18 So, Dr. Hejazi.

19 (Screen.)

20 ATACAND (CANDESARTAN CILEXETIL)

21 DR. HEJAZI: Hi. I'm going to skip the
22 outline as by now you're familiar with them. So I'm

1 going to go directly to discuss the safety review.

2 (Screen.)

3 Atacand, or candesartan, is an angiotensin II
4 receptor blocker marketed by AstraZeneca in the range of
5 doses from 4 to 32 milligram strength tablets.

6 (Screen.)

7 Atacand was initially approved in June of 1998
8 for the treatment of hypertension in adults and
9 subsequently in February 2005 Atacand was approved for
10 the treatment of adults with heart failure. BPCA
11 labeling change was in October 22, 2009, and the
12 labeling expanded the indication for the treatment of
13 hypertension to include children 1 to less than 17 years
14 of age.

15 (Screen.)

16 As you can see here, the dosing for the lower
17 age group is based on milligrams per kg, and it's based
18 on weight bands in the older pediatric age group. It's
19 important to note that doses above 0.4 milligrams per kg
20 have not been studied in children one to less than six
21 years of age and doses above the maximum given to adults
22 have not been studied in older children.

1 (Screen.)

2 A written request was issued for Atacand in
3 January 30, 2007, and three studies were requested under
4 BPCA in children 1 to less than 17 years of age: a PK
5 study, a safety and efficacy study, and a long-term
6 safety study. Pediatric exclusivity was granted in July
7 2009.

8 (Screen.)

9 Now I'm going to talk about the pediatric
10 studies. The first study was a pharmacokinetic study
11 and it shows that the PK profile of Atacand was
12 comparable among children and adults and was consistent
13 across the subgroups of age, weight and gender.

14 (Screen.)

15 Continuing with the pediatric studies, Atacand
16 efficacy was determined in a double-blind, multi-center,
17 dose-ranging study, and with no placebo group, that was
18 conducted in 93 children aged one to six years with
19 hypertension, the majority of whom had renal disease.
20 The primary end point was a change in the systolic
21 pressure and the study showed that the systolic blood
22 pressure dropped by 6, 9, and 12 millimeters mercury for

1 systole and 5, 8, and 11 millimeters mercury for
2 diastole across the doses used.

3 (Screen.)

4 The second study was a randomized, double-
5 blind, placebo-controlled, multi-center study conducted
6 in 240 children aged 6 to less than 17 years of age.
7 The primary end point was a change in systolic blood
8 pressure. The results showed significant decrease in
9 both systolic and diastolic blood pressure.

10 (Screen.)

11 Now we move to discuss the relevant safety
12 issues associated with Atacand. Atacand has a boxed
13 warning for use in pregnancy. Because Atacand acts on
14 the renin-angiotensive system, it can cause injury and
15 death to the developing fetus.

16 (Screen.)

17 I would like to continue with some important
18 contraindication and warnings, and I want to draw your
19 attention to the fetal and neonatal morbidity that can
20 result from the use of drugs that act on the renin-
21 angiotensin system, most commonly resulting in the
22 manifestations of Potter's syndrome, which is related to

1 oligohydramnios and failure of the immature kidney to
2 develop. In addition, Atacand has a negative
3 consequence on the development of immature kidneys and
4 thus it is contraindicated in children less than one
5 year of age.

6 (Screen.)

7 Atacand can cause hypotension in adults and
8 children who have conditions associated with salt and
9 volume depletion, such as those treated with diuretics.

10 Accumulation can occur in patients with impaired
11 hepatic function and therefore a lower dose should be
12 used when treating such patients.

13 It's important to note that Atacand has not
14 been studied in children with low GFR, that's lower than
15 30 mills per minute.

16 (Screen.)

17 With regard to adverse events, during clinical
18 trials one in 93 children in the lower age group and 3
19 in 240 children in the higher age group experienced
20 worsening of renal disease. This is about the same
21 percentage of adverse events in both groups. It's worth
22 noting that the decline in renal function was temporary

1 and did not appear to be progressive with long-term
2 treatment with candesartan.

3 (Screen.)

4 Now we switch gears and talk about candesartan
5 outpatient utilization. As you can see here from this
6 slide, it shows the total number of top ARB
7 prescriptions dispensed to the pediatric population from
8 birth to 16 years of age. In addition, this graph shows
9 that Losartan -- this is the blue line at the top -- was
10 the most dispensed ARB among this age group. At the
11 bottom, the blue bars represent the candesartan, and it
12 shows that prescriptions dispensed to the pediatric
13 population decreased from 3,000 in 2003 to approximately
14 600 prescriptions in 2010. This is a reduction by about
15 80 percent.

16 (Screen.)

17 Continuing with candesartan utilization, there
18 were a total of 20 million candesartan prescriptions,
19 and of those 17,000, that is less than one percent, were
20 dispensed to 3700 pediatric patients in the age group
21 birth to 16 years. Of the 3700 pediatric patients, two-
22 thirds were dispensed to the age group between 6 and 16

1 years, about one-third were dispensed to the age group 1
2 to 5 years, and only a fraction was dispensed to
3 pediatric age group less than 1 year of age, which is
4 mostly an off-label use because candesartan is
5 contraindicated in less than 1 year of age.

6 (Screen.)

7 The top prescribing specialty for candesartan
8 was internal medicine, general practice and family
9 medicine. Pediatricians accounted for less than one
10 percent of candesartan prescriptions. The diagnosis
11 captured was mainly hypertension.

12 (Screen.)

13 I'm going to talk about the adverse events
14 captured. It was covering a period of nine years from
15 April 2002 to July 2011. This figure shows the number
16 of pediatric cases with serious outcomes at 69. Out of
17 these, there is 66 with serious adverse events,
18 including 19 deaths, plus one fatal case that was
19 miscoded as outcome of hospitalization.

20 (Screen.)

21 This slide shows the total number of pediatric
22 reports. We have a number of 85 here, which includes

1 duplicated reports. 69 were due to -- were reports with
2 serious outcomes, plus 16 reports with outcomes of
3 death. Out of these 85 reports, there are 22 reports
4 that were duplicates and 63 were unduplicated reports,
5 including 20 deaths.

6 Out of these 63, 2 reports were excluded. In
7 one of the reports the mother took one dose only. In
8 the second one, there was no serious outcome. So this
9 leaves us with 61 serious cases, including 20 deaths.

10 (Screen.)

11 It's important to note here that the majority
12 of pediatric deaths and serious adverse events were
13 related to in utero candesartan exposure and not to
14 postnatal candesartan exposure.

15 (Screen.)

16 Also -- so this is again -- this is the
17 summary of pediatric -- oops, sorry.

18 (Screen.)

19 Summary of pediatric deaths. That's 20 deaths
20 and, as you can see, the majority are due to in utero
21 exposure and only 3 cases are due to postnatal
22 candesartan exposure. I would like to draw your

1 attention that most of these cases, if not all, were
2 confounded by underlying conditions or they lacked
3 temporal association with candesartan exposure.

4 (Screen.)

5 The first case was a hypoplastic left heart
6 syndrome, the second case was a renal impairment, and
7 the third case was necrotizing enterocolitis.

8 (Screen.)

9 The first case was a newborn female baby with
10 hypoplastic left heart syndrome and heart failure and
11 decreased urine output, who received candesartan and two
12 days after the initiation of the treatment she has
13 decreased urine output and her edema was aggravated.

14 The patients was put on IV furosemide and candesartan
15 dose was increased. The increase was not tolerated and
16 so candesartan was lowered, after which the patient was
17 improved. At the age of eight months, the patient
18 underwent cardiac surgery and later developed cardiac
19 failure and died.

20 (Screen.)

21 The second case was a three-year-old child
22 with nephrotic syndrome and focal segmental

1 glomerulonephritis, was enrolled in a candesartan study
2 and was on concomitant drugs. The child had recurrent
3 viral infections since birth and later developed
4 coagulopathy and died.

5 (Screen.)

6 The third case is a one-year-old with a
7 history of multiple cardiac surgeries since the age of
8 six days, who was started on candesartan at the age of
9 eight months. The patient was on furosemide,
10 spironolactone, warfarin, propranolol, and
11 acetylsalicylic acid.

12 Ten months after candesartan treatment, the
13 patient developed necrotizing enterocolitis and
14 subsequently died. In this case, please note the
15 necrotizing enterocolitis developed ten months after the
16 initiation of candesartan treatment, and the occurrence
17 of NEC is more common in newborns with congenital heart
18 defect due to the associated circulatory disturbance
19 that might lead to intestinal ischemia.

20 (Screen.)

21 Now we move on to the in utero cases, and we
22 have 17 cases, 14 of which were labeled and 3 of which

1 are unlabeled.

2 (Screen.)

3 The labeled cases, as you can see here, are
4 due to the Potter's syndrome, which includes symptoms
5 like oligohydramnios, renal failure, pulmonary
6 hypoplasia. The unlabeled are the bottom three which
7 are underlined. One case is of congenital heart defect,
8 another case of umbilical cord abnormality, and the
9 third case was a fetal disorder unstated.

10 (Screen.)

11 The non-fatal serious pediatric adverse
12 events. There were 41 cases and again most of them were
13 due to in utero exposure.

14 (Screen.)

15 The post-natal exposure, we had 16 cases. 3
16 of them were labeled events and 13 were unlabeled. The
17 labeled events were there was a case of renal failure, a
18 case of hypotension, and a case of pruritus.

19 Again, it's worth mentioning that these cases were
20 either confounded by the underlying disease or they
21 lacked clinical information for assessment.

22 (Screen.)

1 The unlabeled events. There were five cases
2 of accidental ingestion, two cases of intentional
3 overdose, a case of secondary renal failure, two cases
4 of convulsions, one medication error, and one growth
5 hormone deficiency.

6 (Screen.)

7 The hypotension was an 11-year-old female
8 patient with a history of adrenal cortical
9 insufficiency, who presented with paleness, fatigue, and
10 hypotension after receiving one dose of candesartan.

11 The patient was also on hydrochlorothiazide and
12 isradipine for hypertension. The patient improved after
13 candesartan and isradipine were discontinued. In this
14 case, candesartan is labeled for hypotension, and the
15 patient has a history of concomitant drug use, which is
16 hydrochlorothiazide and isradipine.

17 The pruritus case was in a 14-year-old female
18 patient who experienced hypertrichosis and generalized
19 pruritus following candesartan administration.
20 Candesartan was discontinued and the pruritis resolved
21 after switching the patient to valsartan. Candesartan
22 challenge test was negative, and in this case

1 candesartan is labeled for pruritis and it's in the
2 label in the post-marketing section.

3 Renal failure was in a 14-year-old male, who
4 was hospitalized with a diagnosis of congenital
5 abdominal aortic stenosis, renal hypertension, and
6 ruptured cerebral aneurysm. The patient developed
7 oliguria after the initiation of candesartan and was put
8 on hemodialysis and subsequently improved. This case
9 event was labeled because candesartan is known to
10 inhibit the renin-angiotensin system and it can cause
11 these renal function changes.

12 (Screen.)

13 Three cases of convulsions: the first in a
14 three-year-old male patient with a history of
15 cavopulmonary connection for a single ventricle and
16 intracranial hemorrhage. The patient was on warfarin,
17 aspirin, and candesartan. Eight months after starting
18 candesartan, the patient developed convulsions. EEG
19 showed central sharp waves. The patient was diagnosed
20 with epilepsy post intracranial hemorrhage and was
21 started on sodium valproate. No additional convulsions.

22 In this case it's possible that the epilepsy was due to

1 the underlying intracranial hemorrhage.

2 The second case was a two-month-old baby who
3 was breast-fed, developed seizures while the mother was
4 taking candesartan for hypertension. Candesartan was
5 discontinued and there was no information on the outcome
6 of the baby's condition.

7 The third case was a 31-old female baby who
8 presented with intracranial hemorrhage, skull fracture,
9 hyponatremia, and convulsions -- the patient may have
10 been given candesartan by a parent -- possibly as a
11 result of child abuse. The patient was hospitalized,
12 but no report on the outcome. In this case convulsions
13 are likely due to intracranial hemorrhage and skull
14 fracture.

15 (Screen.) The accidental ingestion are five
16 cases. All were reported in females, ages ranged from
17 one year to three years in four cases, and one report
18 was an infant of unspecified age.

19 The intentional overdose case of a 13-year-old
20 male with a history of unspecified mental illness, was
21 suspected to have ingested multiple candesartan and
22 amiodipine tablets. He responded to diuretics and

1 vasopressor treatment. And a 13-year-old female who
2 took her father's prescription of rosuvastatin and
3 candesartan in a suicide attempt. She was hospitalized
4 and improved.

5 The third case was a medication error in a
6 ten-year-old male with a history of chronic renal
7 disease. The patient was on methylphenidate,
8 cyproheptadine, and detrol -- that's an antimuscarinic -
9 - loratadine, enalapril, and desmopressin. Two days
10 later, after mistakenly taking Avandia -- that's
11 rosiglitazone -- instead of Atacand, the patient
12 experienced irritability, visual difficulty, hunger, and
13 profuse sweating. Avandia was discontinued.

14 (Screen.)

15 The case of growth hormone deficiency was in a
16 12-year-old male with coarctation of the aorta and
17 hypertension, who developed growth hormone deficiency,
18 but in this case there is no clear diagnosis of growth
19 hormone deficiency.

20 (Screen.)

21 The in utero non-fatal adverse events cases
22 were 25 and 18 were labeled events and 7 were unlabeled

1 events. The labeled events are again due to the
2 Potter's syndrome.

3 (Screen.)

4 The in utero unlabeled events, adverse events,
5 were a case of acute respiratory distress syndrome,
6 renal vein thrombosis, neonatal asphyxia, neonatal
7 jaundice, hypospadias, a case of osteogenesis
8 imperfecta, cyanosis and hypotonia.

9 (Screen.)

10 This concludes the Atacand pediatric focused
11 safety review. Labeling has been changed to grant an
12 indication for pediatric hypertension in children one to
13 less than 17 years of age. No new safety signals were
14 identified. The FDA recommends continued routine
15 monitoring. Does the committee concur?

16 (Screen.)

17 I would like to thank all the names listed on
18 this slide for their help.

19 Thank you.

20 CHAIRMAN ROSENTHAL: Thank you, Dr. Hejazi.

21 Are there questions or points of discussion
22 for Atacand?

1 DR. MURPHY: Jeff, I'd like to introduce our
2 division representatives.

3 CHAIRMAN ROSENTHAL: Oh, yes, please.

4 DR. MURPHY: Hi. My name is Avi Karkowsky. I
5 used to be a pediatrician, but any kids that I've ever
6 seen are probably relegated to the geriatric section of
7 Zukaty Park at this stage.

8 CHAIRMAN ROSENTHAL: You know, one other point
9 of order. I just didn't note that Dr. Franco has
10 recused himself from the discussion of Atacand, so he's
11 not at the table for this.

12 All right, Dr. Wagener.

13 DR. WAGENER: It concerns me, all the in utero
14 exposure. I know the package insert makes a comment
15 that if a person gets pregnant that it should be
16 discontinued, but it seems like the clinicians aren't
17 getting the message.

18 Is there any advantage to making a black box
19 warning on this drug that says "Absolutely
20 contraindicated in anyone who's pregnant," full stop?

21 DR. KARKOWSKY: I believe it does have a black
22 box warning that's being somewhat modified. But to put

1 things in perspective, almost all the cases were OUS
2 cases and putting a black box warning in the U.S. cases
3 is not going to help OUS exposure.

4 DR. HILLARD: Outside the U.S.?

5 DR. KARKOWSKY: Yes.

6 DR. HILLARD: Thanks.

7 CHAIRMAN ROSENTHAL: Yes, Dr. White.

8 DR. WHITE: Under your warnings: "5.2.
9 Morbidity in Infants. Children less than one year of
10 age must not receive Atacand for hypertension.
11 Consequences of administering drugs that act directly on
12 the renin-angiotensin system can have effects on the
13 development of immature kidneys."

14 I'd like to modify this statement, not so much
15 because it's inappropriate for Atacand, but we use
16 captopril and enalapril and have used that for years and
17 they act as well on the renin-angiotensin system, and
18 they're labeled with dosages for captopril for newborn
19 infants and enalapril for infants more than one month of
20 age.

21 So we're actually contradicting some of our
22 labels by saying that any drug acting on the rein-

1 angiotensin system, even though it may cause damage. We
2 should probably try to restrict that just to those that
3 are ARBs, angiotensin receptor blockers, if that's a
4 fair statement. Does anyone have any thoughts on that?
5 Jeff?

6 DR. KARKOWSKY: I'm not sure that's an
7 accurate statement at this stage. I'll go back and
8 check the captopril labeling.

9 DR. WHITE: I can pull it up. I've got it
10 right here.

11 DR. KARKOWSKY: Okay. But in general, we
12 discourage even studies in kids under one year of age,
13 based both on prenatal information and also on some
14 laboratory animal studies that show renal agenesis in
15 young kids.

16 DR. WHITE: Is that true for ACE inhibitors?

17 DR. KARKOWSKY: I believe so.

18 DR. WHITE: Because we've used captopril --
19 we've been using captopril for 20 years in newborn
20 infants for congestive heart failure, and to my
21 knowledge I've not knocked off anybody's kidneys lately.

22 Geof, do you have any knowledge of that?

1 CHAIRMAN ROSENTHAL: No.

2 DR. WHITE: Okay.

3 DR. KAPLAN: We've studied at Minnesota.

4 O'Day was the first author defining the dosing for
5 captopril a long time ago. A lot of us in neonatology
6 have used it for neonatal hyper-renin hypertension for a
7 long time. It's difficult to use because there's not a
8 good formulation, and there's the triple-phase reaction.

9 We find that cardiology usually starts at a higher dose
10 than we recommend.

11 (Laughter.)

12 DR. WHITE: Well, we start everything at
13 higher doses than anyone would recommend.

14 But the label is clearly labeled with dosages
15 down to newborn infants for captopril. So if we could -
16 - I've got it. Hold on two seconds. I had it a moment
17 ago.

18 (Pause.)

19 DR. WHITE: Sorry. My eyes are not as good as
20 they used to be.

21 DR. MURPHY: We will take it that it is.

22 DR. WHITE: Here it is. I've got it here.

1 CHAIRMAN ROSENTHAL: Dr. White, you're looking
2 at the ACE inhibitors label?

3 DR. WHITE: Yes, for captopril specifically,
4 which is --

5 DR. MURPHY: This says children one to six.

6 DR. WHITE: -- indications and dosage for
7 heart failure or hypertension. For treatment of
8 hypertension: infants, neonates, initially started at
9 .05 to 0.1 milligrams per kilogram PO every 8 to 24
10 hours. Doses may be titrated up to, do not exceed, 2
11 milligrams per kilogram per day. Newborns and premature
12 neonates, initially 0.01 milligrams per kilogram.

13 So we have it -- whether we have it labeled or
14 not, we're giving the dose of the drug in the label for
15 captopril. I'm using the labeling information from MD
16 Consult, which I think is the FDA label.

17 DR. MURPHY: You may have shined some light on
18 a problem we have with old labels. We see this in anti-
19 infectives. Some of the really old antibiotics, you
20 can't believe the way they're labeled. So I think what
21 you've brought up is an issue that --

22 DR. WHITE: So are we going to have to stop

1 using captopril?

2 DR. MURPHY: No. Dr. Karkowsky's going to go
3 back and address this issue about whether we need to
4 catch it up to date with any additional information.

5 DR. WHITE: Okay. Thank you.

6 CHAIRMAN ROSENTHAL: Yes, Dr. Hillard.

7 DR. HILLARD: I have a question just for my
8 information, but to bring us back to this issue of
9 pregnancy and drugs that have contraindications in
10 pregnancy. Clearly the information is in labeling, but
11 for drugs that have a pediatric indication, thinking
12 about adolescents and the fact that they don't tell us
13 before they become sexually active, they don't tell
14 their doctors who are prescribing these medications. So
15 pregnancies are likely to be unintended and pregnancies,
16 as has been noted with the last discussion, are likely
17 to be discovered at a later time.

18 So is there any way to address this particular
19 issue, which is broader than this drug, that -- it's an
20 issue of information to clinicians, but it bothers me
21 that there are these drugs that clearly should not be
22 taken during pregnancy. And the question is prescribing

1 them in an adolescent population where adolescents may
2 be sexually active without discussing it with their
3 clinician.

4 CHAIRMAN ROSENTHAL: Dr. White.

5 DR. WHITE: Actually, I renege what I said.
6 The label in MD Consult is not the same as the FDA
7 label. The FDA label doesn't include the dosages for
8 children and it says it should be use cautiously because
9 there's limited experience.

10 CHAIRMAN ROSENTHAL: Dr. Wagener.

11 DR. MURPHY: Okay. Thank you. It's in the
12 record. That is a problem. You've discovered a problem
13 that a lot of people have, getting the current label.
14 We actually, when we come to this meeting, we have to
15 ask that we have the current label because they change.
16 Well, that's encouraging that we have a more updated
17 label.

18 Sorry.

19 CHAIRMAN ROSENTHAL: That's okay. That's an
20 important point.

21 Dr. Wagener.

22 DR. WAGENER: Wagener. Just commenting on the

1 pregnancy issue, it seems that there may be sort of
2 three categories. One is that we don't know anything
3 about what happens in pregnancy. Two is that it's a
4 drug that's been used and has some degree of safety.
5 But three, there are products such as this one that
6 clearly have a complication related to that.

7 Thinking on your question, when you go to the
8 pharmacy now and you get a bottle of pills, it'll warn
9 you about not taking with milk and all sorts of things
10 are added to the bottle, little stickers are added to
11 the bottle. Is there any way -- I don't know where
12 those stickers come from. I don't know why they're
13 driven necessarily. But is there any way on a drug like
14 this, that has absolutely no question about it harm
15 produced during pregnancy, that they could put a sticker
16 on it that says: Do not use if pregnant, period.

17 That would be something the patient would see
18 directly and would be a reminder even if they hadn't
19 told their doctor.

20 CHAIRMAN ROSENTHAL: Dr. Murphy.

21 DR. MURPHY: Well, I was looking for somebody
22 from CEDR who could talk more to risk management plans,

1 because that would be sort of the area that you might
2 want to look at this for. You know, what pharmacists
3 decide to put on labels, all the little stickers, I
4 don't think we have any authority over all that.

5 But certainly we do have ways of developing
6 risk management programs, some of which say that you're
7 not supposed to give it to certain populations without
8 other steps being in place.

9 Is there anybody here from Center for Drugs
10 who would like to address that? Hari, do you want to?

11 (No response.)

12 DR. MURPHY: No, it doesn't look like we have
13 an expert on risk management here today. We will bring
14 that to them.

15 CHAIRMAN ROSENTHAL: Other points of
16 discussion for Atacand? Yes, Dr. Reed.

17 DR. REED: Thank you. Michael Reed. In the
18 interest of just making comments that may be of interest
19 to the agency, coming back to Dr. White's and Dr. Ward's
20 comment on the morbidity in infants and recognizing that
21 this class of drugs is commonly used in very young
22 infants and throughout the first year of life, the way

1 this -- and I'm learning from Bridgette to pay a little
2 more attention to this.

3 I think the way it's worded here can be
4 misleading, unless there is data in humans that they act
5 directly and can have a negative consequence on
6 development, dot, dot, dot, and then the next sentence,
7 "It's been shown to cause abnormal kidney development in
8 very young mice." Looking at how the quinoline story
9 and certain other drugs relative to children, when no
10 data in humans have been found in follow-up to the
11 animal studies it can lead to confusion for the
12 prescribers.

13 I don't know if there's any human data for
14 this. And if not, it might need to be reworded. Just a
15 point.

16 CHAIRMAN ROSENTHAL: All right. Thank you.

17 Yes, Dr. Ward.

18 DR. WARD: Geof, a couple of things. One is
19 that the adverse events I think illustrate and some of
20 the comments illustrate that one of the predominant uses
21 of this is in children with congenital heart disease for
22 after-load reduction. There's nothing in the label

1 about treatment for after-load reduction and improvement
2 of cardiac output.

3 It may be illustrative of how carvedilol was
4 studied and not studied well, and that was an extensive
5 study, but it's not shown to be effective. I think our
6 adverse event reporting illustrates, I think, this sort
7 of lack of study in those areas.

8 The other is I want to just comment about the
9 French describe this hypoplasia of the skull as
10 osteogenesis imperfecta, a very specific diagnosis. Yet
11 they use that terminology or it comes in in their report
12 forms. When I read the description, it sounds like the
13 very well-described hypoplasia of bone growth, not
14 osteogenesis imperfecta that's a cartilage disorder.

15 CHAIRMAN ROSENTHAL: Thank you. Those are
16 each good points.

17 Other comments or points of discussion for
18 Atacand?

19 (No response.)

20 CHAIRMAN ROSENTHAL: Shall we go to the voting
21 question.

22 (Screen.)

1 So no new safety signals have been identified
2 and the FDA is recommending return of this product to
3 routine safety monitoring. Does the committee concur?
4 All in favor?

5 (A show of hands.)

6 CHAIRMAN ROSENTHAL: All opposed?

7 (No response.)

8 CHAIRMAN ROSENTHAL: Any abstentions?

9 (No response.)

10 CHAIRMAN ROSENTHAL: Okay, it looks unanimous.

11 Dr. White, you want to get us started?

12 DR. WHITE: I concur and would request that
13 you review the label for ACE inhibitors and their use in
14 children, to come up with acceptable language across
15 ARBs and ACE inhibitors.

16 Thank you.

17 DR. RAKOWSKY: Alex Rakowsky, concur.

18 DR. FELNER: Eric Felner, yes.

19 DR. WALKER: Leslie Walker, yes.

20 DR. HILLARD: Paula Hillard, yes.

21 DR. BHATIA: Jatinder Bhatia, yes.

22 DR. MINK: John Mink, yes.

1 DR. WIEFLING: Bridgette Wiefling, yes.

2 DR. BAKER: Susan Baker, yes.

3 DR. KAPLAN: Shelly Kaplan, yes.

4 DR. CASTILE: Bob Castile, yes.

5 MS. EICHNER: Marilyn Eichner, yes.

6 DR. WRIGHT: Joe Wright, yes.

7 DR. KRISCHER: Jeff Krischer, yes.

8 DR. TOWBIN: Kenneth Towbin, yes.

9 DR. WAGENER: Jeff Wagener, yes.

10 DR. MOTIL: Kathleen Motil, yes.

11 DR. DRACKER: Bob Dracker, yes.

12 DR. SANTANA: Victor Santana, yes.

13 DR. REED: Michael Reed, yes.

14 CHAIRMAN ROSENTHAL: All right. Thank you
15 very much.

16 So let's move on now to Benicar and again Dr.
17 Hejazi will present this product for us. And Dr.
18 Franco, you can join us back at the table, and we
19 appreciate you sliding back for the last conversation.

20 (Screen.)

21 BENICAR (OLMESARTAN MEDOXOMIL)

22 (Screen.)

1 DR. HEJAZI: Benicar or olmesartan is again an
2 angiotensin 2 receptor blocker, marketed by Daiichi
3 Sankyo in a range of doses between 5 and 40 milligrams
4 strength tablets.

5 (Screen.)

6 Benicar was initially approved in April, April
7 25, 2002, for the treatment of hypertension in adults,
8 and labeling was changed under BPCA and PREA on February
9 4, 2010 and the labeling change made dosing available
10 for children 6 to less than 17 years of age.

11 (Screen.)

12 Benicar's dosing is based on weight bands in
13 children 6 to less than 17 years of age.

14 (Screen.)

15 A written request was issued for Benicar in
16 May of 2009 and pediatric exclusivity was awarded on
17 October 7 of 2009. Three pediatric studies were
18 required under BPCA: a PK study, a safety study, and a
19 safety and efficacy study.

20 (Screen.)

21 Now I'm going to talk about the pediatric
22 studies. The pharmacokinetic study. The PK profile was

1 studied in hypertensive children 6 to less than 17 years
2 of age and showed that the PK was similar to that in
3 adults when adjusted by weight.

4 (Screen.)

5 Continuing with pediatric studies, the
6 efficacy of Benicar has been evaluated in a randomized,
7 double-blind, placebo-controlled study in two cohorts,
8 an all-black cohort of 112 patients and a mixed racial
9 cohort of 190 patients, including 38 blacks, aged 6
10 through 16 years of age. Benicar significantly reduced
11 systolic blood pressure in both groups, with smaller
12 blood pressure reductions observed in black patients.

13 (Screen.)

14 Now we move to discuss the relevant safety
15 issues associated with Benicar. Again, the same here as
16 with Atacand: Benicar has a boxed warning for use in
17 pregnancy and, because Benicar acts on the renin-
18 angiotensin system, it can cause injury and death to the
19 developing fetus.

20 (Screen.)

21 I would like to continue with some important
22 contraindication and warnings. As I mentioned earlier,

1 the same warning for neonatal and fetal morbidity that
2 can result from the use of drugs that act on the renin-
3 angiotensin system, most commonly resulting in the
4 manifestations of Potter's syndrome. Again, I'm going
5 to talk about this more when we go to the adverse events
6 section.

7 (Screen.)

8 Benicar can cause hypotension in adults and
9 children who have conditions associated with salt and
10 volume depletion, such as those treated with diuretics.

11 Therefore, correction of these conditions should be
12 made before initiating treatment with Benicar.

13 (Screen.)

14 In clinical trials, there were no relevant
15 differences between the adverse events profile for
16 pediatric patients and that reported for adults.

17 (Screen.)

18 Now we will switch gears and talk about
19 Benicar utilization. As you can see from this slide,
20 the top -- it shows the total number of top ARB
21 prescriptions dispensed to the pediatric population from
22 birth to 16 years of age. In addition, it shows that

1 Losartan, the blue line at the top --

2 (Screen.)

3 Oops, sorry.

4 (Screen.)

5 -- it's the most prescribed ARB, and
6 olmesartan use dropped from 2003 from 2,000
7 prescriptions to 1400 prescriptions in the year 2010,
8 which is a decrease by 30 percent.

9 (Screen.)

10 The total prescriptions dispensed is 45
11 million prescriptions and out of these there were only
12 19,000 prescriptions, that is less than one percent,
13 that were dispensed to 6,000 pediatric patients. And
14 out of these, two-thirds were dispensed to children 6 to
15 16 years of age and about a third dispensed to children
16 1 to 5 years of age, and only a fraction went to
17 children less than 1 year of age. Again, this would be
18 mostly an off-label use.

19 (Screen.)

20 The top prescribing specialty for olmesartan
21 was general practice-family medicine and internal
22 medicine, and pediatricians accounted for less than one

1 percent of olmesartan prescriptions, and there was no
2 diagnosis code captured for pediatric patients.

3 (Screen.)

4 The adverse events reports again cover a nine-
5 year period from 2001, July -- April 2002 to July 2011,
6 and this figure shows the number of pediatric cases with
7 serious outcomes, that is 19, and all 19 cases were
8 serious events, including 12 deaths.

9 (Screen.)

10 This slide shows the total number of pediatric
11 reports, that is 24, and out of the 24 reports 19 were
12 serious, including 5 deaths in which the age was
13 unknown. Duplicated reports were 9 and unduplicated
14 reports were 15, including the 10 deaths. This leaves
15 us with 15 pediatric cases, including the 10 deaths.

16 (Screen.)

17 Again here, most of the pediatric deaths were
18 due to in utero, eight cases, and postnatal deaths were
19 only two: a case of a six-month-old infant with
20 ventricular hypoplasia and a second case in a 14-year-
21 old male with completed suicide.

22 (Screen.)

1 The six-month-old infant with ventricular
2 hypoplasia whose father received olmesartan at the time
3 of conception; and the completed suicide was in a 14-
4 year-old male who ingested multiple drugs, including
5 olmesartan, acetaminophen, and fluoxetine.

6 (Screen.)

7 Again, the in utero deaths, eight cases, and
8 all of these cases show the manifestations of Potter's
9 syndrome.

10 (Screen.)

11 The postnatal -- non-fatal serious adverse
12 events: postnatal cases were two, a case of accidental
13 ingestion and intentional overdose. The in utero
14 exposure: Potter's syndrome, that is labeled; and two
15 cases, an ASD and VSD, that was unlabeled, were
16 unlabeled.

17 (Screen.)

18 The accidental ingestion was in a 20-month-old
19 female who accidentally ingested one tablet of each of
20 the following drugs: simvastatin, acetylsalicylic acid,
21 metformin, and olmesartan. There was no report on the
22 outcome.

1 The case of intentional overdose was in a 16-
2 year-old female patient who ingested multiple drugs,
3 including olmesartan, in a suicide attempt. The patient
4 was hospitalized, but there was no report on the
5 outcome.

6 (Screen.)

7 The in utero events. As I mentioned before,
8 they were mostly due to Potter's syndrome; and a case of
9 ASD and a case of VSD. It's worth noting in this case
10 that the mother was -- in the two cases the mother was
11 on multiple concomitant drugs and there is a history of
12 late childbearing.

13 (Screen.)

14 This concludes the Benicar pediatric safety
15 focused review. Labeling has been changed to grant an
16 indication for pediatric hypertension in children six
17 years and older. There were no new safety signals were
18 identified. The FDA recommends continued routine
19 monitoring. Does the committee concur?

20 Thank you.

21 (Screen.)

22 I would like to thank all the names listed on

1 this slide.

2 CHAIRMAN ROSENTHAL: Thank you, Dr. Hejazi.

3 Comments, discussion about Benicar? Yes, Dr.
4 Wagener.

5 DR. WAGENER: I'm sorry to bring this up
6 again, but it bothers me that in these two drugs we've
7 seen more fatalities than in all the other drugs we're
8 looking at, and there are a heck of a lot more use in
9 all those other drugs. It seems like we ought to be
10 worried about these intrauterine exposure fatalities.
11 And I don't care that they're overseas or here. There
12 should be zero in the United States.

13 I think part of it is the warning that exists
14 is to me very poorly worded. When you start out the
15 warning and say "When used in the second and third
16 trimester," the implication is that it is used.
17 Instead, the warning should be very clear; it says: "It
18 never should be used."

19 This is a drug that's contraindicated in
20 pregnancy, period. I don't understand why across the
21 board with all of the receptor antagonists you can't put
22 in a black box that's that clear, so that there's no

1 ambiguity at all.

2 DR. KARKOWSKY: It is not -- Dr. Karkowsky.
3 It's not 100 percent event rate, and if you put in too
4 harsh a warning you're going to push perfectly normal
5 pregnancies to get abortions. There is wording in the
6 label that says what to do. There is also the concern
7 that there are some diseases, such as diabetes, where
8 the risk to benefit is unclear in pregnancy. So I don't
9 know what I would do at this stage, but there are cases
10 where there may be a lot more benefit, because there is
11 not much more therapies out there that don't cause the
12 same problems.

13 CHAIRMAN ROSENTHAL: I think there is some
14 wording in the label that addresses the maternal risk
15 with discontinuation of this class of agents. So the
16 risk-benefit equation is complicated for these, for
17 these agents, I think, for sure.

18 Other points or other ideas regarding Benicar?

19 Yes, Dr. Mathis.

20 DR. LISA MATHIS: There are two points I want
21 to make. First of all, even for products that we have
22 very restricted distribution, like Accutane, it's still

1 not 100 percent no pregnancies. So we will never get to
2 that point because human nature is what it is and people
3 go around programs and they do things because they want
4 to do it.

5 But the more important point I wanted to make
6 is that you have to remember that when we're treating
7 pregnant women we're treating the pregnant woman, and we
8 have to make a decision about her health based on her
9 health. Now, oftentimes the exposure to the infant is
10 unintended. In other words, she becomes pregnant and
11 doesn't know it before she's off of the drug.

12 But I think one critical thing to remember is
13 that we can't contraindicate drugs that don't rise to
14 the level of a contraindication in pregnancy because we
15 can't deny the pregnant woman an important therapy if
16 that's the only therapy that's available for her.

17 So I'm just cautioning against saying across
18 the board if there's any chance of teratogenicity
19 contraindicating it in women, because we still have to
20 treat the carrier of the fetus, and that's the mother,
21 and that's the primary patient at that point in time.

22 CHAIRMAN ROSENTHAL: Dr. Bhatia.

1 DR. BHATIA: Thank you. Not to discount Dr.
2 Wagener's comments, in that case you have, playing
3 devil's advocate, ASD, VSD, Potter's syndrome would be
4 injury early in pregnancy. So his point gets stronger
5 because the in utero exposure things you're showing is
6 Potter's, ASD, VSD, and which have occurred because you
7 knew you were pregnant.

8 So if that language has to continue, then the
9 entire pregnancy has to be included, not just second and
10 third trimester.

11 DR. KARKOWSKY: Excuse me. I believe Potter's
12 syndrome is a late pregnancy --

13 DR. BHATIA: But it goes on --

14 DR. KARKOWSKY: Yes. It's decreased -- it's
15 oligohydramnios which causes the problem. That's why it
16 was proscribed in the third trimester, and only recently
17 did it get pushed up to the second or third.

18 DR. FRANCO: Renal output begins at 14 weeks
19 gestation, so Potter's syndrome is really at the
20 development of the kidneys. So if the kidney is formed
21 abnormally, that's really the underlying problem. So it
22 is an early -- it is an early pregnancy problem.

1 CHAIRMAN ROSENTHAL: Dr. Hausman, I saw your
2 hand up. I don't mean to call on you while you're away
3 from your mike, but if you have a comment this would be
4 a good time.

5 DR. HAUSMAN: Thank you. I pulled up the
6 current Benicar label and just above what we have here,
7 the warning on the label I have here says: "Warning" --
8 there's a colon, and it says: "Avoid use in pregnancy."
9 So it didn't get captured up there, but I wanted to
10 highlight to the committee that FDA actually takes these
11 warnings very, very seriously. Like Dr. Mathis said, we
12 have to -- we take into account the maternal-fetal unit
13 and we try to make a balanced recommendation. But this
14 is actually an exceptionally strong boxed warning. I
15 just wanted to bring that to the committee's attention.

16 CHAIRMAN ROSENTHAL: Dr. White.

17 DR. WHITE: In our fetal cardiac practice, the
18 most common scenario is that the mother comes to us
19 having been started on this medication, or an ACE
20 inhibitor is much more common actually, early during or
21 long, long before the pregnancy, and may not have been
22 back to the doctor for several years, is still getting

1 the medication, and comes in having discovered that
2 they're pregnant seven or eight months after conception.

3 I think those are the cases that are most
4 problematic. Most mothers go to the OB as soon as they
5 find out they're pregnant and they're told to stop.
6 Yes, there are concerns about first trimester use, but
7 they're much less, much less serious usually. But it's
8 the ones where the mother doesn't know that they're
9 pregnant that really gets you in trouble and gets the
10 baby in trouble as well.

11 CHAIRMAN ROSENTHAL: Dr. Wagener.

12 DR. WAGENER: I recognize the FDA takes it
13 seriously. I'm not questioning that. But I'm trying to
14 figure out some way to get doctors to take it seriously.

15 If you don't want to change the number of words or
16 anything, let me suggest an order change, and that is
17 the first sentence should read in the box: "When
18 pregnancy is detected, Benicar should be discontinued as
19 soon as possible." I'm not going to change any words
20 there. I'm just going to change order.

21 DR. MURPHY: Actually, what was pointed out is
22 that that's what it says now --

1 DR. WAGENER: And then the second sentence can
2 be: "When used in pregnancy," da-da-da-da.

3 DR. MURPHY: I think -- I don't know why this
4 slide's up here. In your handout you will see that the
5 warning says "When pregnancy is detected, discontinue" -
6 -the first sentence -- "as soon as possible."

7 DR. WARD: And it begins with "Warning,"
8 colon, all in caps, "Avoid use in pregnancy" in the box.
9 So that's really pretty strong.

10 DR. WAGENER: Yes, I agree with that.

11 DR. MURPHY: Okay. This is one of those
12 things where sometimes there are different labels
13 floating around and people got the wrong one for the
14 slide.

15 CHAIRMAN ROSENTHAL: A rogue slide.

16 One thing that I was hoping to touch on. I
17 found it interesting, a case was described in which
18 there was a paternal exposure and that made me wonder
19 about how -- we talk a lot about the maternal-fetal axis
20 and trying to understand perinatal safety issues. But
21 how does the agency approach paternal exposures in
22 general, and why did that particular case make its way

1 onto the list for this product?

2 DR. LISA MATHIS: I'm so excited to answer
3 this question.

4 (Laughter.)

5 DR. REED: I'll hold her back.

6 DR. LISA MATHIS: Actually, there are a few
7 drugs where there is some transference in the semen, so
8 we do have to be careful about exposure because of
9 paternal use of medications. Prior to the draft
10 pregnancy labeling rule that is in clearance now, we
11 didn't really have a standard way of approaching this.
12 But now, as part of the pregnancy labeling rule, we have
13 a specific section that talks about drug passage by
14 either the mother or the father. So now there's going
15 to be -- well, hopefully there will be a specific
16 section in labeling once the rule is published that
17 actually addresses this particular issue, which is
18 really important.

19 So thank you.

20 CHAIRMAN ROSENTHAL: Yes, I think the
21 teratologists would really applaud this as a great
22 advance. So thank you.

1 Other questions or topics regarding Benicar?

2 Other hands up? Oh, yes.

3 DR. HAUSMAN: Just as an additional comment
4 about paternal exposures, in addition to being a
5 pediatrician I'm also a pathologist. When I transferred
6 over into Pharmacovigilance and OSE, when I started
7 talking to the safety evaluators I started saying: So,
8 has anybody pulled out any paternal exposures? And we
9 just heard from Dr. Mathis about how some of the rules
10 are changing, but I think one of the big things is that
11 when you get people who are aware that it might be an
12 issue asking questions, it's starting to get on people's
13 radars, because some of us are persnickety about it and
14 we keep on asking. So it's starting to get on the radar
15 for that reason as well.

16 CHAIRMAN ROSENTHAL: Good work.

17 Dr. Ward.

18 DR. WARD: I just want to make a comment about
19 the associations, though, between the exposures and the
20 outcomes. There's a finite number of congenital
21 malformations that are going to occur. They occur in
22 specific frequencies, and I think we have to be cautious

1 about concluding that there's cause and effect from
2 exposure and outcome.

3 CHAIRMAN ROSENTHAL: Thank you. Yes, it's
4 hard with rare events to not become sucked into the
5 attribution error, isn't it? Yes, good point.

6 All right. Other points?

7 (No response.)

8 CHAIRMAN ROSENTHAL: Well, why don't we go
9 ahead and vote on this, this issue. The FDA is
10 proposing continued routine safety monitoring for
11 Benicar. All in favor please raise your hands.

12 (A show of hands.)

13 CHAIRMAN ROSENTHAL: Thank you.

14 Any opposed?

15 (No response.)

16 CHAIRMAN ROSENTHAL: And any abstentions?

17 (No response.)

18 CHAIRMAN ROSENTHAL: It looks like a unanimous
19 field. Dr. Reed, will you get us started going around?

20 DR. REED: Michael Reed. I vote yes.

21 DR. SANTANA: Victor Santana. I vote yes.

22 DR. DRACKER: Bob Dracker, yes.

1 DR. MOTIL: Kathleen Motil, yes.

2 DR. WAGENER: Jeff Wagener, yes.

3 DR. TOWBIN: Kenneth Towbin, concur.

4 DR. KRISCHER: Jeff Krischer, yes.

5 DR. WRIGHT: Joseph Wright, yes.

6 MS. EICHNER: Marilyn Eichner, yes.

7 DR. CASTILE: Bob Castile, yes.

8 DR. KAPLAN: Shelly Kaplan, yes.

9 DR. BAKER: Susan Baker, yes.

10 DR. WIEFLING: Bridgette Wiefeling, yes.

11 DR. MINK: John Mink, yes.

12 BHATIA: Jatinder Bhatia, yes, assuming that
13 the new label will replace old label in the
14 presentation.

15 DR. FRANCO: Israel Franco, yes.

16 DR. HILLARD: Paula Hillard, yes.

17 DR. WALKER: Leslie Walker, yes.

18 DR. FELNER: Eric Felner, yes.

19 DR. RAKOWSKY: Alex Rakowsky, concur.

20 DR. WHITE: Michael White, yes, and please
21 review this as well with the ACE inhibitors and ARBs for
22 consistency between the labels.

1 DR. MURPHY: We have flagged it.

2 CHAIRMAN ROSENTHAL: Thank you, yes.

3 Thank you, Dr. Hejazi.

4 DR. HEJAZI: Thank you.

5 PEDIATRIC ADVISORY COMMITTEE MEMBER

6 DIRECTED ABBREVIATED REVIEW PROCESS

7 CHAIRMAN ROSENTHAL: All right. At this point
8 in the agenda, I'm going to just talk for a minute about
9 our abbreviated review process. I'll give Dr. Murphy a
10 chance to speak after me. But since many of you are new
11 on the committee, I'd just like to talk about a process
12 that we have for reviewing products that meet very
13 specific criteria.

14 The reason that we have a different process
15 for these products is that a lot of time and energy goes
16 into the committee's work around review of any product
17 that comes before the committee, and so we've been as a
18 committee trying to improve our efficiency going
19 forward.

20 So let me start by just saying that the FDA's
21 criteria for an abbreviated review are -- the criteria
22 are as follows: one, that there are no deaths; second,

1 that there are either no or very few serious adverse
2 events; third is that there is either very little or no
3 pediatric use or that the product is no longer marketed;
4 and fourth, that there is no new safety signal.

5 So for products that come up for review that
6 meet those criteria, we conclude that they are therefore
7 adequately labeled for pediatric use and we bring them
8 before the committee in an abbreviated review process.

9 Now, there are two different groups of people
10 around the table today. There are permanent members of
11 the Pediatric Advisory Committee. "Permanent" means
12 you've been assigned to a four-year term. And there are
13 consultants, who are here either for the meeting or for
14 a year or in some other capacity. So the permanent
15 members of the Pediatric Advisory Committee sought to
16 modify the process for abbreviated review, again to
17 enhance our opportunity to more fully discuss products
18 that may have important safety issues. So the
19 motivation for considering a process change was to try
20 and create the opportunity for more focused attention on
21 those products that have safety issues and would benefit
22 from our focus.

1 The permanent PAC members have assigned
2 reviews to designated reviewers for five products today.

3 These products are Xerese, Creon, Zenpep, Pancreaze,
4 and Mirena. Now, only the designated reviewers have
5 been through the conflict of interest clearance for
6 these products. As you've seen, when anyone on the
7 panel has a conflict of interest, either direct or
8 attributed or in some cases quite remote, we ask those
9 people to step away from the table and not participate
10 in the discussion. Thank you, Dr. Franco, for being
11 willing to move back and forth a few times today and
12 indulge us in this process.

13 But since only those who've been cleared
14 through the conflict of interest process can participate
15 as advisers to the FDA on this committee, at this point
16 we'll let the designated reviewers provide advice to the
17 FDA. For the rest of us, myself included, who have not
18 been through the conflict of interest clearance process,
19 we should not be providing advice to the FDA on these
20 products at this time.

21 Dr. Murphy, do you have anything to add to
22 that?

1 DR. MURPHY: I think I'm speechless. A rare
2 event. Thank you.

3 CHAIRMAN ROSENTHAL: Okay. So then, without
4 further ado, let's engage in this designated review
5 process. I'll ask the reviewers to engage in discussion
6 freely with the FDA around these topics and the rest of
7 us will not.

8 So who is the designated reviewer for Xerese?

9 DR. MOTIL: I am.

10 CHAIRMAN ROSENTHAL: Dr. Motil.

11 XERESE ABBREVIATED REVIEW

12 DR. MOTIL: Kathleen Motil. I'm the
13 designated reviewer for Xerese. This particular drug is
14 acyclovir and hydrocortisone cream, and in my review its
15 indication for herpes simplex labialis has a very low
16 pediatric volume, very low pediatric use. I agree with
17 the FDA's review in that there was absolutely no safety
18 signal detected and I recommend that we continue -- that
19 the FDA continues its surveillance of this particular
20 drug.

21 DR. MURPHY: So, Dr. Motil, you recommend --
22 you're agreeing with FDA's recommendation to return it

1 to routine monitoring, then?

2 DR. MOTIL: Yes, yes.

3 DR. MURPHY: Thank you very much.

4 CHAIRMAN ROSENTHAL: Okay. And who is the
5 designated reviewer for Creon?

6 DR. TOWBIN: C'est moi.

7 CHAIRMAN ROSENTHAL: Dr. Towbin.

8 CREON, ZENPEP, AND PANCREAZE ABBREVIATED REVIEW

9 DR. TOWBIN: Actually, I'm the designated
10 reviewer for all the porcine products that are being
11 considered. I do recommend that these be returned to
12 routine monitoring. Certainly this particular agent and
13 the other two didn't show any signal in terms of safety
14 concerns.

15 There were two things that did surface in my
16 review that I just wanted to call attention to. One is
17 that there was a REMS that was advised looking at the
18 way in which the products were manufactured and concerns
19 for viral transmission, given the porcine derivative.
20 Just to make sure that finds its way into the documents
21 that you provide going forward, that those studies are
22 under way, that you're monitoring that.

1 I had to go back and look at the initial
2 materials. There wasn't anything in the medical review
3 that indicated that that was in progress and under way.

4 So just hearing about that I think would be good.

5 The second thing was maybe a very rare thing,
6 but apparently the substances can't be ground and given
7 directly for very young infants because of irritation to
8 the mucosa. So the sponsor had recommended use of a
9 gastro tube, and I could understand how for very young
10 children placing a gastro tube could be problematic.
11 But there probably should be something in the package
12 about having an adequate volume of liquid if you're
13 going to be giving it in apple sauce or some other way,
14 so that you don't have that mucosal irritation. The
15 label doesn't say anything about that, just that it can
16 be given. Maybe some statement about how for very young
17 children an adequate volume would be important to avoid
18 that mucosal irritation could be useful.

19 DR. MURPHY: Let me ask you if I have it
20 correctly, that you would like us to, when providing
21 information on these products, where we have a REMS
22 that's been advised for viral transmission to provide

1 that?

2 DR. TOWBIN: Thank you. Yes. The report
3 isn't due until 2021.

4 DR. MURPHY: Better tell somebody else.
5 (Laughter.)

6 DR. TOWBIN: Yes, we're all in the same boat
7 there.

8 DR. MURPHY: Yes.

9 DR. TOWBIN: But I think just the idea that we
10 want to know that it's under way, because of course it's
11 now -- I guess it was 2009 that that was recommended. I
12 would just like a progress report knowing that everybody
13 is aware, because I don't want 2020 to show up and
14 everybody says: Oh, gosh, we forgot to do that. Not
15 that you would.

16 DR. MURPHY: Thank you. I just wanted to
17 clarify that.

18 Then the second has to do with the use of the
19 product when it's going to be ground up and used with a
20 G-tube; is that correct? So that you want us to address
21 potentially wording about adequate volume of liquid?

22 DR. TOWBIN: Exactly. The exact wording in

1 the document that I got is that "Capsules can be
2 difficult to administer to a young child. Even if they
3 can be opened and the beads administered with water or
4 apple sauce, the issue of giving enough liquid to aid in
5 swallowing can still be difficult for the caregiver.
6 Although the sponsor does not recommend crushing the
7 pellets due to oral mucosal irritation and possible loss
8 of enzyme potency, the use of a gastro tube would be the
9 correct choice in the case of swallowing difficulty and
10 would make these concerns less likely an issue."

11 So the issue of volume I think also comes up
12 in this same regard, the volume that it's diluted into.

13 DR. MURPHY: Okay. Thank you.

14 DR. WARD: Can I ask for a clarification of
15 what you mean by a gastro tube? Do you mean a
16 gastrostomy or an oral gastric tube?

17 DR. TOWBIN: I think they probably mean an
18 oral gastric tube. I can't imagine a gastrostomy is
19 what they meant.

20 CHAIRMAN ROSENTHAL: I'm going to ask that the
21 discussion take place between the designated reviewer
22 and the agency for this part of the meeting.

1 Yes?

2 DR. HAUSMAN: Ethan Hausman. I just want to
3 clarify. I have the Creon label up and it specifically
4 says "Do not crush or chew capsules or contents." There
5 are provisions for opening capsules. I want to make
6 sure what we're talking about here. Do you in fact mean
7 a provision for opening up capsules and sprinkling on
8 whatever internal contents?

9 DR. TOWBIN: I think some of these actually
10 can be given in apple sauce for children who are too
11 young to be able to swallow those.

12 DR. HAUSMAN: That's correct. That's my
13 understanding as well. I was just specifically zeroing
14 in on "crush" because these medicines, while they can be
15 opened and sprinkled and put in apple sauce, they're not
16 supposed to be crushed. Actually, it's reflected in the
17 labeling, for reasons that you described about the
18 irritation.

19 DR. MURPHY: I think what you're picking up is
20 maybe I misstated: that they are not to be ground,
21 right, but they're to be put into some other product.
22 But the point, his point, is that he'd like some

1 additional wording about volume.

2 DR. TOWBIN: Precisely.

3 DR. MURPHY: Okay.

4 CHAIRMAN ROSENTHAL: Just a point of process.

5 Then I just want to be clear. Dr. Towbin, for each of
6 these agents you're recommending that the agency return
7 to routine monitoring, but will you just state each one
8 so that we have that in the record, that that's your
9 recommendation for each one?

10 DR. TOWBIN: Of course. So this would apply
11 to Creon, Zenpep, and Pancreaze. Thank you.

12 CHAIRMAN ROSENTHAL: Okay. What is the
13 designated reviewer for Mirena? Dr. Wagener.

14 MIRENA ABBREVIATED REVIEW

15 DR. WAGENER: Jeff Wagener. I was reviewer
16 for Mirena, which is a levonorgestrel intrauterine
17 system. After reviewing the six different pieces of
18 information provided by the FDA, including the pediatric
19 post-marketing adverse event review of 21 September 2011
20 and the drug use review of 11 November 2011, I agree
21 with the FDA's assessment of no new pediatric safety
22 issues.

1 Of interest, this is used less than one
2 percent of the time in children, 99 percent of the time
3 in the adult age group. And the adverse events in
4 children were identical to those that are seen in the
5 older patient population, and it thus seems to have no
6 added safety problems in children.

7 So as such I recommend that Mirena be returned
8 to routine monitoring.

9 DR. MURPHY: Thank you.

10 Anybody from FDA have any questions, which I
11 should have asked earlier?

12 CHAIRMAN ROSENTHAL: So I'll ask. Any
13 questions from the agency for any of the designated
14 reviewers for the abbreviated review products today?

15 (No response.)

16 DR. MURPHY: I just wanted to thank them for
17 the extra time that they took to go through. For a very
18 brief process, I know you have to go through everything
19 just as though it weren't going to be brief, and we do
20 appreciate your willingness to do that and to make a
21 recommendation to us.

22

1 CLOSING REMARKS

2 CHAIRMAN ROSENTHAL: So now it's time for
3 closing remarks. Would you like to make closing remarks
4 or would you just like me to sound the bell?

5 DR. MURPHY: Well, tomorrow is a new set of
6 products. So tomorrow are biologics. We're going to do
7 vaccines and for the committee members who have been
8 oriented to vaccines -- there is the process we try to
9 work with our CEBR colleagues to utilize the information
10 they already have. We won't have another training
11 session tomorrow for everybody else, but I think most
12 pediatricians are aware of the fact that vaccines go
13 through a process with a vaccine committee and with the
14 CDC. So we try to utilize that material that's being
15 generated for our reviews that we provide you, yet
16 follow a somewhat similar approach. So for the rest
17 of the committee that's not used to it, it may be
18 slightly -- those products will be slightly different in
19 some of the reports.

20 Then tomorrow we will also have a presentation
21 from both NICHD and our chemists. And don't worry, it's
22 not going to put you to sleep. I think it's actually

1 quite interesting and it has to do with what the agency
2 and NICHD are doing to try to solve the problem of
3 formulations for children. We now have up on the web
4 the formulations platform and they're going to talk to
5 you a little bit about what those issues are and how
6 they're trying to approach this.

7 It's really an information session for you,
8 because if you're on the committee we do try to provide
9 you something different, that you might not experience
10 anywhere else. So this is one of our efforts to give
11 you some information on formulations.

12 Do you have anything, Lisa or Judith or Ethan?

13 (No response.)

14 DR. MURPHY: Thank you all and see you
15 tomorrow.

16 CHAIRMAN ROSENTHAL: There was some confusion
17 on some of the agendas that went out, but the correct
18 time for us to reassemble is 9:00 o'clock. 9:00
19 o'clock.

20 Oh, and Walt's reminding me to remind you:
21 Please don't discuss the matters in the meeting outside
22 of the meeting context.

1 Thank you all very much for your participation
2 today. We had some really good discussions.

3 (Whereupon, at 4:22 p.m., the meeting was
4 adjourned.)

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