DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Wednesday, June 9, 2004

8:00 a.m.

ACS Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Joan P. Chesney, M.D., Chair
Thomas H. Perez, M.P.H., Executive Secretary

CONSULTANTS (VOTING):

Mark Hudak, M.D.
David Danford, M.D.
Richard Gorman, M.D.
Robert Nelson, M.D., Ph.D.
Susan Fuchs, M.D.
Victor Santana, M.D.
Naomi Luban, M.D.
Judith O'Fallon, Ph.D.
Katherine L. Wisner, M.D.

MEMBER OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (VOTING):

Steve Ebert, Pharm.D., Consumer Representative

FEDERAL GOVERNMENT EMPLOYEE (VOTING):

Janet Cragan, M.D.

INDUSTRY REPRESENTATIVE TO ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (NON-VOTING):

Sam Maldonado, M.D., industry representative

FDA STAFF:

Solomon Iyasu, M.D.
Susan Cummins, M.D.
Shirley Murphy, M.D.
Dianne Murphy, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order, Introductions

DR. CHESNEY: Good morning. I think we are ready to get started. I would like to welcome everybody to this meeting which, for those in the room who don't know, and Dr. Murphy will elaborate on this, this is the last meeting for this group of the Pediatric Subcommittee as currently constituted. I would like to also mention that Dr. Mimi Glode will not be with us because her father became ill on Sunday and she had to cancel at the last minute.

Tom has just told me that traffic is going to become very bad this afternoon because of President Reagan's funeral so we want to keep that in mind as we move on throughout the day. So, I think we will start with introductions and, Dr. Maldonado, would you like to start?

DR. MALDONADO: Sam Maldonado, from Johnson & Johnson, the industry representative on this committee.

DR. FUCHS: Susan Fuchs, pediatric

emergency medicine physician from Children's Memorial Hospital in Chicago.

DR. O'FALLON: Judith O'Fallon, statistics, retired from the Mayo Clinic.

DR. SANTANA: Victor Santana, pediatric hematologist/oncologist from St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. GORMAN: Rich Gorman, pediatric private practice in Ellicott City, Maryland.

DR. EBERT: Steve Ebert, pharmacist, infectious diseases, Meriter Hospital and University of Wisconsin, Madison.

DR. PEREZ: Tom Perez, executive secretary to this committee meeting.

DR. CHESNEY: Joan Chesney, pediatric infectious disease at the University of Tennessee in Memphis, and also St. Jude's Children's Research Hospital.

DR. HUDAK: Mark Hudak, neonatologist, University of Florida, Jacksonville.

DR. DANFORD: Dave Danford, pediatric cardiology, University of Nebraska Medical Center,

Omaha.

DR. NELSON: Robert Nelson, pediatric critical care medicine, Children's Hospital, Philadelphia and University of Pennsylvania.

DR. IYASU: Solomon Iyasu, lead medical officer in pediatrics, FDA.

DR. CUMMINS: Susan Cummins, lead medical officer, pediatrics, FDA.

DR. S. MURPHY: Shirley Murphy, Division Director, Division of Pediatric Drug Development, FDA.

DR. D. MURPHY: Dianne Murphy, Office Director, Office of Counter-terrorism and Pediatric Drug Development, in the Office of Pediatric Therapeutics.

DR. CHESNEY: Thank you. Now Tom Perez will read the meeting statement.

Meeting Statement

DR. PEREZ: Thank you and good morning. The following announcement addresses the issue of conflict of interest with regard to the adverse event reporting session and is made part of the

record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 USC 208(b)(3), full waivers have been granted to the following participants, Dr. Richard Gorman for ownership of stock in a company with a product at issue, valued between $50,001 to $100,000; Dr. Judith O'Fallon for her and her sponsor's ownership of stock in a company with a product at issue, between $5,001 and $25,000; Dr. Katherine Wisner, for her speaker's bureau activities for a company with a product at issue for which she receives less than $10,001 per year; Dr. Patricia Chesney for her spouse's ownership of stock in a company with a product at issue, valued from $5,001 to $25,000 and unrelated

consultant earnings less than $10,001 per year. In addition, Dr. Chesney's spouse owns stock in a company with a product at issue, worth less than $5,001. Because this stock interest falls below the minimis exception allowed under 5 CFR 2640.202(b)(2), a waiver under 18 USC 208 is not required. Further, Dr. Chesney is recused from participating from the subcommittee's discussion regarding Duragesic due to a conflict of interest.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We would also like to note that Dr. Samuel Maldonado has been invited to participate as an industry representative, acting on behalf of

regulated industry. Dr. Maldonado is employed by Johnson & Johnson. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. CHESNEY: Thank you. Our first speaker for the morning will be Dr. Dianne Murphy, Director of the Counter-terrorism and Pediatric Drug Development Office.

Welcome

DR. D. MURPHY: And just as you all understand how those two got to be combined, we have come to the end of an era. That was really the substance of my opening comments this morning and I am going to talk more about this later in the day, that this is a milestone.

But I wanted to take this morning to focus on the importance of the activity of this committee in the review of the safety or adverse events that occur after a product has been granted exclusivity. It has been clearly legislatively mandated that

this is going to occur and that task has come to this committee.

I wanted to make sure that you all realized how much you have contributed to this process. We have received feedback from you during the time about what was useful and have tried to maintain a course, as we have to, that obeys the legislative intent and, yet, makes it more scientifically interesting within the constraints that we have. I think probably years from now we could come and ask you all what are the problems with the AERS data reporting system. So, you have been mandated to participate in a process in which you were told every meeting that you come here that the limitations are numerous with passive reporting; that when we do get reporting it is either poor or limited in nature; that there is little ability to go back and reconstruct in detail any of that information; and it basically doesn't have the same quality as a prospective surveillance or active process. Yet, during this time I think we have evolved a process, again with your feedback

and assistance, that has allowed us to make it more valuable.

I would like to say that I think that what we have been able to identify over the past year or so has been the benefits of this system, and that is that it ensures that attention is focused on what is happening postmarketing to these products that the government initiates and rewards for studies being conducted. As most of you are aware, one of the largest safety databases that occurs with any product is the postmarketing activities. That is where you find your rare serious events. And, this process has been critical for this committee and this has been a very important activity that I do think has focused and ensured that products that are marketed for children are looked at in a studied way, a reliable way, a predictable way, and I think that that is important.

Now, why is it important? Because I don't know how many times you have sat through these meetings where we said, "well, here are the

problems and we didn't see anything. Okay?" But that is good news. We would hope that the majority by far, if not 100 percent of these products that are studied and marketed don't have serious hidden adverse events. So, in a say, it is like prophylaxis. We hope we don't find major issues.

But I think the other thing that this process has done that I wanted you all to know about that was important is that it has the effect on the agency of re-prioritizing pediatric safety assessments. As everyone knows, there are many deadlines the agency has to meet and it is hard often to see the plate for all the things that are on it. But clearly the legislation, your participation and our coming to you says we are having a public meeting and a discussion and it re-prioritizes this activity for the agency, as I said, and ensures that attention occurs.

We are going to hear today about some activities that have evolved during this process, some questions that we want to bring to you because of information that, in essence, was moved forward

a little faster because of this process, not that it was being neglected but because we basically made sure that we facilitated the assessments of some of these products and some of the issues. In the past, as you know, we have had some reviews of the SSRIs and this whole process has been important in helping facilitate moving that activity forward also.

I wanted to just thank you for your scientific input, your thoughtfulness and your feedback which we still would like to receive about the process on adverse event reporting, knowing that we have to work within the constraints of the systems that we presently have. With that, I will speak a little more about the contributions of this committee and where we are going in the future later today. Thank you very much.

DR. CHESNEY: Thank you, Dr. Murphy. Our second speaker this morning, Dr. Solomon Iyasu, is going to talk to us about adverse event reports, per Section 17 of the Best Pharmaceuticals for Children Act. Dr. Iyasu is a pediatrician, a

medical epidemiologist who has fellowship training with the EIS of the CDC and residency training in preventive medicine at the CDC. Prior to joining the FDA, just in 2002, he worked for 13 years as a medical epidemiologist at the CDC, in Atlanta, where he led research and programmatic programs in infant health. He also served as the CDC liaison to the Committee on the Fetus and Newborn of the American Academy Pediatrics for many years, and has served on several HHS committees and inter-agency working groups, including the National Children's Study. His research papers have involved maternal and child health issues. In his current position at the FDA he serves as a medical team leader in the Division of Pediatric Drug Development and also serves as the lead medical officer for safety in the Office of Pediatric Therapeutics, which has become--always was but has become a particularly important office in function. Dr. Iyasu?

Adverse Event Reports per Section 17 of Best Pharmaceuticals for Children Act

DR. IYASU: Thank you very much, Dr.

Chesney, for that kind introduction. Good morning.

In the next few minutes I will provide you with an overview of today's agenda. The theme for today is safety, safety of pediatric drugs. A series of presentations will discuss postmarketing reviews of adverse events for drugs that have been granted exclusivity.

The review of the post exclusivity adverse events is accomplished through the collaboration with the Office of Drug Safety, Office of Pediatric Therapeutics and Division of Pediatric Drug Development. Therefore, at first I would like to acknowledge the contribution of the staff in the Office of Drug Safety for these reviews.

In the morning you will hear adverse event reviews for eight drug products that were granted pediatric exclusivity. These reviews will be presented by medical officers within the Division of Pediatric Drug Development. Several of these presentations are informational while a few discuss important issues, ranging from a lack of age-appropriate pediatric formulations for

fosinopril to a preventable safety signal associated with the use of fentanyl transdermal system or Duragesic. You will be asked to discuss a question of risk management strategies in relation to fentanyl. The morning will also include a time for open public hearing, followed by a short pediatric update by Dr. Dianne Murphy.

We are doing the adverse event review a little differently than before. In addition to the usual format which you are familiar with, we have incorporated some of the clinical trial data available in the public domain into these reviews. You are not going to see this component for all the drugs because the trial data are not yet in the public domain for some of the drug products that we will be discussing.

This is a pediatric page on the external FDA website where you will find all the publicly available summaries of medical and clinical pharmacology of these pediatric studies for exclusivity. The process of making these reviews available in the public domain is evolving,

therefore, some of the reviews that I mentioned before may not be yet available on this website. Nevertheless, I invite you to use it as a resource and urge you to spread the word about this site.

In the afternoon we will discuss two pediatric safety issues regarding the use of SSRIs and SNRIs during pregnancy. As you recall, we discussed several case reports of neonatal withdrawal syndrome related to the use of Paxil and Celexa during the meeting of this committee last February. At that time you requested more information on the syndrome and FDA's efforts to address it.

To address this issue, we have lined up three presentations for you. Kate Phelan, from the Office of Drug Safety, will present the postmarketing adverse event review for this class of drugs. Dr. Bob Levin, from the Division of Neuropharmaceutical Drug Products, will speak on the new class labeling regarding neonatal withdrawal toxicity and its rationale. Dr. Kathy Wisner will address the risk/benefit of treatment

in child depression, a critical issue for both the practitioner and the patient. At the end of this update you will be asked to discuss two questions.

Next, I will present an update on congenital eye malformations, again, as a fallout to the February meeting when we reported a case report about possible congenital eye malformation related to the use of Celexa during pregnancy. This update will review all postmarketing reports of congenital eye malformations for Celexa and some newer anti-depressants.

Before we present the specific adverse events, I will briefly review the data sources used in this review and their limitations. The Adverse Event Reporting System is a spontaneous and voluntary system. Because it is a passive system it suffers from a number of limitations, listed here on this slide, that you are already familiar with and we have discussed several times during previous presentations.

Again the drug use data source and their limitations have also been presented before and are

not new to you. IMS National Prescription Audit Plus is used to estimate the number of outpatient prescriptions but lacks demographic information. The National Disease and Therapeutic Index can estimate drug mentions during office-based physician visits but pediatric use estimates can be unstable for less frequently used medications.

Another outpatient data source is the IMS National Sales Perspectives which provides estimates of units sold from manufacturers to various channels of distribution and, therefore, may be a possible surrogate measure for drug use. An important limitation of this data source is absence of demographic information such as age and gender.

Important drug use data sources and their limitations are well-known to you. To refresh your memory, these are described in this slide and the next slide. The main limitation with all the inpatient data sources, except for Premier, is the inability to make national projections of drug use. However, national estimates from Premier are

available but are selective. Furthermore, drug use cannot be linked to diagnosis or procedure and drug use in hospital or outpatient clinics is not captured in this data system. Data from CHCA are limited to 29 children hospitals and cannot be projected nationally.

This concludes my remarks and now let me turn to the presentations for this morning by introducing the first speaker. But before I do that, I do want to recognize two individuals who have tirelessly worked behind the scenes to make this meeting possible. Please stand up and be recognized, Miss Christine Phucas and Rosemary Addy.

[Applause]

Thank you. Now the next speaker, Dr. Filie is a general pediatrician and pediatric rheumatologist. She conducted research on molecular biology, connective tissue disorders and genetics at NIH for many years before going into private practice. She joined the FDA from private practice about a year ago. She will discuss

adverse event reports for fexofenodine. Dr. Filie?

Fexofenodine

DR. FILIE: Good morning, everyone. I will proceed with the adverse event review for fexofenodine during the one-year post-exclusivity period.

Fexofenodine, trade name Allegra, is an antihistamine by Aventis Pharmaceuticals. The indications for adults and children are relief of symptoms associated with seasonal allergic rhinitis and non-complicated skin manifestations of chronic idiopathic urticaria. It was originally approved in July, 1996 and pediatric exclusivity was granted in January, 2003.

In order to fulfill the requirements for exclusivity, 3 pivotal studies were conducted and 415 children, 6 months to 6 years of age, were treated for allergic rhinitis. One study was a Phase 1 pharmacokinetic study characterizing the dose for children 6 months to 2 years of age. Another study was a Phase 3 study assessing safety and tolerability in 2 groups, 6 months to 2 years

of age, weighing under 10.5 kg and weighing over 10.5 kg.

A previous safety and tolerability study on children 2-6 years of age was also submitted. The adverse events occurred at similar frequencies as for placebo, and no new safety signals were observed.

Efficacy studies were not conducted due to the fact that the disease course and pathophysiology of allergic rhinitis and chronic idiopathic urticaria, as well as the drug's effect, are similar in children and adult patients. The studies conducted on children 6 months to 6 years of age utilized fexofenodine powder mixed with apple sauce or rice cereal. There is no marketable age-appropriate formulation for children 6 months to 6 years of age.

Drug use trends for fexofenodine--currently, fexofenodine is the leading prescription for non-sedating antihistamine on the market since loratadine became over-the-counter in 2002. The total number of

fexofenodine product dispensed increased from approximately 20.9 million in 2000 to 29.6 million in 2003. Pediatric patients accounted for approximately 2.5 million prescriptions of fexofenodine dispensed in 2003. The most common diagnoses associated with the use in pediatric patients in 2003 were allergic rhinitis and allergic disorder.

The adverse events from pediatric clinical trials that I just presented are as follows: Headache, accidental injury, cough, fever, pain, otitis media and upper respiratory infection, and least common, insomnia, nervousness, sleep disorders, rashes, urticaria, pruritus and hypersensitivity reactions.

During the exclusivity period the total adverse event reports from the AERS database was 158, 84 of them in the United States. Among the 158 reports there were 8 unduplicated pediatric reports which included 2 with serious outcomes, 1 hospitalization and 1 life-threatening event. There were no pediatric deaths.

In the 8 pediatric case reports the following unlabeled pediatric adverse events were reported, psychosis exacerbation with suicidal ideation and depression; seizure, visual disturbances; abnormal liver function; fungal urinary tract infection; non-accidental overdose of multiple drugs and prolonged QT, prematurity, maternal experience and medication error.

I would like to present you with a synopsis of individual reports. A 15 year-old with schizoaffective disorder and ADD, on multiple medications, experienced exacerbation of psychosis, suicidal ideation and depression which resolved after discontinuation of fexofenodine.

A 13 year-old child presented with grand mal seizures. The patient was also on multiple medications and one of them was bupropion which has a warning about the potential to cause seizures.

A 7 year-old presented transient loss of color vision and visual disturbances such as black dots and bubbles. It also resolved after discontinuation of the drug in a few days.

A 10 year-old patient developed a bacterial UTI and abnormal liver function tests after receiving fexofenodine for one week. The child was on concomitant medications and one of them was labeled for hepatic function impairment. We do not have the name of the drug on the report. The child recovered after discontinuation of fexofenodine.

A 16 year-old who developed a fungal UTI and pyelonephritis was hospitalized. This patient was also on multiple medications for depression and gastritis.

A 13 year-old had an intentional overdose of fexofenodine, acetaminophen, metoclopramide and tramadol. QT prolongation was observed in the emergency room which normalized the following day.

The last two cases--a 27-week old premature baby, small for gestational age, was born by C-section due to pre-eclampsia. There was a history of abnormal alpha-1 fetoprotein. The mother was on concomitant medications.

The last case--a prescription refill was

mistakenly filled with Zyrtec-D instead of Allegra-D, but no adverse event was reported.

Concluding the report, despite the large number of fexofenodine prescriptions, there were few pediatric adverse event reports during the one-year post-pediatric exclusivity period. It is also very difficult to make any attributions of the adverse events of the drug when there are concomitant medications in the reports. In this case, the FDA will continue to monitor the adverse event reports in all populations. Any questions or comments?

DR. CHESNEY: Dr. Santana?

DR. SANTANA: Do you know if there are any similar adult reports with the use of this medication and concomitant anti-psychotic medications in adults?

DR. FILIE: I don't know that I can respond to that adequately. From the information that we have on the label, the adverse events are very similar in both populations. They resemble pretty much the two groups.

DR. S. MURPHY: Pete Stark I think is here from the Division. Do you have any comments about adult report?

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: It seems to me that the way you keep your data may help you to find things. So, I am wondering when you have these reports, are you keeping track of the various concomitant medications so that you could be looking for trends developing that may be subtle, that there may be interactions, or something?

DR. FILIE: Yes. The hope is to accumulate this data over a long time.

DR. O'FALLON: Yes, but I mean in a way so that you are able to go back, search and find those combos? I am asking about how the data is being collected so that you are going to be able to search on it.

DR. FILIE: Yes, it is possible and we are doing that collecting and the Office of Drug Safety is also involved in this. This is something that has accumulated and we can keep all this data

without losing it.

DR. O'FALLON: But in a computer file that you can search?

DR. FILIE: I don't know.

DR. IYASU: Let me respond to this. The AERS database has been in existence for a long time and the database is searchable both by high risk event terms as well as by the drug name or the trade name. So, it is searchable by a number of parameters and there is an accumulated database which resides at FDA so you can look at one year or you can look at several years since the first time a report comes into existence for a particular product. Once there is approval, there are going to be postmarketing reports that come in. So, there is a way to look at that. But there isn't a whole lot of information to try to look at multiple permutations of different confounders or looking up interactions. It is a limited database in that way.

DR. D. MURPHY: I did want to respond that in your package it does tell you that fexofenodine

has been looked at with the co-administration of acetyl console and erythromycin, the sip interactions. So, what the agency does is where we know that a metabolism uses a certain sip enzyme that will cause increases or decreases, they will frequently look at that interaction but they can't look at all of them. That often is actually a negotiated activity as to how many of them they do look at, and whether there are ones that are more likely to give serious adverse events by the normal drugs that might be used with this specific disease. So, you could see that with an allergic indication you might think that antibiotics would be one of the set of drugs that they would look at.

So, I just wanted to put on the table that prospectively the agency will sometimes ask, knowing what the metabolism is, for these interactions. But, you can imagine that the list could get endless so the agency does not do all possible combinations. Certainly, I think from allergic rhinitis to antidepressants--I mean, unless you had a mechanistic reason for doing that,

you wouldn't up front do it. Your question, I realize, was looking at statistical analysis post but up front there is a certain amount of activity in that area.

DR. O'FALLON: It seems to me that since you only have a handful of reports it might be worth it, that when you see something showing up you would say they took drug A, drug B, drug C, let's look and see if we have any reports in the database, especially in the adults or something, to see if you are seeing if that has been reported before.

DR. D. MURPHY: As noted, ODS has the database and it will have that information in it. So, you could go back and plug in certain drug names. I think, as always, the caveat is that there are those who didn't enter that and were on it so there is always that question of what does it mean when you do it. But, you are right, if you kept seeing that pattern, then it would be something you might wish to pursue further and ask for some additional studies.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: This is mainly for clarification from my reading of the labeling. On page 7 of the label for this product there is a bar on the side and I wanted to know whether this was edited out of the label or is the present labeling wording which says that the safety and effectiveness of fexofenodine in pediatric patients under 6 years of age has not been established. Is that in the label now or out of the label?

DR. D. MURPHY: It is not labeled under 6. Is that right?

DR. GORMAN: It is a question of the bar because it comes up several times later on in labeling.

DR. D. MURPHY: Right, right. We will verify this but I think the point was that because there was no formulation that was available, it is not labeled under 6.

DR. GORMAN: I think one of the issues that was raised at the last meeting, and I would like to have it reemphasized again is that there is

now data. When we started this process two decades ago, that statement meant that there were no studies. Now it means there may well be studies but it is not included in the label. I noticed in the executive summary, which will be available on the web-based FDA data, that there is information about its use in children less than 6 months of age.

DR. D. MURPHY: I think you referred to the clinical pharmacology and biopharm study. Unfortunately, it doesn't have a page number but it is after the label. It does say in there that no labeling changes for pediatric indication or dosing for children less than 6 years old will be made at this time because there are no age-appropriate formulations for fexofenodine for these children, and your point being that it was studied. And, that is not going to be put in the label and I think that is an issue.

DR. GORMAN: That is the issue I wanted to raise and it will now be raised by others for the rest of the meeting.

DR. CUMMINS: Can I just provide one point of clarification? The labels that we provide to you are ones that are publicly available and are the most recent labels. Often the strikeouts are still present. We download them from the labels that are posted on the web often--you know, that we post on the FDA website. If you see a strikeout, as you see on page 7, then that strikeout will be removed in the published label by the company.

DR. GORMAN: Thank you.

DR. CUMMINS: You are welcome.

DR. FILIE: Given there are no further comments or questions, let me introduce the next speaker, Dr. Susan McCune. Dr. McCune is a neonatologist whose previous experience includes academic neonatal practice at Johns Hopkins and Children's National Medical Center. She recently received her masters degree in education and has worked on computer-based education models for pediatrics. She will discuss two oncology products, topotecan and temozolomide. Dr. McCune.

Topotecan and Temozolomide

DR. MCCUNE: Thank you very much, Dr. Filie. Ladies and gentlemen of the committee and guests, Drs. Murphy told me to try to keep things a little bit light to keep you all awake and my Irish ancestry would allow me to tell shaggy dog stories but, unfortunately, I don't do very good jokes so I think we will just move along.

As Dr. Filie mentioned, I will talk about two oncologic agents this morning. The first is topotecan. Topotecan, trade name Hycamtin, is an anti-tumor oncologic agent produced by GlaxoSmithKline. The indication in adults is metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy and small cell cancer sensitive disease after failure of first-line chemotherapy. There are no approved pediatric indications. The original market approval was May 28, 1996 and the pediatric exclusivity was granted on November 20, 2002.

I am going to tell you about the studies for exclusivity for this drug. As you all mentioned, in terms of data that is available for

the label, these studies were done based on what Dr. Iyasu told you already. BPCA mandates that this information be available on the website and this information is available on the website, however, there were no changes to this label based on this information.

The studies that were submitted for exclusivity were summaries of studies that were previously performed by the Pediatric Oncology Group. They were initiated in 1992 and 1993. This was a Phase 2 study in pediatric solid tumor that enrolled 108 patients that were less than 16 years of age. The tumor types were Ewing's sarcoma, peripheral neuroectodermal tumor, neuroblastoma, osteoblastoma and rhabdomyosarcoma. The study endpoint was tumor response rate. Eighty-six percent of patients died, with 10 percent dying within 30 days of the last dose of topotecan. The overall response rate was 8 percent but the response rate for patients with neuroblastoma was 18 percent. Of note, it is important to know that for alternative regimens using combinations of

available drugs in pediatric patients with relapse neuroblastoma the response rates were 35-50 percent. In this case, no patients less than 2 years of age showed any response.

Eight of the 11 patients that died within 30 days of the last dose of topotecan had progressive disease and 3 died with infection which is a known complication. Forty-four percent of patients were hospitalized with adverse events, primarily febrile neutropenia, fever or sepsis.

The Phase 2 study did determine a different dose from adults, a daily infusion for 5 consecutive days every 21 days. The adult dose is 1.5 mg/m 2/day and the pediatric dose that was given was either 1.4 mg/m 2/day without granulocyte-colony stimulating factor or 2 mg/m 2/day with granulocyte-colony stimulating factor.

In terms of drug use trends in topotecan in the inpatient setting, between July, 2001 and June, 2003 there were 10.6 percent of discharges. Just to give you a rough idea, compared to the last drug which had a number of prescriptions, this was

only 425 of 4,001. Pediatric topotecan did increase annually in that time period, from 6.8 to 18.6 percent. It accounted for 407 discharges from 29 CHCA free-standing pediatric hospitals, with the most frequent diagnosis being chemotherapy encounter followed by malignant neoplasm of the adrenal gland. A significant limitation, as we have already discussed, of the analysis is that the FDA does not currently access data capture in the outpatient hospital clinic setting where most chemotherapy is administered.

Now I am going to tell you about the adverse event reports for topotecan for the one-year post-exclusivity period. There were 29 total reports for all ages, 18 in the United States. There were no pediatric reports that were submitted during this time. Of note, in the 7-year period from 1996 there were some unlabeled pediatric reports, none of them during that 1-year post-exclusivity period. There were 4 reports of convulsion, hypotension, edema and speech disorder, and 3 reports each of arachnoiditis,

ascites, Budd Chiari syndrome, caecitis and confusional state.

In summary, the FDA will continue its routine monitoring of the adverse events in all populations. I will stop here and take any questions on this particular drug.

DR. CHESNEY: Dr. Santana?

DR. SANTANA: I think I have made this point before and I will try to reinitiate it again. In contrast to some of the other drugs that we have in front of us, the oncology drugs are usually used in the setting of clinical research. They are not used in the setting of common practice. So, there is a wealth of data from protocols either initiated by the historically previous oncology groups or the current Children's Oncology Group and certainly by other large institutions like St. Jude's that do research in these drugs. How is that data captured and reflected in these reports? Because there is a wealth of adverse event data that is generated through that clinical research that will not show up through these voluntary reporting mechanisms but

will show up in the databases of the clinical research infrastructure.

DR. MCCUNE: A lot of the reports that we get for these particular drugs are actually from study reports. In terms of the studies that were done for exclusivity for this drug, they actually were, as you mentioned, part of the research protocols so they were independent studies conducted by the company.

DR. SANTANA: But I guess the point is that that is true but there is a lot more usage of this drug now, as you indicated in your brief summary of the trends of usage of this drug in pediatric oncology. How is that data eventually going to make it into the adverse event reporting? Because it is not really part of the exclusivity because those studies have not been submitted for exclusivity. Am I correct?

DR. MCCUNE: That is correct.

DR. SANTANA: These are studies that are ongoing.

DR. MCCUNE: That is correct. This is the

one-year post-exclusivity period.

DR. SANTANA: How will that data show up in the current study?

DR. S. MURPHY: It would have to come through the AERS. It would have to be submitted to AERS for us to have that information. Dr. Maldonado may want to comment, but the companies have to report any adverse events to the FDA. So, the companies, you know, keep very close tabs on the medications, especially the medications that are in trials that are using their drugs. So, there is a sort of cross-reference thing. Then, it is even global with the pharmaceutical companies and with the international organizations with the FDA. So, I think it is a very good question. I think Don Mattison might want to make a comment, from NIH.

DR. MATTISON: Just a brief comment. We are currently working with NCI and COG to develop full access to their databases and that information will be shared with FDA.

DR. D. MURPHY: Dr. Santana, I think if

you look at what is in the label now, it just says that the effectiveness in children has not been demonstrated. Then it goes ahead and it does describe the studies. As you know, for cancer this has been a real issue because of the reasons you have stated. The label is marketing approval and if it is not approved for that indication, you know, the agency is in this quandary of how do you make information available when you don't want to give a de facto indication that doesn't exist? So, that is the tension here. Depending on the product, depending on what comes out of the exclusivity studies if we don't have sufficient evidence to say it is efficacy and, as you know, and I don't want to say this over and over again, but these studies are not powered to do that. So, how do we make that information available has been difficult.

I think what they have done here is that they have been able to put into--by saying it has not been demonstrated, first, and saying yet we looked and here is what we found in a very limited

way, and then having some adverse event reporting that came out. Now, does it happen for every product, every time? Not always because it may be that there were other issues with the studies and then what you may end up with in the label if there is a particular safety thing, they would say it was studied in so many kids; it wasn't effective or we couldn't determine effectiveness but we are going to tell you about these adverse events. So, that can happen. The adverse events in those studies could be put into the label if it is a safety issue.

DR. SANTANA: I guess what I am getting at is that the information that is derived from granting exclusivity is for the studies that the sponsor has put forth to reach that point.

DR. D. MURPHY: Right; that is correct.

DR. SANTANA: But there is another wealth of data that is being generated. As I understand it, unless it is throught the sponsor or through some other mechanism that data becomes available to the FDA it is not part of the information that we

have in front of us today or in the future.

DR. D. MURPHY: Well, it is required to be reported to the FDA. It is required to be reported and if the agency sees a signal, then there is a re-review of the data and a determination if that additional information needs to be entered into the label. I would say that if a researcher had access to data that they were concerned about and saw that it wasn't in the label, it is perfectly appropriate to ask--you know, again, it is a requirement. Companies get into big trouble if they have adverse events that they don't report to us.

The other issue--I am not saying it happens, but if somehow you thought something wasn't getting reported, it is perfectly appropriate to call the agency and say I am aware of this; make sure you got those reports.

DR. SANTANA: I want to make it clear for the public record that I am not raising issues with this drug or the next oncology drug. I am trying to understand the process. I just want to make that clear.

DR. D. MURPHY: Yes, and we want to make it clear that it is part of companies' standard reporting activity. Sam, maybe you could say something about the routine things that go on in reporting both during a trial and after a product is marketed.

DR. MALDONADO: Both of you are completely right. Companies are not going to get in trouble by not reporting. That is very enforceable. A lot of not reported events happen when physicians don't report to companies. So, that is where the problem is; it is the education. We are not only talking about sending in the reports, but sending them within 15 days of occurrence. Most of the non-reporting happens because of lack of education from clinicians. In clinical trials it happens much less, or probably very, very close to zero because there is monitoring by the company. Actual people go there and make sure they are doing it. Outside clinical trials it is more difficult because you cannot police physicians so it is up to them to report. But once it is reported to the

companies, it is reported to the FDA and the FDA, of course, can always come to a company and check if we are doing it and actually FDA does that.

DR. D. MURPHY: I think what Sam has said is really important. If a physician sees an adverse event on a product, particularly if you put them on a product, take them off and put them back on--you know, if you have evidence, but even if you don't, if you put a child on a product and you have some serious event and you are not sure whether it is related or not, you don't have to make attribution. This is one of the problems I think physicians don't understand. You don't have to determine individually that this product caused this adverse event. If physicians would, please, make it part of their public health rule to report adverse events that they think are serious to the agency and to the company, I mean, that is a double way--or either way, you know, whichever way you know how to get that information in. It will get to us if it gets to the company or it can come to us directly. So, I would like to keep adding that

commercial. It is a very important part of activity. I have been out there; I have practiced medicine and I know I haven't done it when I should have. So, it is just a plea that we keep putting that out there because you can see how important it can become.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: There is one other issue that is a possible problem. I don't know these particular studies that COG is doing but if they, indeed, have closed patient accrual before the exclusivity period it is entirely possible that the acute toxicities wouldn't be available at this time. You know, not all the data in these clinical trials gets reported out until the final study is done. I mean, the company had to know about it ahead of time, but during this exclusivity period there maybe weren't any from those trials.

DR. D. MURPHY: I think that brings up the other issue just of any follow-up post-trial. As you know, there was a legislative mandate also to put the 1-800 MedWatch number on labels and that

process is proceeding. I don't have any idea when actually you will see it but it is continuing to move forward.

DR. CHESNEY: Dr. Ebert?

DR. EBERT: Just a follow-up to that, is it feasible or even reasonable with these drugs that are specifically under exclusivity for the FDA to make pediatricians more aware of the fact that they are under this particular scrutiny? And, would it heighten their level of interest with regards to reporting adverse events?

DR. D. MURPHY: Joan has a suggestion for you later today I think about maybe one way of doing it. We have been trying to do that in a number of ways by working with the American Academy of Pediatrics newsletter that goes out and doing annual updates of changes in the label, talking about exclusivity, but I think you bring up a good point--have we really made an issue in that reporting about changes in label about reporting adverse events? No. And, that is a good point and we will take that back and pursue that as an

additional piece of information we should try to get out to pediatricians, family practice, people who are taking care of children. We are working with the Academy on the CME activity so that we can put in some case studies that might bring that up.

DR. S. MURPHY: Joan, just one more point, there are really two ways of reporting adverse events. One is to the FDA and the other is to the companies. The larger pharmaceutical companies have these 1-800 numbers and if you call and you say you have an adverse event, you are immediately put in touch with the Pharm.D. who has a whole scheme of questions to ask you right away. All those reports, like Sam said, do go back to the FDA and the seriousness of the report triggers certain times to report it. Having been on the other side in a pharmaceutical company, I was in charge of a drug that had a lot of adverse reactions and we were constantly reviewing all the cases that came in. The company will often send somebody out to the hospital to look at the records and make sure of the accuracy of the reporting. So, it is taken

incredibly seriously on both sides.

DR. CHESNEY: Thank you. We can move on to the next speaker.

DR. MCCUNE: Actually, I am doing the next drug. You get to listen to me again. The next drug I am going to talk about is temozolomide. The trade name for this is Temodar. Once again, this is an oncologic agent produced by Schering Plough Research Institute. The indication in adults is that the capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, in other words, patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. In pediatrics there are no approved pediatric indications. The original market approval was August 11, 1999; the pediatric exclusivity was granted November 20, 2002.

Once again, I am going to tell you about the studies for exclusivity. These are available on the website. In addition, for this particular label safety information is included in the

pediatric section of the precautions part of the label and it does include a description of the clinical studies that were completed.

The studies that were submitted for exclusivity were one Phase 1 and two Phase 2 open-label, multicenter studies. The Phase 1 study was dose escalation in 27 patients with advanced non-CNS and CNS cancers. The first Phase 2 study was in 63 patients with recurrent brain stem glioma and high grade astrocytoma. The second Phase 2 study, a cooperative group-sponsored study, was in 122 patients with various recurrent CNS tumors. The patients ranged in age from 1 to 23 years of age, with the majority of patients between 3 and 17 years of age.

The primary endpoint for these studies was tumor response rate. In the first Phase 2 study there was 1 complete response and 3 partial responses among 27 patients. In the second study there were no complete responses or partial responses in the brain stem glioma patients and no complete response and 12 percent partial responses

in the high grade astrocytoma patients. In the third study the overall response rate, combined complete response and partial response rate, was 5 percent. Only 1 patient achieved complete response and 5 patients had partial responses.

Safety was assessed in 204 patients at doses of 100-200 mg/m
2/day daily for 5 days every 28 days. The toxicity profile that was seen was similar to adults. The most common adverse events that were reported were dizziness, neuropathy, paresthesia, nausea/vomiting, constipation and myelosuppression.

Just to give you an idea of the drug use trends in the outpatient setting for temozolomide, the number of prescriptions dispensed has nearly doubled over the past 3 years from 50,000 in 2001 to 93,000 in 2003, with the top prescribers, as you can imagine, being oncology/neoplastic, neurology and hematology. Of note, only 1 percent of temozolomide prescriptions were written by pediatricians.

The pediatric population of 1-16 years of

age accounted for a small number of temozolomide prescriptions, 3.1 percent in 2002 and 3.9 percent in 2003, with the most frequent diagnosis being malignant neoplasm of the brain both in adults and pediatric patients.

In terms of outpatient sales, they have been on the rise, from 1.8 million capsules to 2.2 million capsules in the last 2 years, with the majority of sales through retail channels, 80 percent of them going to chain and independent pharmacies and other retail channels.

CHCA data demonstrated from 2002 to June, 2003 that there were only 17 pediatric discharges associated with this drug.

The limitations to drug use data in the outpatient setting for these drugs are important to note because we don't have sources that specifically examine outpatient hospital clinics where chemotherapy treatments are provided. What is important to note though is that the retail sales do capture a number of those sources and it is felt that most of the use of this drug is

captured through assessment of outpatient use.

In terms of adverse event reporting for the post-exclusivity period from November, 2002 to December, 2003 there were 250 reports in all ages, 160 of them in the United States. There were 5 unduplicated pediatric reports, 2 of them in the United States, all with serious outcomes and 1 death. There were 4 females and 1 male. Three of the patients were aged 2-5 years; 2 of the patients 6-11 years. There was one patient each for the diagnoses of blastoma, adrenal metastatic neuroblastoma, anaplastic astrocytoma, medulloblastoma and brain stem tumor.

The clinically significant unlabeled adverse events could be divided into 5 groups. One was brain edema; 1 was death. Another, hemangioma acquired; another ITP and another myelodysplastic syndrome. All of these, although not specifically delineated in the label, are potentially related to either a labeled process or the underlying disease state.

Just to take each one of these

individually, brain edema in the patient was associated with concomitant radiation therapy. The death was potentially due to the underlying condition. The acquired hemangioma was potentially related to either the underlying condition, the concomitant medication or the radiation therapy. The ITP was a potentially labeled event or secondary to the underlying condition. The myelodysplastic syndrome was also a potentially labeled event or secondary to the underlying condition.

Just to give you a brief synopsis of these 5 cases, the first was a 3 year-old that was treated for pineal blastoma who died of an unspecified cause.

The second was a 6 year-old who was treated for recurrent anaplastic astrocytoma, was on concomitant medications including radiation therapy, and following temozolomide use, a cavernous hemangioma was noted on MRI. Of note, it was not previously seen on prior MRIs. Following temozolomide treatment, this patient also had

thrombocytopenia requiring transfusions and was diagnosed with ITP and myelodysplastic syndrome. This patient was discharged with an improved clinical status 18 days after admission.

The third case is a 4 year-old treated for medulloblastoma who suffered an infection and there was no outcome of the event that was documented.

The fourth case is a 4 year-old treated for metastatic neuroblastoma who developed thrombocytopenia, anemia and fever which were managed with transfusions and antibiotics. She recovered without sequelae and was given a second cycle of temozolomide without recurrence.

The final case is an 8 year-old who was treated for brain stem tumor. Routine MRI revealed radiation-induced cerebellum edema requiring hospitalization for intracranial drainage. This patient was subsequently discharged in stable condition.

In summary, for temozolomide there have been described both labeled and unlabeled adverse events. The unlabeled events have also been

reported in adults and are not unique to pediatrics, and the FDA will continue to do routine monitoring of adverse events in all of the populations.

DR. CHESNEY: Thank you very much. I just wanted to bring to the committee's attention the fact that at 9:30, although we are getting significantly behind with the very full agenda, the FDA has asked us to address question one, which is at the back of the packet that we were given today with the agenda on it, which involves process issues. So, I think unless you have specific questions related to this drug, if they are process issues, we will have an hour to discuss that later on. So, does anybody have specific comments regarding this drug? Shirley?

DR. S. MURPHY: Dr. Chesney, Dr. Starke from the Pulmonary Division has some late-breaking information on the first drug that we discussed. He was just going to tell us a follow-up on a question that the committee had, what the bar was beside the label.

DR. STARKE: I am Dr. Starke, from Pulmonary and Allergy Division. I am a medical team leader. I went upstairs and double-checked the label for you since there was a cross-out there. That was simply something that was caught as the final label was approved. The current labeling does say for 6 months and older.

I just want to make the comment that even though the studies were done down to 6 months of age and, as you know, certain other antihistamines may be approved down to 2 for SAR and 6 months for PAR, this drug was not approved below age 6 because there was no marketed formulation. A non-marketable formulation was used which, of course, is an issue which you may want to address. Thank you.

DR. CHESNEY: Thank you. If there are no additional questions on your presentation, which I thank you for, I think we can move on to the next speaker.

DR. MCCUNE: It is my privilege to introduce Dr. Harry Gunkel to you. He is the only

person standing between me and the privilege of saying that I am the most junior member of the Pediatric Drug Development Office. Like me, he is a neonatologist who has extensive experience in private practice, the pharmaceutical industry and academic medicine. Many of you may know him for his significant work on surfactant. He is going to talk to you today about two ophthalmologic anti-infective agents.

Moxifloxacin and Ciprofloxacin

DR. GUNKEL: Thank you, Susie. Hello. As Susie said, the next two products on the list are both ophthalmic antibacterials, both fluoroquinolones. The first is ciprofloxacin, known under the trade name Ciloxan and sponsored by Alcon Laboratories. It is indicated in adults and children greater than 1 year of age in a solution dosage form, and adults and children greater than 2 years of age in the ointment dosage form for the treatment of bacterial conjunctivitis caused by the organisms shown on the slide. The solution form is also indicated for corneal ulcer. The original

market approval was in 1990 and pediatric exclusivity was granted in January, 03.

Drug use data shows that dispensed prescriptions for Ciloxan decreased slightly over the period of exclusivity. Almost half of the prescriptions for this drug were for children between 1 and 16 years of age, and pediatricians wrote about a third of the prescriptions during the exclusivity period.

The most common indication for the prescription was conjunctivitis, other or unspecified, and Ciloxan was the most mentioned product for this indication in pediatric patients.

During the exclusivity period there were 9 total reports for all ages; 3 were from the U.S. The age was not specified for 2 of the 9 reports. There were no pediatric reports. We will continue to monitor the adverse event reports, of course.

The next drug is moxifloxacin, also sponsored by Alcon Laboratories, also an ophthalmic antibacterial drug. It is indicated for adults and children 1 year of age or greater for the treatment

of bacterial conjunctivitis caused by a number of susceptible organisms, aerobic gram negative and gram positive organisms. The market approval for this product was April of '03, less than a year ago. So, that will become pertinent when we look at the data in just a moment. Exclusivity was granted before market approval, in January of '03.

Since approval didn't occur until April of last year, the drug use and adverse event data cover less than a 1-year period, unlike the other products you are reviewing today. About 800,000 prescriptions were dispensed since approval in April, '03. About a quarter of the prescriptions were for pediatric patients. Ophthalmologists wrote most of the prescriptions for this agent, just over half of the prescriptions, followed by pediatricians who wrote about a quarter of them. The most common indication, as for ciprofloxacin, was for conjunctivitis, other or unspecified and Vigamox, the trade name of the product, accounted for 4.6 percent of the mentions for children.

There was 1 report in the exclusivity

period and it was a pediatric report. It was an incidence of subconjunctival hemorrhage in a 6.5 year-old female that occurred 24 hours after the use of Vigamox. The child was also using Augmentin. The child recovered after discontinuation of the drug and this event, subconjunctival hemorrhage, is a labeled adverse event occurring in 1-6 percent of patients. We will continue to monitor this product as well, of course.

One study was done for the exclusivity and it actually involved both products. It was a multicenter, randomized, double-blind, parallel group comparison of moxifloxacin and ciprofloxacin in neonates, with the endpoints of clinical cure at day 5 and the microbial eradication rate.

From the data that is available in the public domain, these are the results. The rates of clinical cure are shown for both the agents. These rates are less than the generally expected vehicle rate, and the difference between the two was not significant. Thank you.

DR. CHESNEY: I have two questions. What do you mean by expected vehicle rate?

DR. GUNKEL: If you apply a vehicle to a case of bacterial conjunctivitis the expected cure rate is 70 percent.

DR. CHESNEY: That is what I thought you meant; I just wanted to be sure. And, what were the side effects of Ciloxan? There were 9 reports.

DR. GUNKEL: They weren't pediatric so I didn't see them. I don't know.

DR. CHESNEY: Other questions? Dr. Murphy?

DR. D. MURPHY: Go ahead and finish up with this topic because I was asked to make a clarification on the last one.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: If I were the statistician on this study I would be very concerned. I would be talking to the docs and saying, "wait a minute guys, this looks like it's doing harm." Both of these agents look like they are not helping. If they have a lower response rate or success rate,

whatever you want to call it, than the placebo which is the vehicle without anything in it I would be worried that it is contra-effective.

DR. GUNKEL: I don't know whether that is the case. The information that is in the public domain doesn't allow us to deduce that the rates that were shown in the study that I showed were significantly less than the expected vehicle cure rate. But your point is well taken I would think.

DR. CHESNEY: Dr. Murphy?

DR. D. MURPHY: Dr. McCune has said that I may have confused things in efforts to answer Dr. Santana's question about how we get information in the label because you were talking about the topotecan when I read to you the information that was in the Temodar label. I was trying to point out that there are various approaches depending on the quality of the data. So, for the topotecan the actual information that is in the label now in pediatrics is that there is no safety or effectiveness that has been established versus the Temodar, which is the one that I read you. I

thought I read the product but they both start with T. So, I want to make it clear that it is the Temodar that has all that information in it.

DR. SANTANA: My question was a process issue; it didn't relate to any specific--

DR. D. MURPHY: Yes, and I was trying to give a process where there can be different types of information put in. Anyhow, I just wanted to make sure that I didn't confuse the committee with the Ts when I started talking about the second label before it was actually presented. Thank you.

DR. CHESNEY: I think we are all looking at your last two slides and puzzling over the last one, but I think that wasn't really the issue of this morning's discussion so we will leave that for the moment and move on to the next speaker.

DR. GUNKEL: The next speaker is Dr. Larry Grylack. Dr. Grylack began a career in the Commission for U.S. Public Health Service from 1971-73. His training is in pediatrics in neonatal/perinatal medicine. He was in the practice of neonatal medicine at Columbia Hospital

for Women, in Washington, for 26 years with a particular interest in neurodevelopmental follow-up of high risk newborn and apnea during infancy. Dr. Grylack?

Fosinopril

DR. GRYLACK: Thank you, Dr. Gunkel, for the introduction. It is a privilege to speak to the committee this morning. In case there has been anything said so far this morning that has caused your blood pressure to rise, I will be discussing an antihypertensive drug at this time.

The name of the drug is fosinopril, with the trade name of Monopril. Its sponsor is Bristol-Myers Squibb. Fosinopril is in the renin angiotensin antagonist subclass of antihypertensives. Its mechanism of action is inhibition of angiotensin converting enzyme. Although fosinopril is approved for use in adults, there are no approved pediatric indications. Pediatric exclusivity was granted early last year.

Despite a 20 percent increase in the prescribed use of renin angiotensin antagonist

drugs in the outpatient setting, there was a 25 percent decrease in the use of fosinopril during a recent 3-year period. Conversely, there was a 33 percent increase in the use of the combination drug fosinopril/hydrochlorothiazide during that same time period. The ratio of the number of pediatric prescriptions for fosinopril alone to prescriptions for the combination drug was approximately 10:1.

Let's focus on the inpatient usage data for fosinopril. Two databases from recent 3-year periods report a very low percentage of pediatric inpatients using fosinopril during their hospital stays. There were no pediatric adverse event reports submitted during the post-exclusivity period.

Two studies were done for the purpose of achieving exclusivity. A single-dose pharmacokinetic study showed an age-dependent increase in bioavailability in a population of 43 patients between the ages of 1 month and 16 years. An oral solution containing a dose of 0.3 mg/kg of body weight was used.

Secondly, an efficacy and safety dose did not demonstrate a dose-response relationship in a population of 253 patients between 6 and 16 years of age. A tablet form of medication was used in this study. No deaths or cases of angioedema were reported, the latter being an adverse event reported in adults.

Pharmacokinetic parameters in the children studied are similar to those found in adults. Dosing information is available for children weighing more than 50 kg. However, the formulations used in children in the exclusivity studies are not currently commercially available.

This leads me to the broader issue of the need for age-appropriate formulations. As physicians and parents know, non-liquid forms of medications are not appropriate for infants and preschool children, as for some school age children as well. Therefore, sponsors are being encouraged to develop age-appropriate commercially available, marketable pediatric formulations during their exclusivity studies.

The goal of the FDA, and especially of our Pediatric Drug Development Division, is to have commercially available formulations for the pediatric patient population. If this cannot be done for certain drugs in a pharmacy--and I underscore pharmacy--compounded recipes should appear in the drug label.

This concludes my remarks for today. Thank you for your attention.

DR. CHESNEY: Thank you very much. Any non-process questions for the speaker? Dr. Hudak?

DR. HUDAK: The slide that showed that there was no dose-response relationship in children, is that sort of a euphemism for no efficacy?

DR. D. MURPHY: Yes. It is in our written request as one way for the cardiorenal drugs, hypertensive drugs, to demonstrate efficacy and it is a long description about what you have to do if you don't choose a placebo-controlled trial and you choose a dose effect trial and what sort of effect you have to demonstrate and, if you don't, then you

failed.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: With your indulgence, it is a process comment but it is not about risk process. We have heard two presentations where there has been a lack of an adequate formulation. I guess my question, which may not be answerable today or we may not want to answer it today is that my understanding is a company doesn't get exclusivity unless the FDA determines--or doesn't get a request--that there is a significant health benefit. It is unclear to me how you can decide that there is a significant health benefit to the population when at the end of the day there is no formulation available for them.

DR. D. MURPHY: Again, they have to fairly meet the terms of the written request. A written request is based on what the public health benefit would be and it often will say that you must conduct this trial with an age-appropriate formulation. If they conduct the trial with the age-appropriate formulation it does not say, nor do

I think we would be allowed to legally say, you must market it.

DR. NELSON: Well, I guess I would go back to the attorneys and ask them to reflect on that because--

DR. D. MURPHY: We have.

DR. NELSON: --I guess I don't think that was the intent of Congress, that they would get the money and then have nothing available for that population.

DR. D. MURPHY: Yes, we have gone back actually because, as you can see, this is becoming an issue. We have brought this back to them and we are in the process of discussing again, within our legal regulatory authority, what we can and cannot do.

In balancing that, the other effect, the unintended effect is that you don't issue any written request because they aren't going to do them, or you can issue them and they won't do them at all. So, is there a way we can balance the kind of information that we need--and I really can't

give a final answer on this right now--is there a way that we can set it up so that we say you need to develop a marketable formulation that would be appropriate for children? We have always had criteria that if you can't do that you have to tell us why but make that clear, more definitive.

Then, if you can't--because there are reasons sometimes why you cannot develop certain formulations--the solvents become too large or other reasons, as you all I think know, with some of the proton pump inhibitor types of products--then we are looking at trying to define requirements that have to be met having to do with stability, bioavailability, for kids' use that would be appropriate. We get into other issues for compounding and how do you avoid those issues.

So, the bottom line, Dr. Nelson, is that we are very aware that this is an issue and we are trying to find a resolution that promotes development of products while, at the same time, does not end up in the situation where we have products that are then not available.

DR. NELSON: I appreciate the complexities. In my simplistic view, I suspect that if you went back to those that drafted and then passed the Best Pharmaceuticals for Children Act, they would not interpret significant health benefit to mean that at the end of the day there is no formulation and nothing in the label.

DR. CHESNEY: Dr. Hudak?

DR. HUDAK: Can I just clarify this because I am trying to understand exactly what the data show. The formulations used in children less than 50 kg were not commercially available?

DR. GRYLACK: That is correct.

DR. HUDAK: These are the same formulations used that assessed the PK issues?

DR. GRYLACK: Yes, the initial singe-dose PK study was done in patients between the ages of 1 month and 16 years so, as you can determine, a number of those were less than 50 kg. Then, the second study, the efficacy and safety study, was done in patients between 6 and 16 years and, again, a certain number of those would be less than 50 kg.

DR. HUDAK: So, essentially, the drug with this non-available preparation showed that, as given, it was absorbed and available in the bloodstream like in adults, but showed no efficacy.

DR. GRYLACK: Well, there was the age-dependent increase in bioavailability.

DR. HUDAK: I understand, but giving adequate levels of the drug, there was no level-related efficacy, no dose response--

DR. GRYLACK: No dose response.

DR. HUDAK: No dose response but if you control for the level of the drug in the blood there was still no response. See what I am saying? There may be a difference depending upon the age.

DR. GRYLACK: Yes.

DR. HUDAK: So, the bottom line is that this drug did not work with the best possible formulation in this population and, therefore, there doesn't seem to be any reason to have a formulation available for pediatric patients. Is that correct? For this drug?

DR. D. MURPHY: Correct.

DR. CHESNEY: Dr. Danford?

DR. DANFORD: To Dr. Hudak's point, I wonder if the group in which this drug was studied actually had hypertension or not. Hypertensive children, the younger you get, are harder and harder to come by and if you were just studying the bioavailability of the drug and giving it to volunteer children you would not necessarily expect a drop in blood pressure in a pediatric population. Do you know who these children were?

DR. GRYLACK: I would have to take a minute and go back and look at the detailed description of the studies. I am sorry, I can't answer that off the top of my head. Perhaps I can get back to you a little later.

DR. D. MURPHY: Was the question did we give it to normal children?

DR. DANFORD: Or children without hypertension.

DR. D. MURPHY: That is what I meant, children without hypertension.

DR. DANFORD: There could be a group that

might conceivably benefit from this, who have congestive heart failure who would not have elevated blood pressure. If you were looking at a response in blood pressure and it were given to a group of patients with VSD you might not be able to determine much of a change in their blood pressure.

DR. D. MURPHY: I think the first part of it is that we would not have done the studies in children who were not hypertensive. Now, could we have selected a different population so that potentially mechanistically you could postulate a benefit? You possibly could have but it was felt that the need was in this population so that is why it was written for this population. Again, as this committee has discussed, it would have to be children who had the disease under study.

DR. HUDAK: I am happy to hear that because testing this antihypertensive medication in normotensive children I think would be a real--

DR. GRYLACK: I have some comment here. Thank you for waiting for me. The patient population in the efficacy and safety study

consisted of patients with hypertension or high normal blood pressure.

DR. CHESNEY: Dr. Nelson, one more question and then we really need to move along.

DR. NELSON: It just occurs to me that that question is answerable if you have the pharmaceutical review that is on the website. So, maybe in the future just including that as part of the packet would enable us to have that at hand. I am looking to see if that one is in here.

DR. PEREZ: Use the mike, please.

DR. D. MURPHY: It is in here in what is called the critical pharmacology and biopharmaceutics review; summary of findings--

DR. S. MURPHY: Just to remind you that we can only put what is in the public domain so, as we look at what is being posted on the web I think some of these are more extensive than others. So, it is giving us an opportunity to see what is going on.

DR. GRYLACK: The PK study was done on all hypertensive patients. Are we going to take a

break now for the vote or are we going to pursue to the next one?

DR. CHESNEY: Assuming there are no more questions on this particular issue, Dr. Santana will cover the next drug as I am recused for stock reasons. So, Dr. Santana?

DR. SANTANA: Let's go ahead and get started. Dr. Buckman?

DR. GRYLACK: Yes, it is my pleasure to introduce Dr. ShaAvhree Buckman. Dr. Buckman is a pediatrician who is not a neonatologist, who also has a Ph.D. in molecular cell biology and pharmacology. Dr. Buckman has been a medical officer with the Division of Pediatric Drug Development for nearly two years, and I will add that Dr. Buckman has been a valued colleague of mine during the time I have been here at the FDA.

Fentanyl

DR. BUCKMAN: Good morning. I will be discussing the one-year post-exclusivity adverse events for the fentanyl transdermal system.

The fentanyl transdermal system or,

trademark Duragesic, is marketed by Johnson & Johnson and its subsidiary ALZA. It is indicated for the treatment of chronic pain such as that of malignancy that cannot be managed by lesser means, such as acetaminophen-opioid combinations, non-steroidal anti-inflammatory drugs or PRN dosing with short-acting opioids, and pain that requires continuous opioid administration. It is approved for pediatric use in children down to the age of 2 years. The drug obtained original market approval in August of 1990 and pediatric exclusivity was granted in January of 2003.

The Duragesic label carries a boxed warning that specifically states that due to the possibility of serious or life-threatening hypoventilation Duragesic is contraindicated in the management of acute or postoperative pain, including use in outpatient surgeries. It is also contraindicated in the management of mild or intermittent pain responsive to PRN or non-opioid therapy. It is also contraindicated in doses exceeding 25 mcg/hour at the initiation of opioid

therapy.

I have also outlined in red the pediatric safety information that is in the boxed warning, which specifically states that the safety of Duragesic has not been established in children under 2 years of age. Duragesic should be administered only if they are opioid-tolerant at age 2 years or older.

There is selected additional safety labeling which states that Duragesic should be prescribed only by persons knowledgeable in the continuous administration of potent opioids and the management of patients receiving potent opioids for treatment of pain and in the detection and management of hypoventilation, including the use of opioid antagonists.

Now, the total number of prescriptions dispensed for the fentanyl transdermal systems in the United States have increased by 20 percent in the past 2 years, from 4.5 million in 2002 to 5.4 million in 2003. The top prescribers in 2003 for the fentanyl transdermal systems were internal

medicine, family practice and anesthesiology. Approximately 0.2 percent of fentanyl transdermal system prescriptions dispensed were written by pediatricians.

In the outpatient setting children and adolescents have accounted for very few dispensed fentanyl transdermal system prescriptions over the past 2 years, 4,535 prescriptions from February 2002 to January of 2003 to 5,422 prescriptions from February, 2003 to January, 2004. In both the outpatient and inpatient settings, adolescents age 12-16 years accounted for 60 percent of the pediatric fentanyl transdermal system use over the past 3 years.

In the outpatient setting the most frequent diagnoses associated with the fentanyl transdermal systems in the pediatric, as well as the adult, population were associated with diseases of the musculoskeletal system and connective tissues. In the pediatric population the most predominant musculoskeletal diagnosis was spinal stenosis, followed by injuries involving fractured

bones. One must be mindful though that these are very small numbers that we are capturing.

In the inpatient setting the primary discharge diagnoses most frequently associated with billing during hospitalization in the pediatric population were for cholesterol encounters and various blood disorders, including sickle cell disease.

There was a total of 1,917 adult and pediatric adverse event reports for the fentanyl transdermal system during the 1-year post-exclusivity period. Of these, there were 8 unique pediatric cases. Seven were from the U.S. and 1 was a foreign report. All of these cases were described as serious outcomes, including 5 deaths. There were 4 reports in females and 4 reports in males, and the ages ranged from 4-16 years of age. Of these 8 pediatric reports, most adverse events were mentioned only once. The labeled adverse events that were captured twice included overdose drug abuser and medication error. Again, these are labeled adverse events.

Of the unlabeled adverse events that were captured more than once, they included cardiac arrest, respiratory arrest and self-medication.

There were 5 deaths that were reported during the 1-year post-exclusivity period for Duragesic and I would like to describe these reports to you. The first was the case of an 8 year-old female who was diagnosed with rhabdomyosarcoma who died 2 months after being switched from the fentanyl transdermal system to IV morphine. This was a foreign case and it is believed that this child's death was due to progression of her underlying disease and not due to the patch itself.

The second case is that of a 9 year-old male who was 2 days post tonsillectomy and adenoidectomy, who was treated with the fentanyl transdermal system 25 mcg patch with subsequent respiratory arrest resulting in death. Concomitant medications that were given included acetaminophen with codeine elixir, although the timing of administration of this dosing is unclear from the

report.

This was a U.S. case and I have a couple of comments about this case. One is that this is a case where a non-opioid tolerant patient was prescribed the drug for an acute postoperative pain situation. As you recall from the boxed warning, Duragesic is contraindicated in the management of acute or postoperative pain.

The next case was that of a 4 year-old female who died from cardiac arrest after having the fentanyl transdermal system applied by her grandmother for pain relief. The details of this case are largely unknown. This is a U.S. case, and the only additional information that we have is that the child had marks on her body that indicated that she may have had more than one patch applied because there was adhesive residue on her skin.

The next case was that of a 16 year-old male with a history of drug abuse, including marijuana, methylphenidate and dextropropoxyphene, who was reported to have been using the fentanyl transdermal system several days prior to death and

was found wearing a 100 mcg patch. This was a U.S. case.

The last of the 5 reported deaths was that of a 16 year-old male, with a history of alcohol and marijuana use, who died of cardiac arrest after using 100 mcg patches obtained from another student. He was found wearing a 100 mcg/hour patch and this was a U.S. case.

Now, there were 3 non-fatal adverse events that were reported during the 1-year post-exclusivity period. These included a patient who experienced euphoria, hallucinations and weight loss after initiation of therapy with the fentanyl transdermal system.

The second case was a child who experienced withdrawal symptoms from what was considered a loose patch, meaning that the patch had become non-adherent to the skin and the patient experienced withdrawal symptoms which resolved after replacement of a new patch.

The last case was that of respiratory depression in a patient who had intentional misuse

of the fentanyl patch.

We have reported the adverse events that occurred during the 1-year post-exclusivity period. Due to our concern regarding the pediatric deaths occurring with this product, we decided to investigate the adverse events which occurred since the approval of Duragesic for adults, in 1990. There were 4 pediatric deaths before initiation of the pediatric exclusivity period. There have been 3 additional pediatric deaths since the end of the 1-year post-exclusivity period. Although we are continuing to monitor for adverse events, for the purpose of this presentation we set our internal cut-off for reporting to you at May 15th.

Now I would like to describe briefly those deaths that occurred outside of the exclusivity reporting period. The first was a case of accidental exposure. The second was a case of misuse or abuse. Most concerning are these cases of off-label use. One is a case of a child with post-tonsillectomy and adenoidectomy pain. Another is a case of a child with infectious mononucleosis

and sore throat pain; a child with chronic headaches and infectious mononucleosis; and a child with acute migraine. The last case that was reported was that of a child with rhabdomyosarcoma and, again, this was another situation where it was thought that the child died due to disease progression and not due to administration of the patch itself.

In summary, the cumulative pediatric adverse events for the fentanyl transdermal system since original market approval in 1990 totaled 35 unique cases. Of these, 22 reports were for children who used the product appropriately for an indication of chronic pain. Of these 22 reports, there were 2 pediatric deaths and these were both children with rhabdomyosarcoma which I described.

By comparison, there were 13 reports in children using the medication for a non-chronic pain management indication. Of these 13 reports, there were 10 pediatric deaths. It is important to remember that the Adverse Event Reporting System is a voluntary reporting system which is subject to

under-reporting and other influences, which you have heard described multiple times this morning.

In conclusion, several of the serious pediatric adverse events captured occurred in patients who administered the product for an unlabeled indication, for example, treatment of acute pain in a non-opioid tolerant patient. There is need for additional education regarding the proper use of the fentanyl transdermal system to help further minimize abuse, misuse and off-label use.

In conclusion, instead of answering questions right now, because we have two subsequent presentations that deal with the same product, I would like to introduce the next speaker and then we can take questions at the end of all three presentations. So, Dr. Lee will address the fentanyl pharmacokinetic characteristics following Duragesic application. Dr. Lee is a clinical pharmacology and biopharmaceutics reviewer with the Office of Clinical Pharmacology and Biopharmaceutics, currently working with the

Division of Anesthetic, Critical Care and Addiction Drug Products. Dr. Lee?

DR. LEE: Thank you, Dr. Buckman. Good morning, ladies and gentlemen. I would like to present to you this morning on unique features of fentanyl pharmacokinetics after Duragesic patch application, but first, before I go into my slides, I would like to give you some overall background information on the Duragesic patch.

First on the patch strengths, Duragesic patches are available as 25 mcg, 50 mcg, 75 mcg and 100 mcg fentanyl delivered per hour patches. Secondly on the site of application, patches are applied mostly on a flat skin surface, mostly on the upper torso, such as chest, back, flank or upper arms. In young children, however, the upper back is a preferred location to minimize the potential for the child to remove the patch. Lastly on the intended use, as we all know, each patch can be worn continuously up to 72 hours but, if analgesia for more than 72 hours is required, a new patch should be applied to a different skin

site after removal of the previous patch.

Gollowing the patch application the fentanyl drug molecules move from the patch reservoir through a rate-controlling membrane and continue to be absorbed into the skin. At this juncture a depot of fentanyl concentrates in the upper skin layer and fentanyl then becomes available to the systemic circulation. Peak serum concentrations of fentanyl generally occur between 24 and 72 hours.

However, after patch removal the serum fentanyl concentrations decline slowly, falling about 50 percent in approximately 17 hours, which is the elimination half-life of the fentanyl patch drug delivery system. Due to the continued absorption of fentanyl from the skin because of the skin depot effect, fentanyl disappearance from the serum is slower than is seen after an IV infusion. The elimination half-life for the IV infusion route is approximately 7 hours compared to that of 17 hours.

So, what are some of the potential

implications? With respect to initial patch application, the full drug benefit, analgesic effect, may not be seen immediately. Thus, there is a potential situation for applying another patch. This can become a safety issue I think.

With respect to post-patch removal, substantial drug effect may be felt for a significant period of time. Thus, there is a potential safety situation for a patient who will be switching over to another opioid therapy.

If you have any questions, I will be happy to answer any, otherwise I will introduce Dr. McNeil. Dr. McNeil is a medical reviewer with HDF-170. Prior to coming to the agency she trained in pediatric neurology and oncology. Dr. McNeil?

DR. MCNEIL: Good morning. I am with the Division of Anesthetic, Critical Care and Addiction Drug Products and, in collaboration with our pediatric colleagues, we have been considering ways to manage the risk of off-label use.

We have been coming up with preliminary strategies for managing this risk, and the

preliminary strategies that we have come up with are labeling changes; prescriber education through the company or, one thing that has been used in the past, are "dear healthcare professional" letters, or prescriber education through physician groups. We will, of course, be in contact with the company and with our colleagues in pediatrics as we try to come up with a method of managing this risk.

DR. SANTANA: Did you have further comments, Dr. Buckman?

DR. BUCKMAN: We can go ahead and entertain questions at this time.

Discussion of Question 1

DR. SANTANA: Good. I do have a question for Dr. Lee. Is there any data either in pediatrics or in adults that other concomitant problems, like fever or skin rashes, change the absorption? I was struck by a couple of the deaths in patients who had infectious diseases or had postoperative conditions that could be associated with fever or some of these associated skin rashes. So, is there any data to suggest that there is a

different pharmacokinetic profile under those circumstances?

DR. LEE: As far as I know, I don't think we have any information from the pediatrics which were involved with PK studies. However, Dr. McNeil may--she says no.

DR. SANTANA: Do we know from the adults about postoperative fever and things of that nature?

DR. MCNEIL: No, we don't. It is actually in the label that if you apply heat externally to the drug patches you can increase the serum concentration of fentanyl, but that is what is known about it.

DR. SANTANA: Dr. O'Fallon?

DR. O'FALLON: I have been watching these things because my 93 year-old mother-in-law has been outcome this--now she is 96 and a half--for three and a half years. When I first looked at it what bothered me was the slow--she is allergic to lots of different things; as it turns out she is fine with this, but with something that moves so

slowly what would happen? It would seem to me that after 24, 36, 48 hours, something like that, a person might reach a level where they would not be able to tolerate it. Then, there is this 17-hour, which is really up to a whole day--before you can drop the levels down sufficiently. What do you do if somebody--I don't see anything in the label about how to manage somebody that has a bad effect. How do you do it when it is in your system for so long?

DR. LEE: My first answer could have been that the person who is experiencing adverse events may just peel off the patch and then for 17 hours, for that I don't have any answers.

DR. O'FALLON: It is actually up to 24 almost. I mean, there is a terrific range on these things.

DR. LEE: Yes, the range is very large. Yes.

DR. S. MURPHY: Dr. Lee, could you show your backup slides with the kinetics? I think they are very helpful.

DR. LEE: I would just like to remind you that the information in this study is from a limited number of patients and the pediatric subjects were non-opioid tolerant subjects. This study had full pharmacokinetic profiling and, therefore, it was a very useful study for me.

The Y axis is in nanograms per milliliter concentration versus time. We put a patch on and take it off at 72 hours. This is the adult population where we see the increase in the fentanyl concentration at approximately 22 to about 40-some odd hours.

Compared to the adults, this is a pediatric population and I would just like to mention at this time that the patch strength size was 50 mcg/hour for adults and 25 mcg/hour for the non-opioid tolerant pediatric patients. As you can see, time to maximum concentration has shifted at earlier time points and it is higher. Where I have marked it with the shaded ovals, that is where we need to kind of think again as far as having the pain relief because it takes so long in order to

reach that plasma concentration. And, then for the black square, because it takes so long in order to have the fentanyl concentration either eliminated from the system or what-have-you, it takes so long, even up to maybe 140 hours you could have some of the residual fentanyl concentration after patch removal. So, I guess this is what we have.

DR. MCNEIL: Excuse me, I should mention that my answer on fever was related to the information we have, actual data from patients, but in the label, by PK modeling, there has been some association that fentanyl doses could theoretically increase up to a third but, again, that is from PK modeling and not from actual patients.

DR. SANTANA: And we have no postmortem information from any of these deaths regarding measurement of drugs in these patients?

DR. BUCKMAN: In looking at a couple of MedWatch reports we do have a couple of cases where we did get levels. In one case that I reported to you, the 16 year-old that died from an overdose of the fentanyl patch had an autopsy that was

performed. The cause of death was cardiac arrest due to highly toxic levels of fentanyl. The fentanyl level was 16 ng/ml. He also had cannabinoids in his bloodstream as well. So, that was one case where we did actually have a concentration.

DR. SANTANA: Dr. Fuchs?

DR. FUCHS: Well, two things that strike me from reading all your cases are that three of them were used in kids with tonsillectomy or mono, and if you have ever looked at kids with mononucleosis, those are kissing tonsils and, yes, they do hurt. That may be something where we might add a warning, "do not use when there is any airway problem or tonsillitis or mono" because that is an airway issue to begin with and then if you have respiratory depression, which this drug is known to cause, and you have no airway obviously you will get hypoxia and that will then lead to respiratory arrest and then lead to cardiac arrest.

The second thing is that in the cases where you mentioned cardiac arrest, I suspect

mostly in kids this is respiratory arrest. Once again, we can't really tell from the reports but I suspect they are all respiratory related.

DR. BUCKMAN: That is a very good point. We can only report to you exactly what is captured there but I agree with you that in most pediatric cases it is respiratory arrest leading to cardiac arrest. But that is how it was captured in the reports.

DR. SANTANA: Dr. Nelson?

DR. NELSON: Looking at the label, my understanding is the strongest warning that the FDA can do is the black box, which is what you have at the front. So, unless we think it needs to be worded differently, there is already a black box. The only thing that doesn't seem to be in that black box that is elsewhere is the comment about the qualifications of who should prescribe this. Working in critical care and having used this in the past and no longer using it in the way that I had used it simply because of the labeling change, it is unclear to me how much stronger you could

make this, other than perhaps moving the information about prescribers to the black box. And, it is unclear to me--I am assuming there was a pretty good malpractice loss for these deaths, or there should be--so it is unclear to me how much more you can do in your labeling if, in fact, people are going to use it when it says not to use it that way. It seems pretty straightforward to me.

DR. BUCKMAN: Can I respond to that briefly? That was why in the presentation we wanted at the outset to show you exactly what was in the labeling because that is what we need to hear from you as far as comments as far as how can we get that word out there anymore so. It seems as if the greater propensity of what is happening is that patients are being administered this product for an unlabeled or contraindicated use. So, that is the feedback that we want to get from you all. You know, what other things can we do? That is going to be the question that we will be asking.

DR. SANTANA: Dr. O'Fallon first and then

Dr. Hudak.

DR. O'FALLON: I think that the letter to patients is very helpful that is included in our packet. Is that normally given to the patients? I don't know your process here. Between the executive summary and the actual label there is a patient information thing.

DR. MCNEIL: Patient information?

DR. O'FALLON: Yes, and I don't know where that comes into the Act.

DR. MCNEIL: In theory, what happens is when you buy your box of Duragesic is that you should get this.

DR. O'FALLON: Yes, I don't think we did. She said theoretically we should get it when we buy our box but I don't remember that we did.

DR. D. MURPHY: Remember, it is not required to be given to every patient.

DR. O'FALLON: That is what I was wondering.

The other thing is that I don't think it addresses the issue. You see, I was worried the first time I

saw this about the long-lastingness of this drug. What happens if they get into trouble? Is there any information that the patients could have if they are seeing something? I don't even see that it says call your emergency room immediately, or something. I don't see anything about what to do in case the kid gets in trouble or the person gets in trouble, the 90-odd year-old gets in trouble.

DR. MCNEIL: Under "how do I use Duragesic" in the patient information section it does say if you use too much Duragesic or overdose get emergency medical help right away. But I guess from what you are saying that is not enough.

DR. O'FALLON: Well, I didn't see it in the patient letter but maybe I missed it.

DR. SANTANA: Dr. Hudak?

DR. HUDAK: I guess in comment to Dr. Nelson's comment, I am not sure what can be done for language and what the limitations are but I think many physicians are sort of jaded when they see "serious" or "life-threatening" written down somewhere because that seems to be on a lot of

different drugs, and maybe something very specific about deaths have occurred due to, you know, inappropriate use in these situations should be in there in some form that makes it very concrete.

DR. SANTANA: Do we know from these adverse event reports if, in the cases that were postoperative, those were actually prescribed by a person before the procedure or subsequently by a pediatrician or family physician? I mean, what is the sequence of prescriptions here?

DR. BUCKMAN: In one case it was prescribed by a family physician. In another case it was prescribed by the pain control team in the ICU, and the mother had asked--and Joe Wyeth, our ODS person, please correct me if I am wrong; she has done an incredible job of helping us get all these reports together--but in another case it was prescribed in the ICU by the pain control team for this child. The mother asked that two of the vital checks be suspended. They were overnight vital checks. She wanted the child to rest, and by the morning when they did the next vital check the

child was dead.

DR. SANTANA: Dr. Gorman, I would like to hear your opinion on this since you are a practicing pediatrician in the community.

DR. GORMAN: First of all, all of these patches as they have come out, these long-acting patches--I think I remember the same event with a patch that came out for hypertension with another product where children had it applied inappropriately or retrieved it from wastepaper baskets. There were several adverse outcomes which were slightly different than these.

I would have to echo Dr. Hudak's very explicit comments. I think the hypothetical that is put in the black box warning now is a reality and there should be a statement--and I understand that labels are a negotiated legal document between the FDA and the pharmaceutical company, but a simple statement that deaths have occurred through the inappropriate use of this in the following settings, and then a listing that you have contraindicated would take this out of the realm of

hypothetical and say it is real.

Then to echo a little bit of what Dr. Nelson said, there could be a little asterisk on the bottom--which I know you are not allowed to use--that says and big malpractice awards were awarded.

[Laughter]

DR. SANTANA: We don't want to get into that! Any other comments? Dr. Lee?

DR. LEE: I just wanted to make a clarification that for the data that I presented for the non-opioid tolerant patients, the age range was from 1.5-5. I just wanted you to understand that. It doesn't give us an overall 2-16 year-old range.

DR. SANTANA: Dr. Luban, you deal with patients with sickle cell who have chronic pain issues. Would you like to comment on this issue?

DR. LUBAN: I think the biggest issue there is the complex use of more than one analgesic, and the occasional failure of families, when discharged, to follow the pain team's

recommendation and to really abuse the medications because of continuing needs of the child. So, I see sickle cell disease and the use of this as a real avenue of education that really should be followed up on.

DR. SANTANA: Dr. Murphy?

DR. D. MURPHY: Do you think that it is clear--getting back to Dr. O'Fallon's question--from the patient insert that after you remove this product it is still absorbed? Do you think that is clear enough in here, for longer periods of time?

DR. SANTANA: Dr. Luban?

DR. LUBAN: I think that is not at all clear. I think that this is written at a very sophisticated level for some families to interpret. We certainly don't have high level language use when we are doing informed consent, so why should we if we are trying to educate patients and families?

DR. MCNEIL: Thank you. We will talk more with the folks--there is actually a whole team of

people who help us write these patient information inserts and they are supposed to be geared to the sixth to eighth grade level. By the giggles in the room, I guess we have not hit that mark so I will talk with people and we will see what we can do. If I understand you correctly, we should make it slightly simpler.

DR. LUBAN: Speaking for our patient populations, I would say yes. The use of the term "opioid tolerant" is not a term that most parents can understand.

DR. SANTANA: And I am not even sure a lot of physicians understand it.

[Laughter]

No, that is a fair observation.

DR. MCNEIL: The reason that we used "opioid tolerant"--I mean, I understand your comment but the reason that we used "opioid tolerant" was just to reflect the language in the boxed warning, but I do understand what you are saying and we will try to come up with something.

DR. SANTANA: Dr. Gorman and then Dr.

Nelson.

DR. GORMAN: It strikes me how attractive this product would have to be to people doing ear, nose and throat surgery on tonsils. You have a population with generally poor options for oral medications in terms of their taste and tolerability and adverse events of vomiting. So, you have a product that looks really attractive to them because it is applied to the outside to an obstreperous 4 year-old and you don't have to try to get them to drink something. If I was targeting my educational process, ear, nose and throat physicians and ambulatory surgery centers would be at the top of my list.

DR. MCNEIL: Excuse me, may I just go back to Drs. Luban and O'Fallon? I just want to make certain that what we were speaking about before, that the language is a bit too sophisticated is in the patient information section, not the actual label? Correct?

DR. LUBAN: Correct.

DR. O'FALLON: The statement "call your

healthcare provider right away of get emergency help if you have trouble breathing or have other serious side effects," that is in there on the fourth page, without a bullet in a wholly bulleted thing. I think you should move it up to what is the most important information I should know. It should go there.

DR. MCNEIL: Thank you.

DR. CHESNEY: Dr. Nelson, you had your hand up?

DR. NELSON: Well, I think my comment follows from both of the last two, which is to also look at the order within which you are putting things, particularly given Dr. Gorman's comment. The first thing probably shouldn't be only use it in the way that your healthcare professional tells you to.

[Laughter]

Because we are talking about healthcare professionals not using it appropriately.

DR. SANTANA: Dr. Hudak?

DR. HUDAK: I guess this is sort of

getting at the question here, but the other avenue for education, it seems to me, since some of these more egregious events occurred in the hospital setting, is perhaps to have a letter that goes out to the hospital pharmacies, pediatric pharmacies about this, and in this day and age where there are computerized physician order entry systems it seems that this would be a big way to sort of capture that before it might become an issue.

DR. DANFORD: Does the FDA ever communicate directly with risk management individuals for hospitals and clinics? Several of the speakers have suggested that the adverse events might most likely be prevented by having a general understanding that lawsuits can happen over misuse. Perhaps the lawyers from hospitals and clinics who try to reduce their exposure to big settlements, if they received something from the FDA about the misuse of such products might actually do a lot of work of educating the people who work in their institutions.

DR. SANTANA: Dr. Nelson?

DR. NELSON: I think, at least in my setting, if a letter went out to the pharmacist you effectively would accomplish that because it would then go to the control mechanisms for prescribing that would be used within a facility at least to establish risk management strategies. I would probably prefer going that way because it is at least then directed to the provision of care rather than the other way.

DR. SANTANA: I would support that. It is within the scope of their care of what they should be doing with patients in terms of educating as they get prescriptions filled, and so on and so forth. So, I would support that too. Any other comments? Dr. Murphy?

DR. D. MURPHY: I just wanted to summarize and ask the Division to also pitch in here if they don't think I have summarized correctly what we have heard from the committee.

DR. SANTANA: I took some notes. Would you allow me to do that? I think the committee would like the FDA to move in three directions that

you have pointed out in this slide. One of the comments I heard very strongly from the committee is that the label needs to be re-looked at in the context of maybe providing stronger statements, regarding the inappropriate use resulting in deaths that have already been observed, somewhere earlier in the actual label so that physicians and others prescribing this can see that clearly early on.

I also heard a comment that there is a section about qualifications of the prescriber and those qualifications were kind of hidden in the back of the information, and it should be brought forward into the label too. So, it is not a matter of re-writing the label but maybe providing some of the information in different sections, particularly at the beginning that would be more evident to those that are prescribing. Those are the comments that I heard about the label.

I heard a lot of comments about patient information and using the patient as an advocate for him or herself. I heard comments that probably the reading language was inappropriate for the

populations that are being targeted in which this medication could be used. So, that needs to be looked at very carefully.

I also heard some comments that I think were very appropriate about clearer statements in the patient information regarding how, when this medication or patch is removed, there will be sustained levels that may continue to put you at risk of having respiratory depression and associated side effects.

Related to the patient information, I also heard some comments about how the information in that patient information leaflet should be reorganized to put some of the highlights earlier on and make them more self-evident.

Then I heard a brief discussion about education, primarily to prescribers. I heard various comments about some of the incident cases that received care that had been by ENT, by anesthesiologists, by pain teams. I didn't hear a lot of discussion about how we could accomplish that so I am going to seek a little bit more advice

from the committee on how potentially that could be accomplished. But I did hear that there needs to be reeducation of people prescribing this and potentially starting with some target populations and then moving it more openly, including pharmacists, of course.

Then I also heard a very strong statement about educating our patients who are using these products and parents, and how we can best accomplish that.

So, maybe the committee wants to spend maybe one more minute probably advising the agency on potentially what educational systems may already be in place that they could target or the company could target. If anybody wants to add to that? Dr. Murphy?

DR. D. MURPHY: Thank you very much. I only have one question I want to clarify, and that is the label--the statement you had, Dr. Santana, was that we want a stronger statement concerning the deaths early in the label. I thought I heard that you wanted it in the black box.

DR. SANTANA: Yes, in the black box. That is what I meant. That is correct.

DR. D. MURPHY: Thank you.

DR. SANTANA: Any further sort of advice to the agency on this issue? I think we have discussed question one actually. Am I correct?

DR. MCNEIL: Thank you for your comments. It is very helpful to us. I am going to take them back for further discussions with the company.

DR. SANTANA: Thank you so much. I think we are going to take a ten-minute break and start a little bit after 10:30. Thank you.

[Brief recess]

DR. CHESNEY: While everybody is finding their seats, I wanted to thank the FDA for clarifying one issue which had to do with the use of ciprofloxacin and moxyfloxacin in ophthalmic preparations. In the last two slides the expected cure rate of 70 percent, is that for conjunctivitis in adults? This study was actually done in neonates. So, probably one can't extrapolate from one to the other, just for clarification. Dr.

Iyasu is going to introduce our next speaker.

DR. IYASU: Thank you. Our next speaker is Dr. Hari Cheryl Sachs. Dr. Hari Sachs is a professor of pediatrics at GW and Children's Hospital National Medication Center. She has over 15 years of experience in private practice. She also served on the FDA non-prescription drug advisory committee and is one of the FDA liaisons to the AAP committee on drugs. She will be presenting the adverse events for venlafaxine.

Adverse Event Reports per Section 17 of BPCA (cont.), Venlafaxine

DR. SACHS: Thank you very much. I am glad to be here to talk to you, guys. It is actually nice to see some familiar faces among the crowd.

I will be discussing the adverse events for venlafaxine, and I think you, guys, are familiar now with the basic organization of the talk. Venlafaxine, or trade name Effexor, has been on the market since December, 1993 for the treatment of major depressive disorder, generalized

anxiety disorder and social anxiety disorder. Although these are the indications in adults, there are no approved pediatric indications despite the fact that exclusivity was granted in December, 2002, and the sponsor now goes by the name of Wyeth Pharmaceuticals.

Venlafaxine and its active metabolite, whose name I am not going to try to pronounce, is a potent inhibitor of both serotonin and norepinephrine reuptake so this is actually an SNRI but for convenience I am going to refer to the whole class as SRIs. It also is a weak inhibitor of dopamine reuptake. These actions, along with the lack of significant muscarinic cholinergic and histaminergic effects, do alter the side effect profile of the drug. The half-life, which is about 5 hours for venlafaxine and 11 hours for the active metabolite, is relevant for the timing of potential discontinuation symptoms when they occur.

Venlafaxine was the fourth most commonly prescribed antidepressant in the U.S. during 2003 and, as with other SRIs, prescriptions have been

rising in both pediatric and adult populations. Although pediatric use seems to account for only about 2.5 percent, this represents almost half a million prescriptions. This use is all off-label. Disorders of mood and anxiety, along with ADHD are the most common indications that kids have been treated for with venlafaxine.

I will now briefly describe the results of the studies performed for exclusivity. There were 4 large, multicenter, double-blind, placebo-controlled, parallel group, flexible dose studies for each indication, that is, major depressive disorder and general anxiety disorder. The dose used was flexible dosing between 37.5 mg and 225 mg, and the age was 6-17 years. None of the studies in major depressive disorder showed a significant difference in placebo and, interestingly enough, only one of the studies for generalized anxiety disorder showed a positive study result.

The endpoints in both the trials were age-appropriate clinical symptom rating scales for

major depressive disorder. It was the CDRS revised. For the GAD trial it was the Columbia Kiddy Scale for Affective Disorders, or the KSADS. Since only one study showed efficacy, that is why no approval was granted.

Safety information was based in part on these 4 studies, as well as 2 open-label trials, a 6-month trial in major depressive disorder and another study in conduct disorder. In these studies decreased weight gain and growth was noted which was unrelated to treatment emergent-anorexia. You can see the numbers for the approximate weight loss and weight gain in the placebo population, and the height. If you actually read the results of the studies posted on the web, these numbers differ slightly from that because the FDA received additional information and analyzed it. The other thing that is kind of interesting is that it is actually important that the height effect was seen in the exclusivity studies. It is pretty significant because it was a very short period of time that the drugs were studied.

The other adverse event that was noted, mild adverse event, is that there were elevations in cholesterol and blood pressure that were similar to those seen in adults. That also was added to the label.

Since we are speaking of the label, let's turn to the relevant safety labeling. I would like to highlight several things about the labeling, some of which is relevant to the safety discussion or the adverse events that we see, but also many of the changes are physically highlighted in yellow to kind of emphasize that these are the new changes that have been added actually since March.

In terms of neonates and pregnancy, venlafaxine is considered a category C drug. That means it should be used in pregnancy only if clearly needed. Language regarding the discontinuation syndrome in newborns was added fairly recently, first in January, 2003 and then updated last month. It is found in the section under "non-teratogenic effects." What the labeling describes is that you can see discontinuation

effects in newborns with complications that may require prolonged hospitalization or respiratory support that may arise even as soon as delivery. You may also see some clinical findings, including neurologic, respiratory and systemic symptoms. These symptoms are consistent either with discontinuation of the drug or potentially actually a direct toxic effect of the serotonin.

As you know, in part because of the deliberations in February, a warning recommending close observation for deterioration or emergence of psychiatric symptoms in patients that are treated with these SRIs was added in May, 2004 to the label, and this warning actually supersedes and replaces some of the information that was in the label previously regarding the association of suicide with depression and other co-morbid disorders, and a statement that Wyeth had added on its own that there were some suicidality seen in the pediatric trials. The other thing that is mentioned is the occurrence of sustained hypertension.

These slides show an extensive list of precautions which are listed in the order that they appear in the label. Most of these things were seen in the top 20 adverse events that you have in the main report for venlafaxine, and we see some of these in the post-exclusivity adverse events that occurred during the year. I draw your attention to the risk of bleeding and also the problems with seizures, and then in the new labeling which is regarding the weight loss and slower rate of growth in children.

In addition, under adverse reactions the risk of symptoms with discontinuation, and this is in adults and older children, include both physical and psychiatric symptoms. In March there was some labeling added to the postmarketing reports on dyskinesia and rhabodomyolysis.

So, now that you are familiar with all the changes in the label, let's look at the adverse events for the year. These are actually the raw counts of all the adverse events. There were approximately 1,500, of which about half are in the

U.S. and they may represent some duplicates. Pediatric reports are really a relatively small proportion, less than 4 percent of total reports and this has been pretty consistent over the past several years since marketing. There were only 2 deaths that occurred, and I will be discussing them in a few moments.

Turning to the specific 1-year post-exclusivity period, there were 49 unduplicated events. I apologize for the busy nature of this slide. There were 19 events that involved in utero or maternal exposures and 30 that were direct pediatric exposures. The gender and age distribution is seen here. Of interest, there is a male predominance of the adverse events in the infants and neonates while the gender distribution is pretty similar in the older children. Outside the neonatal period, most of the direct exposures involved adolescents and children, as would be expected.

Looking more closely at the in utero events, there were actually no deaths reported

among the 19 in utero events, 3 of which also had concomitant breast feeding. There were 4 unrelated congenital anomalies; 2 had cardiac malformations, 1 with an ASD and the other with dextrocardia. Another infant had hypospadias and the last infant had extra syndactyly, which is a fusion and webbing of the digits. Co-morbidities and other medications were actually involved in all these congenital anomalies.

Neurologic events were described in 11 infants. We saw 2 infants that had hypotonia; 3 infants who developed seizures; and 6 infants who had disordered movements.

Just to illustrate how difficult it is to sort out causality for these events, on follow-up for one of the infants who had seizures the event was considered unrelated to venlafaxine because the patient had experienced a subarachnoid hemorrhage. But, if you will recall, abnormal bleeding can be associated with venlafaxine. So, it is potentially possible that the baby had subarachnoid hemorrhage related to the medication. Of course, that is

conjecture but just to show how hard it is to sort out the information.

The losartan in utero exposure events were really 4 reports that detail complications that occurred in babies with co-morbid conditions and medications. They are described here. While it is less serious, it is something that has emerged in the literature so it is interesting that we did see 2 cases here as well.

Co-morbid disease and medications, as I have explained, may contribute to some of these events. Although 2 events were coded specifically as neonatal withdrawal, there are actually up to 5 others where symptoms that emerged, like jitteriness or tremor or seizure, could have reflected neonatal withdrawal but it was just not coded that way.

Prematurity was reported in 4 infants but in 8 cases there actually was insufficient information in the case report to determine whether or not a baby was premature. Three infants were breast fed. One mother reported smoking and

drinking but that information about tobacco or substance exposure or illicit drugs is actually not present in the majority of the reports. About half the infants were exposed to concomitant medications, 4 of which were psychotropic. When I looked back, 5 included benzodiazepines. In only 2 the case report expressly stated that there were no other medications involved, and whether or not medicines were involved in 7 of the other cases is not known.

So, in looking at the neonatal events, they do seem to reflect the ones that are labeled in adults, for example tremor, convulsion and hypotonia. The role of concomitant medicines and co-morbid conditions, such as prematurity, is unclear. And, whether or not symptoms such as jitteriness or tremor or seizure are related to withdrawal or serotonin toxicity is also unclear, and this will be discussed later today by Miss Phelan and Dr. Levin.

Now I am going to turn to the 30 adverse events that have been associated with direct

exposure. The majority of these were neurologic, psychiatric or related to overdose. Of the 30 direct exposures, dose range and indication for use is not available for all of them but the doses were generally within the approved adult dosing. Note again that there is no pediatric dosing. The indications were combinations of depression, anxiety or ADHD.

Health providers were responsible for the majority of the reports. You might recall that that is in contrast to the information presented at the last session. Many patients were on other medicines in addition to venlafaxine. Twenty were on concomitant medication, about two-thirds, and 10 patients were on other psychotropic medications.

The majority of adverse events were psychiatric. The 2 deaths in the sample were due to completed suicides. Four attempted suicides also occurred. All of them were overdoses, 1 case of suicidal ideation and 2 cases of self-injury where there was no clear intent of suicidal ideation. There are also 3 cases of aggression and

agitation and 2 cases of behavior changes. Once again, there were concomitant medications in a majority of these cases, 6 of which were psychotropic.

Neurological events were the next most frequent adverse events reported, and seizures, loss of consciousness and motor or sensory impairment are all labeled events and many of these cases, again, involved other medicines or underlying medical conditions.

There were 4 patients that developed symptoms of serotonin toxicity, such as hyperexia and/or neurological symptoms that were related to overdoses. One of them, a 3 year-old, may have accidentally ingested his sister's medication. The other 3 were deemed non-accidental as the intent was unclear. The remaining adverse events occurred singly and are labeled or related to labeled events, with the possible exception of the specific drug interaction between Augmentin and venlafaxine in this one case where the effectiveness of the antidepressant was decreased.

As with the SRIs, you can see symptoms with discontinuation or decrease in dose, and we did see physical symptoms or emergence of psychiatric symptoms in 6 patients in these adverse event reports. So, the adverse events really are related to labeled or already labeled events, with the possible exception of the events seen in neonates.

Warning concerning the increased risk of suicidal behavior did exist in venlafaxine's label prior to our advisory committee in February but, as you know, there is now a new class warning for the SRIs. The new labeling was added as a result of the exclusivity studies regarding the effect of growth and that was very recent. The new class labeling regarding maternal exposure and potential occurrence of neonatal withdrawal with serotonin toxicity will be discussed further this afternoon. Routine adverse event monitoring for venlafaxine, as with all other drugs, will continue. I hope you are not depressed.

[Laughter]

Are there any questions?

DR. CHESNEY: Thank you very much. Questions? Dr. Ebert?

DR. EBERT: Is a non-accidental overdose similar to a suicide attempt? Are they classified together or separately?

DR. SACHS: The reason these actually were not classified as suicides, although, truthfully, I made every attempt to do so, is that you can't tell. In one case, for example, the kids may just have been exchanging medication. In another case you don't know if they were taking it to get high. That is actually why.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: It may be because it is more recent, but I haven't been able to find in the label that we have in our book the growth change.

DR. SACHS: Yes, that change is very recent. What I think you got the handout of the whole statement of the adverse events that is kind of a summary of what our presentation is and these sections of the label are included in that in

entirety. But I think this issue is the point. I mean, we are trying very hard, at FDA, to make the labels available and there is a website now called drugs at FDA. You can see that for just this drug alone there have been three changes to the label since March.

DR. NELSON: Just as a follow-up question to reinforce something I think Dr. Gorman said at the beginning of the day, if there is information about that placed in because of pediatric exclusivity, I would strongly recommend that the standard comment about safety and effectiveness not being established in children is changed to where it actually says 2 randomized, controlled trials involving 353 children failed to demonstrate safety and effectiveness. If you look right under it, under geriatric use, it actually does list a number of adults[sic]. So, I think it is somewhat, in my mind, duplicitous to leave that general statement in which many pediatricians interpret as there were no studies.

DR. SACHS: And I think there is always a

tension between kind of somehow having some tacit approval if you put too much information in the label.

DR. D. MURPHY: I think the other issue too is that in this field particularly 2 studies does not mean the product doesn't work. I think your point is that at least there is information and we ought to indicate that there is information. Is that really what you are trying to get at? And, I think we ought to be able to find a way to do it. The issue is getting agreement within the Division that they think that is an appropriate thing to do. So, you are telling us to get feedback to the Division that you think it is an appropriate thing to do?

DR. NELSON: Yes, and no matter how many footnotes you want to put in about assay sensitivity, I would still put it in there. I mean, you can quote everything Bob Temple ever wrote on the topic, as far as I am concerned, in the label if you want to do that.

[Laughter]

DR. D. MURPHY: Joan, is there additional concurrence with Dr. Nelson's comment?

DR. CHESNEY: Dr. Santana would like to comment.

DR. SANTANA: I want to take it further. I have heard a lot of comments about this at various meetings and I wonder if the direction that we should be taking--and this is a suggestion--is that we start thinking about creating an area in the labels that is related to pediatric exclusivity. It is here. It is being done. There is data. It doesn't imply that there is enough data to provide an indication or that there is enough data to do all these other things that are in the label, but I wonder if a part of our mission is to educate practitioners and to educate the public whether having a section in labels that relates to pediatric exclusivity studies and trying to explain what those mean, obviously, in the context of what those are really done for, would be helpful.

Because, if not, the information is not

going to get there. The label is not created for that information. So, unless we use the label in a different way that information is not going to get there. I don't know what the challenges or the barriers for doing that in the label are. I grant I am ignorant on that, but maybe that is something we should be aiming towards.

DR. CHESNEY: Can I comment? I think this is almost a slippery slope. I think by putting studies and results in the label--we already have people prescribing for totally unapproved indications, in fact contraindications, and if they see something in there, that there were really no bad side effects seen, and even though it is not efficacious and approved, "hey, the studies were done." I don't know if I am expressing myself very well but I think this is a very difficult area.

On the surface I would agree with what Dr. Nelson is saying, but I think that it has to be worded very carefully because I think when people say there are studies and, "hey, they haven't said not to use it so why don't I just go ahead," to me,

this is a little more complicated. On the surface it seems like a no-brainer, but I think maybe there are some other issues. Dr. Hudak?

DR. HUDAK: Well, I would echo prior comments here. I look at this and there are half a million prescriptions of this in the pediatric population a year, and I presume by the other information you shared that most of that is in association with treatment for depression, although you don't have any hard figures on that. You know, you look at the labeling here and in terms of the adult efficacy it talks about 5 studies that demonstrated efficacy in adults that showed improvement in at least 2 of 3 different clinical measures. I think it is critical to have the pediatric trial information in there because you have 2 studies with a significant number of patients for this type of disorder where you have no effect. I think any information like that is very important to get out there.

I guess I may take a different tone than Dr. Chesney on this, but I think, you know,

information is good and I think the reason we have a half million prescriptions in pediatrics is because we are looking at the adult studies and, as someone else said, "well, it worked in adults, you know, the same disease and it might work in children; let's use it." On the other hand, if you have specific information that says we now have 2 studies that cannot find efficacy in 353 patients, providers might have a different philosophy in terms of what medication they will use in this population.

DR. CHESNEY: I agree with that. I think it is just that you have to be very careful about the wording because it does provide a very subtle endorsement in a sense, just because it is there. I am probably not expressing this very well. Dr. O'Fallon and then Dr. Gorman.

DR. O'FALLON: One of the issues here is that a lot of these were pharmacokinetic studies. You know, if a child is not treated at an effective dose level it is not fair to count them as not being very effective. In a certain sense, by just

quoting, you know, 500 children were treated, that is not quite fair if they were being treated at lower levels that were being used for pharmacokinetic studies and that sort of thing.

What I am saying is I think you have to be a little careful how you do it. I vote to have that information in there, but I am not an M.D.; I don't treat these patients. But I think you should have the data in but don't just dump it because you have to be careful about where that data came from.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: It strikes me that for the last six years with this group we have talked a lot about the label. I have had the opportunity to go back and read old drug labels and they are very brief, a page, maybe two pages. The label continues to try to struggle under its present format to encompass new realities. I am impressed, and I both dislike this and find it very valuable, that in the era we now live in there are documents that present executive summaries with embedded links to information for those who want to pursue

more information.

I wonder--I love proposing work for other people so let me do this really carefully--is there an effort at FDA to create a new labeling structure? You did that with OTC medicines and I think with great success. I think the new drug fax label is a major step in the right direction. Could not a similar design be done for prescription medicines with embedded electronic links, and the official label stop being the piece of paper in the document and start being an electronic form while there is an official executive summary that continues to go out with the product?

DR. D. MURPHY: Yes, there has been years of work on this. You have to notify industry that they have to submit things electronically. You have a whole process. There is a deadline of when they have to be doing that. One of our problems since I have been at FDA, since 1998, is that we have been struggling with the fact that FDA doesn't have available the labels. We have been trying not only to have them available to the public but

electronically available so you can link in these ways. Yesterday I met with a group that has literally been working on this for years now. You would think it would be simple. It is not. As I said, one of the first steps is getting things electronically. The second thing is getting it maintained, updated, etc.

There is a new group that now has a business plan associated with it so that we are hoping that we actually will be able to have this resolved, and there has been a lot of activity and attention to this, I guess is what I am trying to say. Everybody who is in FDA fundamentally agrees. This is our product. This is our work. We need to make it current and available and linkable and searchable. From our perspective, we also would like to be able to search our labels so we can go and say I want to relabel that it has QT prolongation as an adverse event. We are trying to accomplish more than just having a scanned-in label up on the web. That is what I am trying to say.

There also is, and has been for a number

of years a concerted effort to simplify and change our label, and there have been public announcements of that and feedback on that, making these labels more user-friendly and that also is one of those continuing works in progress. It is very near but, God knows, I have been terrible at predicting.

So, yes, and I think that actually one of the things that I was thinking about because of this tension, this dichotomy, you know, is you may get 5 positive studies but you may have 10 others. The label cannot become a repository of negative studies. But we need to be able to find a way to transmit the fact that there is information available. What I think the challenge for the committee is how can we go forward with finding a way to put a statement in the label that there has been data collected and how to get to that data, at a minimum--at a minimum. This whole process of having some sort of linkage would really make it much easier.

DR. CHESNEY: I like your comment that the label can't become a repository of negative

studies. That is a good way of phrasing it. Other comments on this issue? Dr. Hudak?

DR. HUDAK: I would say in a way it has to be because those negative studies don't make it in the literature where they can be otherwise accessed.

DR. D. MURPHY: There has to be a way of making the point of the negative studies and where they are available, I think, and that they have been done. That is what I think you are saying.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: I think that is an issue we have been struggling with, that is, how do we remove the veil that seems to be present for what has been done and is important clinically but isn't out there? One of the many goals of pediatric exclusivity and the process was to try to get studies done in children and have that material disseminated. If when it comes up for reauthorization, this continues to be an ongoing problem of a continued veil of information, that there is negative information out there, negative

either in terms of effectiveness or negative in the fact that there are significant safety issues that are not presented, then that will have to be readdressed in the legislative process.

DR. D. MURPHY: I think that the positive part of this is that, as you have noticed, actually the clinical review is up and it is for a non-approval action. I don't think you, guys, realize what a watershed event this is. This information is otherwise not available except for pediatrics now. So, it is getting out there. One of the problems, as you know, is we have to re-notify industry, as we explained last time, and until we re-notify them we cannot put information up. That is now happening.

There is another potential problem. It may or may not play out, but I do want to say that the agency agrees that one of the intentions of the legislation was to try to make this information available and to put what we would see as quality information into the label. But we are in a situation where if we had a non-approval or an

approval it had to go up publicly and that is happening. So, I think that is a major watershed event that is occurring for pediatrics.

DR. CHESNEY: Dr. Sachs, did you want to comment?

DR. SACHS: I just wanted to say that this was a drug that was not approved and you can access this information.

DR. CHESNEY: All right, I think we will move ahead then. We will have more anticipated discussion that includes venlafaxine when we talk about the class this afternoon.

I want to clarify one issue. I thought that since question 1 had its separate bracket that it was for everything we discussed but I understand it was just for fentanyl. So, that has been taken care of.

Our next issue is the open public hearing, and before I read this two-page statement let me ask if there is anybody who wanted to present at the open public hearing this morning.

[No response]

No? Thank you very much. Our next speaker is Dr. Murphy, who is going to give us a pediatric update.

Pediatric Update

DR. D. MURPHY: I don't have any slides for you. Actually, this is a ruse. I am going to give you a very short update and then I hope to indicate to you how much we have appreciated the work of this committee.

Who is it that said "the best of times and the worst of times?" A dissolution has led to an evolution. By that, I mean that you had better watch out what you wish for. We have long wanted there to be a full pediatric advisory committee which Congress has seen to do, to provide the agency with, which is about the only way we were going to get it because there are certain other laws regulating how many advisory committees we can have. So, Congress stepped in and mandated that there will be a full pediatric advisory committee, which should help a lot with transparency so that when we are having a meeting to talk about

pediatrics, it won't come out under infectious diseases, and it was gracious of that committee to chair you and to grow this subcommittee but it has been very misleading to the public.

So, the good news is we have a new full pediatric advisory committee, and it is charged with a fair number of substantial activities which you have been told about previously, such as the reporting of the post-exclusivity safety and adverse events, such as the ethical issues and any activity involving pediatrics within the agency across all centers. So, there will be the construct of a new pediatric full advisory committee.

The legislation also clearly tells us some of the representation that we need to have on that committee, and we are working on that. That committee will be administered out of the Office of the Commissioner's Office and Tom Perez and others have really done yeoman's work for us. Jan Johannssen, are you back there? Would you like to raise your hand so they will see that we now have a

new exec. sec. for this committee and Jan is in charge of making all of this happen. As I stated, this is also going to work across centers for issues that may be coming up.

So, we have a new committee but with that one has to dissolve the old committee and this is your last meeting as a pediatric advisory subcommittee. It is really sad. You know, we have developed such an enormous database--I guess is the way to put it--of information with you that I wish we could just roll everybody from this committee over to the new committee but I have been told that is not possible, and we did try to call and explain that to everybody.

I want to take one more moment and just quickly remind you of the work that you have done, and that is, we began this process thinking it was going to be a typical sort of scientifically-based activity and, clearly, it immediately became evident that we would have to address the ethical issues. This committee has struggled with many ethical issues, and you have advised the agency on

how to approach trial design. When the patient doesn't have the disease, is that ethical? How can that be done or can it be done at all?

You have advised us on placebo-controlled trials in children and you have advised us on how to conduct research in a vulnerable pediatric population. That advice has resulted in consensus statements that are now on the web, which I think are very helpful in answering questions that people may have because they were very thoughtful discussions with a range of opinions and have been referred to a number of times.

The scientific issues that you have dealt with, in addition to the adverse event reporting which you have a marathon day on today, you have done on numerous occasions. You can see some of the important scientific issues that have arisen during this process, again, looking at the SSRIs, looking a Duragesic patches, the neonatal withdrawal, a number of events that you have all asked for additional information on I think have been important in helping us move this area

forward.

Another big milestone for this committee and an important one was the whole discussion of therapies or interventions for infants who are jaundiced. I think that was a very important discussion and will continue to be important. I think that this committee contributed very significantly in the agency's assessment of how to proceed in that arena of developing interventions for neonates who have hyperbilirubinemia.

You also dealt with issues of should we even develop a product for children and I think a very important contribution was to say no, such as the development of certain sleep products--don't issue a written request for this. This is not a public health need we want to advocate.

Other big issues that you have addressed--long-term follow-up, and this is an ongoing problem. You didn't solve it but you helped us work at it, as we will continue to work at this because it is a very complicated process. Also, I don't want to forget the topical products.

Things that one applies to the skin are not as innocent as may always seem and this committee has dealt with adrenal access suppression and potential long-term carcinogenic effects and immunosuppression of some topical products.

That is a lot. That is sort of on top of your ongoing activities and learning about all your new tasks that keep getting assigned to you with the new legislation.

Now, what I have to do today is say goodbye to all of you because I guess the technical legal term is that we have to declare you dissolved.

[Laughter]

I have asked Raya McCree, who is our administrative person who really runs the Office of Counter-terrorism and Pediatric Development. She is why we get through every day, and she also rescued your presentations today. You would think this would be simple to get but it is one of those cartoons where the kid goes every which way, the process that getting these plaque presentations

took. So, Raya, if you would come up here?

I would like to start out with presenting a plaque and a certificate to Joan Chesney who, as we know, is the chairman of this committee and has been the chairman of the subcommittee and who is a professor of pediatrics at the University of Tennessee. Joan, I tried to think of how to say this, what you have done has been so important, you have helped bring this committee a level of credibility within a scientific organization. I am sure you, in academic medicine know, pediatrics is always fighting for its academic recognition. It was really important that this committee be perceived as a good science-based committee, and I think Joan--all of you have--and Joan's leadership has been very important. She not only helped bring together this group and made sure that you all had your say. She didn't try--and I have seen chairmen do this--to intimidate people on the committee; not let them speak when a chairman didn't particularly agree with their opinion. I think she has been very important in making sure that the committee

had a say, whether they agreed with her or not, and has brought forth that consensus, and then helped to synthesize it. She has been very helpful in helping us synthesize what we think the committee said.

Joan, if you would come on up here, I would like to present you--I will ask each one of you actually to come up and I will give you a little token of our appreciation. Joan, thank you very much.

[Applause]

Be careful where you put these. They will knock somebody down if they fall down. Joan's indicates that she was chair of the advisory committee.

Judith O'Fallon has been our statistician. One thing that has been wonderful about Judith is that she takes the statistical talk and makes it applicable to the clinical. The way she has been able to condense the questions has been wonderful and much appreciated. As somebody said, we talk about therapeutic options and I don't think anybody

at the FDA will forget the extra quivers that you said we needed. Thank you very much.

[Applause]

Let's see, who is next? Mimi isn't here. Steve Ebert. After all this time, I am still mispronouncing your name. Steve has been our consumer representative, who goes through a particular process to get to this place. It is an independent parallel process. We wanted to thank him very much because I think your contributions have been very thoughtful and have been the type of comments that we would hope somebody in your position would contribute.

[Applause]

Bob Nelson, Dr. Nelson. Dr. Nelson, professor of pediatrics, as you know, Department of Anesthesia and Critical Care Medicine at Children's Hospital in Philadelphia where he also serves on an IRB. I went through that long title because I think it is important to know that one of the roles that we hoped Dr. Nelson would play would be as our point person for ethical issues and, boy, has he

done that! He has been invaluable and has also helped us identify other people to assist in the more extensive discussions that we have had, and has been a critical person in the development of this committee. Bob, thank you so much.

[Applause]

Victor Santana, Dr. Santana is the associate professor in hematology and oncology at St. Jude's. He has been our alternate chair at times; has been very helpful in helping us with this whole issue of oncologic development where the process is different, and has brought that expertise to this committee. He is also on the Pediatric Oncology Subcommittee. So, this has been an important liaison that we have had and we really appreciate your time and effort. Thank you very much.

[Applause]

Dr. Danford is associate professor of pediatrics and pediatric cardiology at the University of Nebraska Medical Center and has been our cardiac expert. I know we haven't had specific

drug issues in your area but we finally got one for Dr. Danford. In the last meeting on cardiac imaging he did an outstanding job of synthesizing that entire technical day and it has been very useful to us and I really want to recognize that specific effort, besides your overall efforts on the committee. Thank you very much.

[Applause]

Dr. Fink. Is he not here? Oh, shoot! We always count on him to give us a comment nobody else would have thought of.

[Laughter]

Dr. Fuchs, Dr. Susan Fuchs. Dr. Fuchs is our emergency medicine person. Actually, Dr. Fuchs, you are one of the people that we haven't had a real product for but today we were counting on you to be able to provide some specific input as far as Duragesic is concerned, and we appreciate your overall contributions very much. Thank you very much.

[Applause]

Dr. Gorman, general pediatrician in

Ellicott City, chair of the Committee on Drugs for the American Academy of Pediatrics and--how can I say it?--I am amazed at this man, I really am. How he does this, continues to practice, stays up to date, provides really insightful comments, is chairing the Committee on Drugs at the Academy--he just puts us to shame and I just want to thank you for your tremendous contributions.

[Applause]

Dr. Luban, who is the Vice Chair in the Department of Laboratory Medicine, Director of Transfusion Medicine and Quality Assurance for Children's National Medical Center in Washington, and is our hematology and lab expert on the committee. Gosh knows, the diagnosis depends on the correctness and validity of the laboratory and we have been counting on her and she has provided that type of expertise and helped to us and we want to thank you very much.

[Applause]

Dr. Sam Maldonado, Dr. Maldonado, we can't give you a little thing--we don't give gifts to

industry.

DR. MALDONADO: I understand.

DR. D. MURPHY: But we can recognize the tremendous effort that you have provided by giving us your perspective, and you know we have relied on you many times during the conduct of these committees to provide us that perspective and input. We thank you very much and you can come back and give your carrot talk. I just love your carrot and stick talk.

[Applause]

Tom, I did recognize your efforts while you were out of the room. I want to make sure that you knew that.

DR. PEREZ: Well, thank you, and I would like to recognize you for doing what you are doing because, believe it or not, the bureaucracy gets in the way of doing things of this nature and it takes a little bit of money, clout and neither of those I have.

[Laughter]

DR. D. MURPHY: Dr. Hudak, somehow your

certificate isn't here. Dr. Hudak, as you know, is a professor at the University of Florida Jacksonville in neonatology. Dr. Hudak has not only contributed to the arena of information on neonatology for drug development but, as I reminded him when I spoke to him the other day, he has had the joy of working specifically on the proton pump inhibitor drug development program which continues also to be in the process. I wanted to thank you very much and I am sorry we don't have your certificate. We will get it to you.

One last announcement is that I am dissolving myself too from being the Office Director for the Office of Counter-terrorism and Pediatric Drug Development as of September. Somebody asked me was it not too much because I was not only doing counter-terrorism and pediatrics but I also was doing part-time in the Office of Pediatric Therapeutics within the Office of the Commissioner, and it got to be too much. So, I am going to go full-time to the Office of Pediatric Therapeutics in September. So, I will be seeing

many of you again, or some of you again, I hope. But no longer will I be with the Office of Counter-terrorism and Pediatric Drug Development.

Dr. Shirley Murphy, who is a division director for pediatrics, has done such an outstanding job bringing together so many wonderful people and getting this information to you, she is going to continue to be here. And Dr. Rosemary Roberts--I had hoped she would be here but she said if I don't make it, they know what I look like--will be the Acting Office Director. So, you are in very good hands anyway that you look at it. Again, thank you all very much for your participation.

[Applause]

DR. CHESNEY: I am going to take the chair's prerogative and add to the agenda. I just wanted to say in our state of dissolution--

[Laughter]

--there are some people we would like to thank. I am looking at the list here and I hope I don't forget anybody but, first of all, we have to

thank all the people that developed the legislation that allowed us to be here at all. So, I think that involves people in the back of the room. It involves mainly the Academy of Pediatrics but also pediatric department chairs, just a whole host of people that even had the concept that children had to be recognized in terms of drug use.

I would like to thank Elaine Vining, in the back, and particularly Richard Gorman. I think they have done an amazing amount of behind-the-scenes activity speaking in front of Congress. In fact, Richard, you did have dinner with the President. Is that not right?

DR. GORMAN: No, that is not right.

DR. CHESNEY: Elaine may have. Elaine, why don't you stand up? I don't know that everybody in the room knows Elaine but she is the legislative lobbyist--is that the correct term?--for the American Academy of Pediatrics and she is really the one that has negotiated with all the congressional aides that work with the senators. I had the opportunity two weeks ago to

go to the Hill to do some lobbying for the first time and these legislative aides are really key, and Elaine has worked very, very closely with them for years now getting all these different laws passed. So, I am so glad you are here, representing what the Academy does.

[Applause]

Richard, I don't know if you want to say anything further about the Academy and the Committee on Drugs.

DR. GORMAN: Never give up a chance to talk! I think this has been an issue for the Committee on Drugs for at least 35 years where it has ben written down, and Ralph Coffman, who is not in the room today, and Chet Berlin and Bob Ward, my previous committee chairs, have carried this torch and just passed it to me to, luckily, run the last 100 yards to get this legislation passed. But the Academy has been organizationally, systematically and bureaucratically involved in this effort and I just happened to be the face at the end of this process. As we know, we are not at the end of this

process as refinements on our initial efforts continue to be made.

DR. CHESNEY: Thank you. I also wanted to particularly thank all the members of the staff who have really made our job easy. We really do 0.001 percent of the work when we sit here on the committee because they have done all the work behind the scenes. They have selected what it is we are going to talk about--and who knows what they don't give us to talk about. But I have always been assured that they don't bring the easy things to the committee so when we sit and struggle, I think that is often correct.

But many, many people--and I will try to recognize the few that my memory will allow me to pull out--but Rosemary Roberts just walked in. Stand up. I think everybody knows Rosemary, but she has been almost as key to this effort from the beginning as Dianne has. Shirley Murphy, obviously Susan Cummins. You don't know that there are always phone calls behind the scenes and Susan and Shirley are on those. Rosemary Addy, who most

recently has been extremely helpful in all of this, and, Solomon, I feel like you have become one of this group of staff because you present to us so often and represent so many of the issues. Tom has been a wonderful executive secretary. I think we are all befuddled by everything that goes on in the FDA, but Tom is one of the people who tells us what we can and can't say and tells me when I can and can't announce lunch and some very fundamental things like that.

[Laughter]

But Tom has been just enormously helpful and gets our emails to us on time, gets us our reservations and gets us our limousines to the airport, which he will do today in spite of the ongoing events.

Then, all the medical officers who have presented to us--I can't tell you how impressive and what an inspiration it is how clearly you present; your slides are perfect. They are always readable. They are succinct. They are right to the point. I don't know who rehearses behind the

scenes all the time but I assume it is Susan and Shirley and Solomon, and lots of other people. But we really respect that you respect our time and make it so much easier for us.

I think Bill Rodriguez and Don Madison are both in the room, and Don Weis, but they have also been very helpful to this whole process.

I am only going to say thank you to Dianne because you have been key. As you can tell, I am an intuitive person and I don't handle this kind of dissolution very well.

[Applause]

Anyway, thank you Dianne. You have been everything to this committee. Thank you.

[Applause]

I have discussed this with a few members of the committee and I wanted to bring it again to the committee's attention. I mentioned it to Dianne yesterday when we were at a very interesting meeting of which I will just give you a two-sentence summary, the Food and Nutrition Committee has very serendipitously discovered the

presence of furan, which has some very remote similarities to dioxin. It is used to dissolve resins, to prepare lacquers in a variety of industries, but they have discovered very small concentrations of it, on the order of parts per billion, in a number of foods, primarily those that have been canned and prepared. Interestingly, because the issue came up with the pediatric formulation of apple juice, they looked at other pediatric foods and it is in formulae and it has been in a number of pediatric baby food which is prepared in bottles by heating.

They have been extremely diligent about putting this on the web. It has been out there since May 7 if you want to look and find all the details. They are still very busily trying to look at other foodstuffs. They are working very closely with the folk in Canada. They have an extremely sensitive mass spec assay now which has allowed them to detect this. Of course, nobody knows if it means anything at all. But it is out there now and they are working very hard, and Dianne and Susan

were kind enough to ask me and Dr. Gorman, who wasn't able to come, if we would go and listen and comment. Dianne was also there. We represented the committee in telling them that we would like them to look for the presence of furan in a variety of situations, including the fetus, the mother-fetal diet, the newborn infant who may have extremely permeable guts, and look at whether this furan is concentrated in specific tissues, look at fetal and infant animal models, and so on and so on.

I won't elaborate any further, except to say that that should all be up on the website and that will be evolving. But in the process I had an opportunity to talk to Dianne and I told her what many of us have felt, which is that the issues that are covered on this committee are so important and so interesting and generally not available to 99 percent of those caring for children just because most of us don't go to the Federal Register on a regular basis or go to the FDA website even though we have a vested interest in it.

So, one thought we had was that this committee provide a synopsis of the events of each of its meetings to be published in potentially a pediatric journal. Pediatrics comes to mind right away because it is the official spokes item for the Academy and generally one that is read by all those who care for children. This is at the moment a total hypothetical construct because the editors of Pediatrics may say they don't want to have anything that is not pure science and heavily peer reviewed, but that was the suggestion because issues like the whole bilirubin issue I think are just fascinating and they are just not out there.

I have talked to my colleagues and I have told them about it; most of them don't know it. So, that was the suggestion and I would be very interested in comments from the committee and the FDA and anybody else. The thought might be that somebody on the committee would write a brief summary and perhaps it would be the person who specialized in that particular subject or area, or perhaps it would be the chair, which I can say

since I don't even know whether I will be on the next committee. Then the FDA would review it to be sure that there was nothing that had been accidentally included which is still confidential, and then submitted to the journal. So, I would be interested in comments or suggestions, other places to publish it--New York Times, Wall Street Journal. Anyway, if you have comments, please let me know or let Dianne or Susan or Shirley or anybody else know. Shirley?

DR. S. MURPHY: I would just like to say that we have been discussing internally about how to get information, how to disseminate information, and I totally agree with you that it is just not out there. It reaches sometimes the newspapers if it is really controversial but I think a systematic way of having a regular column and reporting in Pediatrics, and I think your idea of sharing the responsibility, and then we would be happy to fact check it because the slides are publicly available on the web, it is all in the public domain, what is discussed here, unless it is a closed session. So,

I think it is not too onerous a job and we would be happy to pitch in an help with that.

DR. CHESNEY: Skip?

DR. NELSON: Two comments, I think if the idea was to have an ongoing mechanism by which information could get out to pediatricians, that probably wouldn't be Pediatrics as a venue but might be something like AP news where there could be an interest in more timely and less sort of academic discussions. Part of the problem with this is who is going to write the first draft. I mean, there are some practical things. But if, in fact, that was done one of the questions would be to what extent it could be a broad sort of reflection on pediatric drug development--where has it been; where is it going, with a focus on the committee but not just simply a historical basing of the topics but also stepping back and looking at some of the broader process issues that we bring up; labeling issues that we have discussed; and those kinds of things. If we did that, it would probably have to be more of a product of the

individuals on the committee and not of the committee nor of the FDA because I presume there are some things that people in the FDA couldn't in fact say.

DR. D. MURPHY: I think there are a variety of ways to approach this. One possibility is just this synthesis of the discussion. At least in one option here it would be limited to the facts that were presented and the discussion, and it would be synthesized--these were the issues; these were the pros and cons; this is what the committee advised; this is what might be happening. So pediatricians, family practice people who take care of children would know that this is you, out there.

The broader topic I think is always something that is an option for anybody on the committee who can use this information because it was publicly presented. But I think what Joan was talking about was trying to identify maybe not every meeting but those scientific issues that have come up. You all are a panel of experts that were brought together; you think about it; and when you

think that it is important that somehow it be synthesized and made more available.

DR. CHESNEY: One other group I forgot to thank is the committee itself. I think this has been a wonderful group and we have enjoyed each other's company when we were allowed to talk to each other. Thank you all for making the little bit that I have had to do so much easier. Tom, do we have permission to eat now? Why don't we plan to reconvene no later than 12:30 so that we can continue to move things ahead in terms of traffic? Thank you.

[Whereupon, the proceedings were recessed for lunch, to reconvene at 12:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. CHESNEY: I think we are ready to start. There were two people that came in after we did the formal introductions this morning so I wondered if they could both introduce themselves. Dr. Cragan and Dr. Luban.

DR. CRAGAN: I am Jan Cragan. I am a pediatrician with the Division of Birth Defects and Developmental Disabilities at CDC.

DR. CHESNEY: Thank you. Dr. Luban?

DR. LUBAN: Naomi Luban, pediatric hematologist, Children's Hospital National Medical Center in Washington, D.C.

DR. CHESNEY: Thank you. Now Dr. Iyasu is going to--my apologies. As I told you, Tom keeps us in line. He has to read a second meeting statement before we have the next session. Thank you.

Meeting Statement

DR. PEREZ: Thank you and good afternoon. The following announcement addresses the issue of conflict of interest with respect to the update on

neonatal withdrawal syndrome and congenital eye malformations reported in infants whose mothers' used an SSRI during pregnancy and is made part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topic at hand. Because there has been reported interest in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the special government employees who required a waiver under a waiver under Title 18 U.S. Code Section 208 which permits them to participate in today's discussion.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, the potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Samuel Maldonado is participating in this meeting as an industry representative, acting on behalf of regulated industry. Dr. Maldonado is employed by Johnson & Johnson.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. CHESNEY: Thank you. Dr. Wisner, could you introduce yourself, please?

DR. WISNER: My name, is Kathy Wisner and I am from the University of Pittsburgh. My work involves studies of depression and its treatment in childbearing aged women.

DR. CHESNEY: Thank you. What department are you in there?

DR. WISNER: I have academic appointments primarily in psychiatry, but secondary appointments in OB-GYN and epidemiology.

DR. CHESNEY: Thank you. Dr. Iyasu?

DR. IYASU: It is my pleasure to introduce the first speaker for this session, which is an update on neonatal withdrawal syndrome. Kate

Phelan is a pharmacist and works at the FDA. She has spent six years as a drug information specialist at the United States Pharmacopeia before coming to the FDA. In her current position she is a safety evaluator in the Office of Drug Safety. She has been with FDA since 1999.

Update on Neonatal Withdrawal Syndrome

MS. PHELAN: Hi. My name is Kate Phelan. I am a pharmacist. I work as a safety evaluator in the Office of Drug Safety.

In November of 2001 I completed a review of reports of neonatal withdrawal syndrome of serotonin uptake inhibitors. I will present that review to you today. First, I will give a brief overview of the FDA Adverse Event Reporting System, or AERS, so you will understand the context and the source of the neonatal withdrawal syndrome cases that I reviewed. Second, I will describe the process of evaluating an adverse event. Third, I will present my review of neonatal withdrawal syndrome after in utero exposure to SRI drugs. Finally, I will give a few conclusions.

The FDA's database of adverse events reported for drug and biological products is known as AERS, which stands for Adverse Event Reporting System. Adverse event reports come from healthcare professionals, consumers, medical literature and postmarketing trials. Healthcare professionals and consumers report to manufacturers and, through MedWatch, they report directly to the FDA.

Reporting by healthcare professionals is voluntary. However, drug manufacturers are required to send adverse event reports that they receive to the FDA in various time frames based on the severity and expectedness of the event. Expectedness is determined by drug labeling.

There are some limitations to AERS data. Some limitations pertinent to the issue of neonatal withdrawal syndrome are that the reporting is voluntary and, therefore, adverse events are under-reported. The FDA does not have drug usage data for use during pregnancy. For these reasons, we cannot calculate true incidence rates using these data.

Many reports lack information, especially about other drugs that may have been used by the mother. Also, most reports do not specify what steps were taken to eliminate other possible cause for the signs that are seen in the neonate. Reporting biases affect adverse event reporting. For example, media attention, such as Paxil has received in recent years, can stimulate uneven reporting between drugs. Also, the length of time a drug has been marketed affects adverse event reporting. Reporting bias can invalidate comparisons of drugs that are made based on the numbers of reports. Therefore, AERS data can suggest but it cannot confirm that a drug caused an adverse event or that drugs differ in relatedness to the adverse event.

So what good is AERS? AERS is invaluable in helping to discover previously unknown adverse drug events, especially adverse events that occur too rarely to be seen in clinical trials or that occur in populations that are excluded from clinical trials such as pregnany women. AERS data

must be supported by further investigation. Safety evaluators obtain follow-up information from reporters of important cases if possible and we review the medical literature. Also, FDA new drug review divisions may revisit previously submitted drug trial data or even request additional study by a drug sponsor. So, attempts are made to obtain data from numerous sources in determining association between the reported adverse event and a suspect drug.

Each safety evaluator in the Office of Drug Safety monitors a fixed group of drugs for adverse events that are possibly related to the drug and are unexpected or of greater severity, frequency or specificity than is described in drug labeling. Safety evaluators may contact reporters for additional information and we search AERS and the medical literature for similar reports, as I mentioned.

Each report is evaluated for relatedness to drug and included or excluded from the case series using case definition criteria developed by

the Office of Drug Safety or by the safety evaluator. Case definitions are used to provide consistent characterization of the adverse event and to facilitate retrieval of clinically relevant cases. Findings and recommendations of the Office of Drug Safety are sent to the new drug review divisions for their consideration.

Now that you have a general understanding of the Office of Drug Safety's reviews, I will present my review of neonatal withdrawal syndrome with SSRI drugs. The drugs that I led are citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine. Collectively, I am referring to these drugs as serotonin reuptake inhibitors or SRIs. As you know, the first 5 drugs selectively inhibit serotonin reuptake and venlafaxine inhibits both serotonin and norepinephrine uptake. Citalopram was not approved in the U.S. at the time this review was completed.

Because adult discontinuation syndrome is a known effect of these drugs, when reports of neonatal withdrawal syndrome appeared in AERS it

was logical to believe that there might be an association between the reported signs in the neonate and the abrupt discontinuation of the SRI that occurred at birth.

Reports in AERS are coded using the medDRA terminology. MedDRA is a hierarchical dictionary designed for use in drug regulation. In fact, MedDRA stands for Medical Dictionary for Regulatory Activities. I began with a review of AERS cases with the MedDRA code drug withdrawal syndrome, neonatal. This review showed predominantly neurological, neuromuscular and autonomic effects so I broadened my AERS search accordingly.

Ultimately I did 3 AERS searches, focusing on neurological, neuromuscular and autonomic events. In the first search I used MedDRA terms specific to neonates. In the second search I used general MedDRA terms but I restricted the search to cases in which the patient was reported as age 0-3 months. The third search was performed because complications of maternal exposure to therapeutic drugs are sometimes reported and coded in AERS as

though the mother were the patient so if I had searched restricted by age, I would not have retrieved those reports.

I also searched PubMed for related studies and cases. All cases retrieved from PubMed were also in AERS and will be covered in this talk. The few studies available at that time will be mentioned by Dr. Levin who will speak after me.

In deciding whether to include each case as neonatal withdrawal syndrome possibly associated with SRI, I applied these criteria. These criteria were adapted from the article "Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Hypothetical Definition," by Schatzberg et. al. that appeared in the Journal of Clinical Psychiatry in 1997. Please note that the case definitions that we apply to AERS data evaluation are not synonymous with diagnostic criteria. Our case definitions must be useful in the setting of incomplete data.

The case should have all 4 of the following characteristics: First, the mother had to be taking an SRI up to the birth. Cases were

excluded if the SRI was discontinued before the birth.

Second, the observed signs should not be attributable to factors other than the discontinued administration of the SRI. Many cases were excluded because the mother was also taking a benzodiazepine which could cause withdrawal in the neonate.

Third, the signs of withdrawal should not be present at birth but should appear with some delay after birth. It is possible for withdrawal to be seen at birth depending on the timing of the mother's last dose and the half-life of the drug but I applied this criterion in an attempt to distinguish withdrawal from serotonin toxicity in the neonate.

Fourth, the sign should resolve. Part of the hypothetical definition of SSRI withdrawal in Schatzberg is that withdrawal syndrome is a transient phenomenon. In a few cases the adverse event was persisting months or years after birth. These cases were excluded.

Finally, most cases were reported by healthcare professionals. I did not want to question the clinical judgment of the healthcare professional who had witnessed the event. So, if the reporter called the adverse event suspected or diagnosed SRI withdrawal and the information in the case did not contradict either the first or the second criterion that I have here, then the case was included in the case series. In many of the cases included on this basis the adverse event was present at birth or was persisting at the time the case was reported.

My AERS search retrieved the number of cases that appears in the column headed "2001." I reviewed the cases and applied the case definition that I just described. The number of cases that met the case definition of neonatal withdrawal syndrome possibly related to the SRI appears in the middle column, headed "met definition." Numbers of cases received by FDA since the November, 2001 review of this issue appears in the final column, headed "2001-4." I need to stress that the counts

in that column are raw case counts, the cases that had no evaluation, and I have included it merely to illustrate that we are still receiving cases.

A total of 57 cases met the case definition. In 47 of these cases suspected or diagnosed withdrawal syndrome was reported. Thirty-seven additional cases were excluded because the adverse event was present at birth. This contributed to the new drug review division decision not to distinguish withdrawal from toxicity that Dr. Levin will discuss.

As an example to show you why so many cases were excluded from the case series, I will present fluoxetine. Fifty-six unduplicated cases were retrieved for fluoxetine and 52 of these cases were excluded for the reason shown. I will elaborate on only 2 of these reasons. In 8 cases the reported adverse event was not consistent with the characteristics of the other withdrawal cases. These cases included 4 congenital anomalies, 3 adverse events that occurred during breast feeding, and 1 report of dehydration. Also, 1 case was

excluded because fluoxetine administration to the neonate did not relieve symptoms. Although this was not a criterion of the case definition, it is a characteristic of withdrawal. Administration of a similar drug should relieve symptoms.

In the neonatal withdrawal case series there were 56 pregnancies and 1 twin birth. The mother's age was unknown in most cases. The diagnoses for maternal SRI use was depression in the majority of cases that included this information. There were several diagnoses reported in one case each that I did not include here. SRI dosage was within labeled recommendations except for one venlafaxine case in which the mother was taking 450 mg/day. She was taking venlafaxine tablets which have a maximum recommended dose of 375 mg/day for severe depression. Some cases include drug use that may have been confounding and perhaps, in retrospect, I should have excluded some of these cases. These were occasional alcohol, in 4 cases; cigarettes, in 7 cases; and marijuana, in 2 cases. However, these cases were distributed

among the SRIs so they should not greatly affect the data.

Neonates were premature in 5 of 35 cases that included length of gestation. These were 1 fluoxetine and 4 paroxetine cases. There were 25 males and 17 females. Birth weights averaged 3.04 kg in the 28 cases that included birth weight Apgar scores averaged 7-9 at 1, 5 and 10 minutes.

On this slide the drugs are listed in order of increasing half-life. Time from birth to onset of the adverse event and duration of the adverse event are presented as median times if there were 3 or more cases that contained this information. The reported times to onset and the duration of signs actually covered rather broad ranges. However, the median times to onset somewhat follow half-life. Onset and resolution of signs may be difficult to pinpoint clinically and there are few cases here so we can't really draw conclusions from this.

These are the adverse event terms that were reported in more than one case. They are

grouped by body system and presented by decreasing number of mentions. The profile is similar for all SRIs, with nervous system and neuromuscular excitation most frequently reported. Feeding and breathing difficulties and temperature dysregulation were also reported. Additionally, a number of breathing difficulties were reported in one case each, including apnea episodes, gasping, shallow respiration and hypoventilation.

A comparison with reported signs and symptoms of discontinuation syndrome for venlafaxine and SSRI class labeling show some terms in common with the neonatal reports. These are irritability and agitation. Most of the other terms in the class labeling are subjective and would not be observable in a neonate.

More than half of the cases reported some treatment for withdrawal, most commonly increased hospital stay. Regarding outcome, the case definition for accepting cases as neonatal withdrawal possibly related to the SRI specified resolution of signs unless the reporter said SRI

withdrawal or was diagnosed or suspected. So, most of the cases did resolve.

In conclusion, there are possible cases of neonatal withdrawal reported for all of the SRIs approved at the time of this review. They reported similar signs in the neonates. Thus, the AERS data support the occurrence of neonatal withdrawal as a class effect of the SSRI drugs.

The most frequently reported signs of neonatal withdrawal are excitatory nervous and neuromuscular effects. Breathing, feeding and thermal regulation difficulties have also been reported. Neonates exhibiting signs of SRI withdrawal may require supportive treatment. Therefore, healthcare professionals should be made aware that adverse events may occur soon after birth in neonates exposed to SRI drugs in utero at the end of pregnancy.

The purpose of my review was to examine SRI withdrawal. However, some of the cases that I excluded from my case series, particularly those excluded because the adverse event was present at

birth, suggest that SRI toxicity may also occur in neonates exposed to these drugs in utero. Dr. Levin will discuss that issue further. Thank you.

DR. CHESNEY: Should we hold comments and questions until the other two speakers? Are there any technical questions that anybody has for Dr. Phelan?

MS. PHELAN: I am not a doctor. That is why I said I was a pharmacist. I don't want any false expectations!

DR. CHESNEY: I call pharmacists doctors also. Next speaker?

MS. PHELAN: Dr. Robert Levin is the next speaker. Dr. Levin is a medical reviewer in the Psychiatry Section of the Division of Neuropharmacological Drug Products. Prior to coming to FDA, he was with the NIMH where he worked as a health policy analyst in the Office of the Director and as an NIMH staff fellow in the Geriatric Psychiatry Branch. Before working at NIH, Dr. Levin had practiced in clinical psychiatry.

DR. LEVIN: I will be talking about a recent FDA class labeling initiative regarding SSRIs and SNRIs. In particular we are focusing today, of course, on the neonatal adverse events. With that initiative we are also discussing and proposing class labeling for adult discontinuation symptoms which we will discuss a bit today in comparison and contrast to neonatal symptoms.

Here is an example of one of the little boys and girls we will be discussing.

These are the particular drugs that we will be discussing as well. They are all marketed SSRIs and one marketed SNRI, venlafaxine as well.

Here are the objectives. One is to present highlights of the proposed class labeling that we have for both precautions sections, pregnancy and also dosage and administration. Also, I would like to provide a rationale for our decision to propose such class labeling. As Kate suggested, within the topic of providing a rationale for the labeling, I would like to emphasize that the neonatal adverse events that we

will discuss appear to be consistent with either neonatal withdrawal from SSRIs, SNRIs or toxicity, or perhaps both in some cases.

These are the sources of information that led us to our decision to propose class labeling. Kate mentioned and detailed the usefulness and limitations of the AERS data system. Subsequently I will discuss the benefits and limitations of the other three sources I have listed here.

This is some of the verbatim language, proposed language in our precautions section. There are two important points in the first bullet. One is that all the SSRIs and SNRIs have been implicated or associated with the adverse events at the time of our analysis. The other major point under bullet number one is that the adverse events to be discussed have only been reported in association with third trimester exposure to the drugs, not the first or second trimester.

As Kate mentioned, the most severe complications and treatments required have been prolonged hospitalization, admission to special

care nurseries, respiratory support including ventilation and CPAP, tube feeding as well as use of anticonvulsants, IV fluids, and in some cases, just a handful of cases, clinicians have decided to use antiserotonergic drugs such as thorazine. Also, clinicians have used propranolol. Apparently, they made the claim that there was improvement in the symptoms but it is hard to tell. It is hard to interpret with those few cases.

Whereas symptoms may arise immediately upon delivery, they can also arise anywhere from a day and a half to five days. It seems that the most typical time for presentation of these signs or symptoms is roughly several hours to a day and a half. Beyond a day and a half it seems to be rare that these events arise.

This is a list of the most commonly reported neonatal signs associated with maternal use of SSRI and SNRI during pregnancy. You can read those. As Kate suggested also, we can roughly categorize these in several clusters. One is feeding difficulty. Another is respiratory

distress/autonomic instability. Also, there are cases in which signs are consistent with temperature instability, as well as abnormal tone, both hypotonia and hypertonia; tremor and jitteriness and the non-specific sign of "constant crying" or "increased crying." Also, sleep disturbance is a very common sign reported in these cases.

One of the more important points in the precautions section in pregnancy is that, as I mentioned, the signs reported look to be consistent with either SSRI or SNRI discontinuation symptoms, so analogous to the adult symptoms, or direct toxic effects of the drugs in question.

In the more severe cases these neonatal signs resemble or are consistent with serotonin syndrome, quite a severe form of serotonin toxicity. We refer to that warning section which contains language about serotonin syndrome.

This may be a bit controversial but we have included this based on some evidence, admittedly not on data for controlled studies.

There is some suggestion that when treating a woman with SSRI or SNRI one might decrease the risk of both SSRI withdrawal and toxicity by carefully tapering the drug roughly 10-14 days before the expected due date and in the case of fluoxetine perhaps abruptly discontinuing the drug at about 14 days. That is why we made the suggestion included in that dosage and administration section.

These are the six terms, all of them have been used and reported for what appear to be somewhat identical syndromes, meaning the signs and symptoms we just discussed that are in the labeling and that we have been talking about and that Kate has talked about. I will go over one in particular because it is probably one of the terms that is least familiar to most of us. Poor neonatal adaptation is defined by Chambers et al. as tachypnea/respiratory distress, oxygen desaturation upon feeding, hypoglycemia, poor tone, weak or absent cry. That is the extent I think of the consensus definition of poor neonatal adaptation. Maybe there will be other investigators who will

use a slightly different definition but those are typically the signs and symptoms that are included under that definition.

The other terms listed have various levels of definition as far as consensus goes but SRI withdrawal, as Kate mentioned, does have a hypothetical definition as per Chambers et al. which we will discuss subsequently. We will talk about the other syndromes in a few minutes too.

This is Schatzberg. This paper is the result of an expert panel that was convened for two basic reasons: The participants wanted to decide upon a hypothetical definition of adult SSRI/SNRI discontinuation syndrome, and they also wanted to identify particular symptoms involved, cluster of symptoms. You can see the six clusters that they have agreed upon. I think in general it is fair to say this is well accepted by clinicians and investigators for definition of adult SSRI/SNRI withdrawal.

These are very common reports. It is quite common for patients to report dizziness upon

discontinuation or light-headedness. GI disturbance is quite common, as are reports of flu-like syndromes. It is quite common for patients to report "electric shock" sensations or "my brain is shorting out" or "my head is shorting out." It is very common also to have sleep disturbance and neuropsychiatric symptoms that are listed on this slide.

One of the main points of the neuropsychiatric symptoms is that, of course, they can resemble the very disease patients are being treated for but there are also "new" symptoms that are not identical to a patient's previous symptoms. If one does have those signs and symptoms, it is more suggestive that this may be a discontinuation or withdrawal syndrome rather than a recurrence of the illness. That has practical implications for how to treat and interpret the symptoms.

This is a brief list, a well-accepted list of toxicity symptoms in adults. Kate suggested this too. There are largely CNS effects, neuromuscular effects and GI disturbance.

A more severe for of serotonin toxicity is serotonin syndrome. This can be life-threatening, and these are the three main clusters that are involved. Notice that the more severe symptoms include convulsions, disorientation, cognitive impairment, abnormal muscular tone as in the case of the infants, and serious complications such as autonomic and temperature instability. One can note the similarities of these symptoms to some of the neonatal cases reported. Again, those neonatal cases that overlap with these symptoms are the more severe cases. It is likely that cases of SSRI and SNRI withdrawal toxicity are probably under-reported, as are many adverse events, and as a result of the various biases that we see the most severe cases are reported. So, even though the labeling reports the most severe, we include also some typical symptoms. Admittedly, we have purposely included the more severe symptoms.

You can look at this slide and my point here is to try to make the case that what investigators are reporting to be neonatal

withdrawal is, in fact, consistent and analogous to adult withdrawal. As Kate mentioned, it is quite difficult to elicit symptoms in a neonate. We must rely on signs. But in the ones that I have listed here there does seem to be an overlap, in the first bullet, between the neonatal withdrawal syndrome report and the adult withdrawal symptoms. The timing of onset of symptoms is also important to consider and may help us make an interpretation of whether the syndrome is withdrawal versus toxicity. Time to resolution also might help but that is a little more difficult to interpret.

This is an analogous slide. here I am trying to make the case that in some cases neonatal toxicity of SSRIs and SNRIs is consistent with and perhaps identical in some cases to adult toxicity. In my opinion, there is more overlap in many cases with adult toxicity than with neonatal withdrawal but, again, both cases probably exist.

What is especially suggestive are several things, both the quality and severity of the symptoms and the treatment required, as well as the

immediate onset of symptoms in many cases that Kate referred to as well. The cases that seem suggestive of toxicity also appear to have a longer duration. The other suggestive piece of information that is rarely available, but in some case reports clinicians have obtained serum levels of the drug and the active metabolites to try to correlate symptoms and resolution with drug levels and the decrease of drug levels. That has been somewhat successful but, admittedly, it is just a handful of cases and one study which we will review uses that approach.

Actually, it is this study. This is a study by Laine et al. It is a prospective study, not randomized, with matched controls. The point was to prospectively assess the possible association between SSRI/SNRI use during pregnancy and subsequent neonatal adverse events that we have discussed, in the short term, meaning 0-4 days, which we will discuss.

The subjects included were women who either had depression or panic disorder. There

were matched controls who were not receiving these drugs. The two drugs that the women had been treated with before--in other words, these were not randomized women but had been treated with fluoxetine or citalopram, hopefully, by other clinicians, and were included in the study and they must have been using one of the two drugs throughout pregnancy up until delivery to be included in the study.

In yellow I have highlighted two of the important points about the study. One of the benefits of the study compared to others is that the investigators used specific outcome measures that were quite helpful in making an assessment of whether or not the drug exposure was related to the subsequent symptoms. Of course, they elicited spontaneous adverse events. They looked closely, in a serial fashion, at both maternal and neonatal drug levels and active metabolite levels and they looked at monoamine levels, including serotonin as well as their active metabolites.

Also quite helpful was their use of the

specific 7-item assessment looking in particular for potential signs of toxicity that have been well accepted in adults. Their scale is based on 2 validated scales by authors who had studied serotonin toxicity in adults.

Those are the 7 items that they monitored prospectively. They found that the 3 most common adverse events among the 7 were tremor, restlessness and rigidity. One important finding was that in the group treated with SSRIs throughout pregnancy, compared to the control group, had a 4-fold increase in serotonergic symptom score and severity during days 1-4, from birth to day 4. They also compared groups at day 14 and day 28 but did not find a significant difference at those 2 points.

The mean neonatal drug levels were in the usual adult range, the "normal" range of adults. There may have been a few in the abnormally high range but generally the levels were within the normal adult range. They also reported that symptom resolution correlated with decreasing serum

SSRI drug level.

Another interesting finding was that the SSRI group had a mean lower cord 5-HIAA which is a metabolite of serotonin and purportedly suggests a higher serum of CSN serotonin activity and the serotonergic symptom score correlated inversely with that measure.

In this slide I want to make the point that if one looks at the green cubes, they represent the numerous factors that are involved in pregnancy, in the normal physiology of pregnancy as well as perturbations of the physiology of pregnancy. I am referring to drugs such as SSRIs, SNRIs, other psychotropic drugs, drugs such as alcohol and other drugs of misuse, vitamins, nutrients--all those obviously have an effect on the outcome of pregnancy and we must consider the numerous variables when trying to interpret these neonatal adverse events that we are talking about.

In the cases that Kate has discussed and that I am referring to, I think it is fair to say that the majority of the cases had confounding

variables, either depression itself--and that is one of the most important points to focus on--depression itself clearly has associated adverse events that are similar to the adverse events that we may attribute to SSRI/SNRI withdrawal or discontinuation. For example, babies born to mothers who are not treated for depression but who are clearly depressed can have jitteriness, low birth weight. They are described as being hard to soothe frequently. So, the signs do overlap with the symptoms we are talking about in relation to SSRI exposure. Also, there are clearly numerous factors that we don't know of in the case reports, which are limited in the AERS system.

Another important point in trying to sort out to what extent other drugs in this class are similar or different is that we really don't know what the denominator is. We don't know what the actual quantitative use of these drugs in pregnancy is. We also don't know the background rates of the adverse events in pregnancy or other conditions. So, these are huge problems in making certain

determinations. I mentioned the limitations of the data.

Another difficulty in interpreting these neonatal adverse events is, of course, the limited repertoire of neonatal behaviors. We can't elicit symptoms per se and the signs that they exhibit are within a fairly tight range so it makes it more difficult, of course, than making an interpretation in adults with adult adverse events.

One of the other problems with interpreting whether or not, for example, these drugs have a causal relationship to neonatal adverse events, either the drug effect or the discontinuation, is that many of the SSRI/SNRI symptoms of neonatal withdrawal or toxicity have an overlap. The very symptoms that are reported for withdrawal such as jitteriness, for example, or tremor or increased tone are also reported for purported neonatal toxicity.

Despite the uncertainty that we discussed, we feel that there is a strong association between the use of these drugs with neonatal adverse events

that these should be listed in labeling. Again, we emphasize that this is only associated with third trimester use of these drugs.

To repeat one of the points, we feel that the adverse events can be consistent with the SSRI/SNRI withdrawal or toxicity and perhaps both in an individual case. In fact, there were several cases that were suggestive of a neonate having toxicity several days or perhaps a week later going through withdrawal so that is theoretically possible.

Several other reasons for deciding to place this language in labeling is that, at least in the cases reported, many of the neonates required serious specialized care such as hospitalization, ventilation, etc., the types of treatments we have mentioned. Of course, because of this, clinicians need to be aware of the potential for development of these adverse events in neonates who had been exposed in utero to these drugs. It may be possible, and Dr. Wisner may discuss this, that there may be prevention

strategies that are practical and effective. We also need to consider diagnosis, meaning, making differential diagnosis between withdrawal and toxicity, or neither. Of course, in many cases these symptoms may have nothing to do with the drug. We can't make definitive attributions.

On the last slide I want to emphasize that, of course, it is very important to treat depression during pregnancy. There is extreme morbidity of depression and everything that applies to a man or woman, pregnancy or not, in depression applies to women during pregnancy--suicide, severe dysfunction, social dysfunction, poor weight gain, malnutrition which, of course, impacts the development of the neonate.

In contrast to previous years during which many authors reported that pregnancy "protected" women against mood disorders or recurrence of mood disorders, it is becoming more clear that the prevalence of depression during pregnancy is quite high, as high as 10-16 percent. With more information that is available as time goes on,

physicians and the patient can weigh potential risks and benefits to the mother and neonate when deciding whether to treat depression or not or other psychiatric symptoms.

That is another important point, that we are not just talking about depression. These drugs, of course, are used for anxiety disorders such as panic disorder and PTSD and obsessive-compulsive disorder so it is a larger population than I was actually referring to.

Also, it is possible that the clinician might reduce the risk of neonatal exposure to these drugs by tapering near term and that they might reduce the risk of recurrence of depression or postpartum depression by promptly restarting the drug in some cases upon delivery in the delivery room. That is one potential strategy. Of course, we do not have a consensus about interpretation and management of these complicated neonatal adverse events and ideally controlled trials are needed in this important field.

The last point--of course, it is hard for

many of us to imagine, including myself, that one can conduct truly randomized, controlled studies in pregnant women but it is possible to consider the ethics of not treating, not knowing what is happening in these studies. It would be interesting to see what might happen, particularly whether or not investigators might be able to conduct randomized, controlled trials.

Finally--I thought the last slide was final; this is the last slide and I want to point out the status of the proposed class labeling, and this is for both labeling in pregnancy and labeling in precautions in adults and for dosage administration. Firstly, all the drugs have incorporated the proposed labeling. Those listed in the first bullet have included the language. The sponsor of fluoxetine has verbally accepted the class labeling and currently our Division is in discussion with the sponsor of sertaline about whether or not they will consider incorporating the class labeling. Thank you very much.

DR. CHESNEY: Thank you. Any technical

questions? Dr. Gorman?

DR. GORMAN: In accepting this class labeling, do the sponsors have the opportunity to modify it in any way or is it a whole or none, up and down quote?

DR. LEVIN: They have the chance to attempt to do so.

[Laughter]

No, seriously, we had discussions about that. Of course, as you might guess, especially with drugs that have a longer half-life, companies might argue that qualitatively and quantitatively these adverse events are different but, in fact, that is probably not true from the data available. So, for practical reasons, probably each company did request making modifications but in the end they accepted the verbatim language that we proposed.

DR. CHESNEY: Dr. Ebert?

DR. EBERT: I hope this is a technical question, but does the AERS database enable the FDA to do any long-term follow-up on these children?

You have the immediate postnatal adverse events but are you able to follow-up these individuals two or three years later to identify the long-term effects?

DR. LEVIN: I think one answer is that it is extremely difficult based on the fact that these are spontaneous reports and voluntary reports. It would be great if we had that. It is very hard under the current system. There are companies, maybe one company I can think of that is prospectively monitoring women who are using an antidepressant during pregnancy. That seems to be a more productive strategy. At this point, although what you are suggesting would be ideal, I am not really sure to what extent one can request further follow-up unless there are serious adverse events. If it is a serious adverse event, defined by regulatory language, then the companies are obliged to give follow-up reports. But the typical reports describe, as Kate mentioned, the type of symptoms and signs, the timing of onset, a few of the obstetric factors and co-morbidities, some

concomitant meds, but my recollection is that it is fairly rare for those reports to have included the duration of the adverse event or the time to resolution.

DR. D. MURPHY: Just to reinforce that, AERS is not set up for long term. Also, it would be difficult to sort of imagine how someone would make that connection later on to a therapy given earlier so you really would need to set up some sort of prospective study.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: It seems to me it is crucial to be able to distinguish between withdrawal or discontinuation versus toxicity because you have to treat them totally differently. Correct?

DR. LEVIN: Right, yes.

DR. O'FALLON: So, I am looking at your list and I don't see how you could possibly, just by looking at these descriptions, tell. Is there any way you can? Here is a person who has this problem, can you distinguish which one it is? Is

there something you can do?

DR. LEVIN: Yes, you are right. Exactly. That is one of the major points. It is extremely difficult in some cases primarily because of the relative lack of information as you are saying, also there is clearly an overlap in the wording for withdrawal and toxicity.

DR. O'FALLON: Yes.

DR. LEVIN: In my mind, and of course I acknowledge that people can disagree completely, but I think it is the severity of the symptoms.

DR. O'FALLON: The severity?

DR. LEVIN: The severity is one point. One reason I mention that is it is comparing and contrasting to adult syndromes. Typically, in the adult syndromes with withdrawal they can be quite distressing. In adults they are usually mild to moderate and transient but in some cases they can be quite distressing and temporally disabling, meaning, people are not be able to take care of their families for days or miss work for several days. But it is quite rare. Usually they are mild

and transient. Most likely there are neonatal cases that are withdrawal that aren't reported. In personal communications clinicians have suggested that the most common scenario if neonates have these type of symptoms, they have things such as feeding difficulty and increased crying which doesn't require specialized care and resolves fairly quickly.

But, yes, you made several important points. There is an overlap in the symptoms. Another way to answer your question is that I think getting serial drug levels would be very helpful. It has been done in several cases. I think it is one of the most important pieces of information given the confusion and uncertainty about these symptoms.

People have also given sort of treatment/ diagnosis. In other words, I remember only two or three cases in which a clinician decided or thought it was probably withdrawal syndrome and they gave the neonate the very drug that they may have been withdrawing from. I remember two cases. In one

case they reported that the infant became better, I don't know in what time frame. In the other case it got worse. The symptoms were exacerbated.

There was a handful, three cases in which--this is interesting actually, there were three cases in which the clinician clearly diagnosed the infant with having withdrawal syndrome and he decided to give the drug thorazine which is known to have antiserotonergic properties. Even though we can't make attribution, the chronology was such that within minutes to hours the infant was "remarkably" better. We don't really know what that means but it is interesting that he chose to use the drug while still using the term withdrawal. Beta blockers also may be helpful.

DR. O'FALLON: It just seems to me that we can't even deal with this very well until we have a good idea of which problem it is.

DR. LEVIN: Exactly. That is true.

DR. O'FALLON: Do you think you will have an opportunity to explore that further as we get to

the questions? It is an issue.

DR. CHESNEY: Dr. Danford has a technical question.

DR. DANFORD: Well, I wonder if there are observable fetal effects that we ought to be looking for to help make this distinction. Is there an impact on the baby's biophysical profile? Is there observable jitteriness, abnormal movements, that sort of thing that, if we just were to look in an organized fashion for those among fetuses of pregnant ladies on these medicines we would either find them or not--

DR. LEVIN: Right.

DR. DANFORD: --and were we to find them, we would think that toxicity might be in effect. And, if were to find them only after delivery perhaps that would be withdrawal.

DR. LEVIN: Right. Exactly. That is why we are considering that and perhaps beginning studies to look at that with ultrasound, especially with ultrasound, to look for potential abnormalities of movement. I haven't read anything

as far as results. There may be some, I just don't recall seeing results of any studies, even preliminary studies looking at that but that is a critical question to ask and to answer. It would be extremely helpful. That would be an excellent piece of information to have in sorting out whether this might be toxicity or withdrawal.

DR. CHESNEY: I think those will all come up when we try to answer the questions. I guess you are going to introduce Dr. Wisner.

DR. LEVIN: Yes, I would like to introduce Dr. Wisner. It is my pleasure to introduce her and I am very glad that she is here. Dr. Wisner is the Director of the Women's Behavioral Health CARE, a specialized treatment research program for childbearing women at the University of Pittsburgh. Parenthetically, I was a resident in psychiatry there and had the great pleasure and privilege to learn from Dr. Wisner so that is another reason why I am especially happy to see here. Dr. Wisner conducts several NIMH-funded studies involving pregnant women and postpartum women with mood

disorders. She is trained in a number of fields in adult and child psychiatry, as well as pediatrics. She has done a postdoctoral program in epidemiology. She has academic appointments in psychiatry, obstetrics, gynecology and epidemiology.

DR. WISNER: Thank you, Bob, for that very nice introduction, and it is a great pleasure to be here and I thank you for the invitation. Again, it is a real pleasure to be here and I am thankful for the opportunity to address you.

I have several goals for the talk this afternoon. The first is to discuss an approach to making treatment choices for pregnant women who are depressed. The second is to think about how to conceptualize the diagnosis of the effects that we have been talking about. In other words, how do we think about whether what the neonate is experiencing is acute side effects or what has been called toxicity or, in fact, is a withdrawal syndrome from the same medications? Finally, I would like to tell you about a study that I am

doing now, an RO1 that is funded by NIMH in which we are actually trying to address some of these issues.

Well, how big of a problem is this, that is, depression and other disorders that require treatment with medications during pregnancy? In fact, it is a major public health problem. Bob had a rate of about 10-16 percent of women who experience depression in pregnancy. In fact, that fits with the kind of rates that we see in childbearing age women. If we look at the rate of depression across ages in women compared to men, about twice as many women have depression during their childbearing years as do women [sic] and, in fact, somewhat unfortunately, it is right in the childbearing age time that women experience this devastating illness.

Given that many women are going to have this disorder during their childbearing years, how do you deal with the fact that at least the pharmacologic therapy is a chronic treatment for this illness and, in fact, women want to conceive

while they take this medication? Our American Psychiatric Association put together a committee to look at these issues several years ago and a number of papers resulted. One of them is referenced in which we defined what kinds of issues docs would need to think about in talking to women who are contemplating pregnancy if they are depressed or they are already taking an antidepressant medication.

This is a somewhat complicated slide but I am just going to break it down into components. The first area is what are the responsibilities of the physician. Of course, talking to patients about what depression is is incredibly important because many patients feel like the depression is like having a bad day, or they have a lay person definition and, unfortunately, the word depression is used colloquially--"I had a fight with my boss; I'm depressed." This major depression that we are talking about is a clinical diagnosis called major depression and it is a dysregulation illness in which the physiologic functions of the patient are

affected. We will talk a bit more about that a little bit later.

But just the criteria of this disorder are very weird. Here is a medical illness where dysregulation of mood, ability to enjoy life--those things are affected but the dysregulation is confounded. You can either have too little sleep, for some patients an hour of sleep a night; or some patients sleep 23 hours. Those are both dysregulated sleep that count as part of the diagnosis. Another example is agitation. You can have excess motor activity and not be able to sit down, be very agitated, or be so slowed down you can barely move. Again, it is indicative of not just something that is "I feel sad emotion" but this is a whole body dysregulation illness.

In talking to patients, what I typically do is discuss what treatments are available for major depression, and there are many. Then I talk to her about what specifically might be appropriate with respect to her clinical history and then, secondly, how that might be modified because she is

either pregnant or she wants to become pregnant. We have many options for depression in pregnancy in terms of treatment. Many patients are already taking effective medications. Psychotherapy has certainly been studied as a treatment for depression in pregnancy. Due to some of the issues we are talking about in this very meeting, my group has begun to pilot light therapy for treatment of depression in pregnancy. We also talk to patients about the risks of no treatment during pregnancy, which I think is a very poor option.

We are also then obligated to talk to patients about what are the outcomes if she accepts a particular form of treatment during pregnancy, and what are the outcomes for her depression if she doesn't accept treatment or wants to consider moving to a different treatment which may or may not be effective for her. Our discussion today really focuses on this final area of neonatal toxicity. In this paper we meant to designate the kind of broad construct that Bob talked about. That is, negative symptoms that occur in the

post-birth period for those neonates.

But there is another issue here that I don't want to exclude from the discussion, and that is the idea of behavioral teratogenicity. That is, of course, the idea that these potent central nervous system acting agents when brain, as vulnerable as the neonatal brain, is exposed through pregnancy and perhaps there may be effects that occur that manifest later on in life. That is often talked about as later on in life, like way down the line. A hypothetical example might be that a child might be at higher risk for learning disabilities as a school age child. But there is a very real question of when behavioral teratogenicity occurs, meaning that there is no time point so that some of the effects that we see may be really due to this particular kind of mechanism as opposed to either withdrawal or acute side effects or toxicity. That is another issue that hasn't been explored. I think that that question is inherent in some of the questions here which are how long does this thing, whatever we

call it, last. Because it will help us define the mechanism.

Treatment of depression in pregnancy is important. The outcomes for untreated depressed women in pregnancy are not good. Unfortunately, every paper that has been cited in this meeting today has not uncoupled the occurrence of the illness, that is depression, from the drugs used to treat it. That is like saying we want to study a hypoglycemic agent as an exposure in pregnancy but we are not going to control or look at the blood sugars of the pregnant women, and that is our major problem with this field.

An interesting area is what kinds of treatments do women select in pregnancy. There is a common belief that because women are pregnant they might want psychotherapy or light therapy but, in fact, in my research program many of the women, particularly those who get very good responses from antidepressants, are very interested in continuing those medications in pregnancy.

These large blocks are just there to show

that the decision is really a dynamic one and the choice of providing, say, a medication treatment in pregnancy means that we have decided that the benefit of that is greater than the risk for that patient. But if, in 4-6 weeks, that medication does not produce an antidepressant effect or sustain an antidepressant effect, then that decision-making process has to be reconsidered.

This committee that I spoke about, the American Psychiatric Association committee, wrote this first paper in which we reviewed the prospective data for antidepressant use in pregnancy. Although I am not going to go into that in detail because I want to focus on poor neonatal adaptation and neonatal effects that are the topic of this meeting, one issue that I think is important is that because these agents are not major morphological teratogens there has been over the last several years a relative comfort about their use in pregnancy. So, there is a much larger population of mothers being exposed to these agents, and I think we are seeing these kinds of

outcomes, like neonatal toxicity, that are becoming more frequent, in fact, because of the increased use.

Tina Chambers' article which Bob mentioned, I think is a very important article because the agent studied was fluoxetine. About a third of patients have this poor neonatal adaptation and 24 percent of her patients were admitted to special care nurseries. Because that is a prospective study specifically of fluoxetine at least it gives us a rate in which the denominator is known.

Well, I want to focus on treating maternal depression and the importance of uncoupling that factor in these data sets because there are papers that show that maternal depression and anxiety increase the odds ratio or the risk of multiple bad things in pregnancy, like preeclampsia, and also that there are investigators, particularly in England, who have looked at uterine artery resistance in the face of depression and anxiety. These factors have been related to growth

restriction in fetuses as well as preeclampsia. So, again, depression itself can create negative outcomes, and how to uncouple the disease-produced negative effects from the medication is incredibly important.

We also know that maternal stress and certain anxiety disorders and mood disorders result in dysregulation of the HPA access and that, in fact, that has ramifications for the fetus as well and has effects on fetal ability to respond to stress.

The question was asked before about ultrasound and in utero behavioral studies of fetuses to look at this issue. In fact, I have an MT at Brown, named Amy Salisbury who is working with me and Gianne DePitro, whom you know, who has done these in utero studies. They are doing parallel studies of fetuses with the same three groups that I will talk about in my study. So, those kinds of investigations are being performed right now.

We also know that even before an infant is

born to a depressed mom it interacts with that depressed mom. Those infants have been seen by nursery care staff to be irritable, difficult to console. So, these same kinds of behavioral effects that we have been talking about as due to medication also occur because infants are born to moms who have this dysregulation disorder we call depression. Again about depression, the point that I want to emphasize is that depression is this physiological dysregulation but it really is probably a variable. That is, the presence of depression that really brings with it a whole multitude of factors that contribute to poor outcomes for pregnancy if it is left untreated.

We talked about appetite changes and food choice changes that occur. Certainly, the ability to comply with prenatal plans, such as vitamins and other prescribed treatments in pregnancy are less. Women can be irritable. They can have isolation and alienation of psychosocial relationships right at a time when it is natural for families to begin to think about being parents, to begin to bond

together. Many women who are depressed also use other drugs and smoke, which create confounds, and many women who are depressed elect not to breast feed which then deprives the infant of that particular favored choice of feeding.

This is a model from Dawn Misra that I like to use to think about this whole group of factors that relate to outcomes for mothers and babies no matter what the disorder is. The way she conceptualized it is very relevant to this discussion in that depression is an illness with genetic factors. It runs in families, like most disorders. Physical environments affect it, including light. Where you live and the amount of light affects your risk for depression, and social environments affect it. So, if you are in a wonderfully comfortable neighborhood versus a neighborhood in which there are drive-by shootings every day that makes a big difference. Those are factors that are more distal risk factors in terms of distal from the pregnancy, but they shape the biological and behavioral responses that the woman

brings to conception. So, those factors which increase the risk for depression are what she brings along with her to the pregnancy. Again, you have the physiologic dysregulation, the HPA access dysregulation and other difficulties that she brings to the pregnancy state with her.

What we are trying to do as healthcare professionals at these intervention points is say all right, we know there are these whole groups of variables that come with a mother who has major depression. How can we deal with that so we maximize the outcome for both the mother and the baby? And, how can we do that not only in a short-term way but in a long-term way? How do we get the best result? Because we know that we would rather not use pharmacotherapies for these depressed women but leaving them untreated is not particularly good either. I think this particular mom sums it up the very best when she says, "believe me, mommy's mood stabilizing drugs are not something that anybody wants mommy to just say no to."

[Laughter]

I have many patients who really feel like they are in this particular situation.

Well, let's look at some specific issues related to use of SSRIs during pregnancy, especially the final part of pregnancy, and the risk of neonatal complications. We have talked about several papers, especially Laine's paper, which have shown this increase in the risk of difficulties in the neonatal period related to fluoxetine. Now, fluoxetine is unusual among the SRI medications in that it has an incredibly long half-life and it has a metabolite that is equally active with an even longer half-life. So, it is distinct in that pharmacologic way which may make it distinct in the way it behaves in neonates as well.

Paroxetine, or Paxil, has been most commonly identified in case reports, but there is a recent article in one of the pediatrics journals in which the investigators sought to replicate the finding that paroxetine was the SSRI that was

particularly problematic and was unable to do so. Paroxetine is unusual as well in that it is not only a serotonergic antidepressant, it is the only one that has significant anticholinergic effects as well so that one could imagine having cholinergic overdrive in addition to the serotonergic mediated effects in newborns. And, we have less data on the other three agents, sertaline, citalopram and fluvoxamine, so we sort of make inferences based on the pharmacology of those agents.

One issue is certainly placental passage. Vicky Hendrick has looked at this particular problem and shown that these agents have lower placental passage, and these agents have higher. So, one would expect that agents with greater access to the fetal compartment might have more effects as well. Again, there is a look to could we think about, or is there enough evidence to suggest that certain agents might present less distribution into the fetal compartment and, therefore, might be less problematic. So, that is again another area of investigation.

The other issue is the variability in fetuses and moms in general so that why some kids have major difficulties and other kids don't becomes probably related to individual variability differences. So, one of my concerns is not so much about the full-term babies lately, but we have had some premature babies born where you have all the sequelae of prematurity in addition to a significant amount of drug on board in those patients.

There are also additional exposures that might complicate the baby's ability to metabolize the drugs with which it is born. The overall health and nutrition of the newborn are major factors. There are also genetic issues so that we all know that our and our baby's ability to metabolize drugs really depends on the ability of hepatic enzymes to metabolize them and there are poor metabolizers as well as rapid metabolizers distributed in the population. The activity of the particular enzymes within the fetus and within the parent are important as well. Some people can

break down serotonin rapidly; others really can't. Then, there is the final issue of how available are serotonin precursors. So, there are a number of factors that really go into this decision about what is really happening in the neonatal period and how do we understand it.

This point has been made by Bob very well. If we look at poor neonatal adaptation defined by Tina Chambers and Carey Laine's paper which looks at serotonin over-stimulation, and you say, well, these are the symptoms here, these are the symptoms there, and these are the overlapping symptoms, you are really struck with the sense that we have different groups defining different things, and how we can really put them together is somewhat problematic.

Bob mentioned something that I think is very important, and that is that Carey Laine's paper really suggests that the babies born to women who take antidepressants through the final trimester, if they are going to experience something at birth based on those high serum

levels, the suggestion in that paper is that it truly is serotonin effects. So, what this group is saying is that essentially there are side effects and in the severest form you have serotonin syndrome. Those babies are essentially born with an adult level of the drug on board so these are acute side effects and, in fact, maybe they have those in utero, and we will find out with some of the fetal studies.

As the cord is cut though, the source of the drug is not there so there is an abrupt discontinuation but since babies don't metabolize these drugs particularly well there is a rate at which those drugs come down in the baby's body and it is possible, in fact, to have both these acute effects. It is possible to have what are really more consistent with withdrawal effects down the line. The other possibility we have entertained with paroxetine is that, depending on the receptor occupation, it may be possible to have one or both of those syndromes related to cholinergic receptors versus serotonin receptors. So, it is a very

complicated picture.

Bob and others have already talked about these domains of symptoms that are really affected in neonates exposed to SSRIs. The other point that I think is interesting is the repertoire of babies to tell us that they are not particularly comfortable. In fact, there are likely to be symptoms and signs that overlap across time that can be indicative of either of those. So, the time course is particularly critical.

So, the questions that I think we need to understand are what are the symptoms that characterize these syndromes? What is the incidence? Because we really don't know that. The data from Tina Chambers' paper is probably the best and it is for one agent. Is this withdrawal or intoxication or some form of neurobehavioral teratology? Are they all equally likely to cause it? The answer to that I think we can say pretty confidently is no. Because the risk of not treating depression in women typically outweigh the risks, what can we do to prevent these things,

minimize them or even treat them so that when we get back to that model I showed you we are really maximizing the short- and long-term outcomes for moms and babies?

What our group has done is to take Loretta Finnigan's wonderful scale that was designed to look at withdrawal from drugs of abuse, and we integrated these symptoms and signs that have been described here into the scale to try to understand what is happening. I will show you that scale in a minute.

In this particular investigation that I have under way now what we are doing is picking up women before week 20 of pregnancy and studying the moms and their babies out to month 24 postpartum. We have exposures week by week in this study. So, originally they come in; they have 20 weeks retrospective exposure history, and by exposure I mean drug, not only SSRI but anything else they have taken, and we think of depression as an absolutely separate exposure. So, on the exposure chart you will have criteria for major depression

or depression scores because we get continuous measures as well.

We are after three groups, although we have ended up with a fourth group here as well. The three groups are pregnant women with depression who refuse medication. You cannot say they can't have other therapies and many of our patients do but many of the women don't respond. So, it is positive depression, no drug group. The second group is women who are not depressed because probably they are taking an antidepressant so it is negative depression, positive drug. We have a normal control group. And, not in the original design but certainly as a part of life, we have patients who are partial responders. You know, they are a little bit better but they are exposed to both the drug and some level of depression as well. We are studying these four groups.

At week 36 of gestation, what I do is I talk to them about a choice they have, whether they are going to continue the drug right through the end of pregnancy, or whether they would like to

consider tapering the drug 2 weeks before the EDC. If it is fluoxetine we just discontinue it, again, because of the long half-life.

At this point I can tell you that over half, probably close to two-thirds of the women we offer this option and give a careful risk/benefit discussion to elect to stay on their medication through the end of pregnancy, and their reasoning typically is every time I go down on the dose or I stop this medication I get sick very quickly and I don't want to go into labor and delivery like that. The women who can say, gee, it is a couple of months off and when I taper my drug or discontinue it before I get symptomatic again--those women are willing to do this alternative strategy but it has been very intriguing to see under what circumstances they choose this strategy.

What we then do is monitor weekly with a continuous depression measure through whenever they give birth, and we are looking at a number of outcomes at birth and at two weeks and beyond to compare across the two groups.

Here are some questions that we are struggling with. Does this taper regimen--let's say they decide to go off the drug in the latter part of pregnancy--we don't abruptly discontinue it, we taper down--does that affect the near-term fetus in utero? We make the assumption that if we are withdrawing the drug, that slow withdrawal is better than the abrupt discontinuation of cutting the cord at birth, but the kinds of studies that were mentioned about fetal well being are critical in that context.

Does the baby or infants who are born of mothers who taper their drug in the latter part of pregnancy compare to unexposed moms? I mean, does it really work?

Do mothers become symptomatic during the taper phase? By and large, they don't and that probably has to do with the fact that they are choosing based on their history of how long it took them to get sick and, you know, it takes a while before women respond to antidepressants. It takes 2-4 weeks. We are trying to take advantage of that

time frame with withdrawing the medication to try to get more of the drug out of the fetal compartment before the baby is born. Does that work? We are finding out.

Does restarting the medication at birth prevent recurrence of the episode? I can tell you that, by and large, it does. The baby comes out; mom goes back to her room; the drug goes right in--you know, no delay in getting the drug in.

An intriguing question is that small amounts of all these drugs occur in breast milk. Does breast feeding provide some partial protection against at least the component that we think may be withdrawal?

In our study the raters are totally blind to not only the status of the baby in terms of exposure but to the study hypotheses. So, the raters for the birth assessments and 2-week assessments are totally blind. We do maternal serum and cord blood antidepressant levels. We also do cortisol and other hormone levels as well. We do a mother and baby breast feeding level at

week 3. We do cry analysis at birth and 2 weeks; a pediatric neuro exam at 2 weeks. It is an exam that was given to us by Lynne Singer who works with addicted moms in Cleveland; and we do the modified Finnigan scale.

I had a heck of a time trying to figure out how to put this document on Power Point but I finally figured it out last night. Essentially, what we have done with Dr. Finnigan's scale is to say here are the items for her scale that we don't think are relevant to these syndromes. Here are the items that seem to overlap with her particular scale. As you look down, they are pretty much the symptoms that we have been talking about. These are additions that didn't occur in her scale that we wanted to assess. So, this scale is now integrated into our study that I told you about. In fact, Amy Salisbury, at Brown, who is doing the other study I told you about, is having these as well.

Well, the point has already been made that we really have to understand how to diagnose this

because the treatments are exactly opposite. If you think, because of the high level that a baby might have a birth that it is a serotonin toxicity that is side effects, which is what I think the majority of these kids have, when it is an early presentation, then it is toxicity and what might you do?

Our main interventions have been parental education and cognitive strategies. These are moms who are very prone to feel guilty. You know, "what did I do to my baby?" So, we really do a kind of a therapy to help them understand what is happening and that it is transient. Certainly, the strategy I mentioned in terms of an attempt to taper in the final part of pregnancy is an option, but we tend to be very conservative and we have a very good pediatrician that talks to the moms about kangaroo care and swaddling, and do more behavioral management strategies.

What if, though, a baby had very severe symptoms? In fact, the case that was described by Manna et al., which is one of the first ones in

Cleveland, was actually a baby born to one of the moms that I treated and that baby was really quite ill. Might we think about an antiserotonergic drug like cyproheptadine? There you always get into the issue of we don't know what kind of dose to use so some sort of dose-ranging safety and efficacy study would be appropriate. What if we give too much? Do we then give back the agent? Those kinds of studies are important to think about and we have begun working with our neonatal pharmacologists to think about those as well.

Well, what if it is withdrawal? Again, does lactation provide some potential prevention against withdrawal? Again, the kind of conservative management strategies that we have already talked about may make sense. Bob mentioned that if you really think it is withdrawal, for adults you give a dose of the medication they are withdrawing from and they really feel better fairly rapidly. Is that the case for these babies as well, and might we think about a dose-ranging safety and efficacy study to define a model so that

if they are a certain number of days postpartum and they are having withdrawal symptoms you give a dose and then taper it in some prescribed way? That is all work that needs to be done.

Let me finish with this thought, that mental health truly is fundamental to health, and how to package this so we get the best result for the mom and baby who are clearly not independent is critically important. Thank you.

DR. CHESNEY: Any technical questions for Dr. Wisner? Dr. Maldonado?

DR. MALDONADO: Excuse my ignorance, I just have a couple of concepts that I want clarification for. These concepts are new to me, behavioral teratogenicity. Is there biological evidence for that, or any animal models? If there is, what kind of hypotheses do you think need to be tested in clinical trials to answer that question?

The other is the symptoms of depression you said are equal to physiological dysregulation. Are there biological markers that can be used as surrogates to test where the dysregulation is or

whether those biological markers actually may be good markers to use to see response?

DR. WISNER: How long do I have? Those are really good questions. Let me deal with the biological markers issue first. There is a lot of interest in working particularly at HPA access regulation changes in patients with depression. The majority of patients, particularly those with what we call typical depression, have high levels of cortisol and they have accentuation of the HPA access products. There are patients, those particularly with post-traumatic stress disorder, who have high proactivation of that access. There are some interesting differences diagnostically in how those axes are affected.

Secondarily, we have studies that look at, say, osteoporosis in depressed women, which tends to be higher. The extension of that is, well, in women who have depression with HPA access difficulties, are there changes in pregnancy that we need to know about? In the National Children's Study, I was in the stress and pregnancy work group

and talking about looking at cortisol, CRH and other measures in pregnancy were important and, of course, there are papers which have shown that CRH levels may actually be somewhat predictive of premature birth. So, there is an attempt to look at some of the changes that we know occur in depression and bring it into a much broader construct of medicine and say, well, what does that really mean? One of those is what would potentially be the effects for pregnancy.

The other question was about behavioral teratogenicity. There certainly are studies. The ones that I have looked at more recently are studies on long-term effects of fluoxetine during pregnancy in rats and long-lasting changes that occur that result in behavioral problems, but they are not manifested until a later point in development, or the point in development when they occur is delayed or made earlier. So, the issue is that as these potent central nervous system agents occur in the fetal brain, changes happen that we might not see directly at birth but we might see,

say, at age 7 as development unfolds.

The problem that I was trying to identify is an interesting concept. There certainly are animal data, and I am more familiar with the animal data on this to support it. But then how far back in time do you go to say that is the mechanism? Or, what if the exposure was at birth, whatever it was happened at one month or two weeks, how would we distinguish something that is the result of that mechanism from either withdrawal or acute side effects? That is the point I was trying to raise.

DR. CHESNEY: Thank you. I think that last point you made is something that has been puzzling me and I think that is one of the very subtle aspects of this whole issue that we are going to be wrestling with.

DR. WISNER: In the study that I am doing, although I focused just on the birth and 2-month effects because we are looking at this neonatal issue, it is embedded in a study in which we are also doing a minor physical anomalies assessment because Tina Chambers' paper found higher minor

anomalies in the fluoxetine-exposed kids, as well as far as major anomalies and overall developmental progress as well. So, it is couched in a study that goes out to 24 months.

DR. CHESNEY: Any other technical questions for Dr. Wisner? Naomi, you had one. Go ahead, Dr. Luban.

DR. LUBAN: I am just curious. The only articles that I could find that actually quantified the drugs were in a very, very small case report. Is there a broader-based data set that has looked at the differences in clinical manifestations apropos of drug level actually measured in the cord or in a newborn infant?

DR. WISNER: Carey Laine's paper that Bob mentioned is really the best paper because they have not only levels of drug and metabolite but levels of serotonin metabolites as well. They also scanned the babies' brains to show that there were no structural abnormalities. But as far as a paper which really needs to be done in which the cord and then potentially serum levels have been tracked

across time and related to symptoms, that has not been done to my knowledge.

DR. LUBAN: Thank you.

DR. CHESNEY: Yes, Dr. Sachs?

DR. SACHS: I was just curious about two things. One thing that struck me is that I know for lithium, for example, there is a lot of variation in the way the drug is metabolized right around delivery. It kind of occurs to me that that might be the case here and I am curious if your study is going to look at that.

DR. WISNER: That is such an interesting point. With respect to antidepressants and how their dose and metabolism might change across pregnancy, there is one paper that is published that looks at serum levels across pregnancy and antidepressant dose. It is a paper that my group published about tricyclics in '93. That is pretty bad. Essentially, what we showed was that there is an increase across pregnancy, particularly starting with the second half of pregnancy and then in the third trimester the oral dose required to achieve

the same serum level was an average of 1.6 times as high. Others have described that but not looked at serum levels for SSRIs.

In this study, in fact, we have serum levels and cortisol hormones--all kinds of stuff, at weeks 20, 30 and 36 across pregnancy. So, we are looking at that issue. We have, again, very careful mapping of depressive symptoms. My major interest is in sorting out what are the things on these scales that happen with depression with no drug, and what are the things that happen with drug but no depression, and what is the mush in between. We call that fourth group affectionately that I defined our mush group because they are probably going to give us that answer.

DR. SACHS: And you mentioned that you are doing I guess questionnaires about substance abuse and things like that. Are you actually doing drug screens, alcohol levels?

DR. WISNER: Yes, at the 20-week intake we do a drug screen and exclude any women with any substances of abuse. In fact, that has been very

interesting. The number of positive drug screens from women who declare absolutely that they never took anything, those women are excluded. You still can't exclude everybody based on a drug screen and some of our women consume what I think are unhealthy doses of alcohol after they are in the study. We keep them in but we continue to track that. But my guess is we will have to analyze those patients separately.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: Of particular interest to me was the longer-term follow-up to 24 months. Will there be any objective non-maternal, non-physician office evaluation of those babies?

DR. WISNER: Objective? Well, let me tell you what we are doing and you can tell me if it fits into your categorization. At 18 and 24 months we were very interested in more subtle behaviors like task persistence. So, we have our mastery motivation model that Kay Jennings developed that has to do with the toddler's ability to attend to a prescribed task. There are timed measures in that.

It is sustained attention, propensity to be activated to continue to solve a task. It is that kind of measure. It is a measure that is affected by maternal depression so, again, we are interested in that in the four groups. Across the postpartum period for all time points we have an appropriate measure. The Bailey scales. We do the full scales. One of our neonatal psychologists does the Bailey scales across the postpartum period for kids as well. We have standard pediatric exams at all points. Is that what you meant? What are you thinking of?

DR. GORMAN: No, those are commonly accepted and I think perhaps the state-of-the-art evaluations, sometimes some of the global impression scales that I have very little faith in, except I think they actually do work. When Kennedy Kreeger asked the mothers in the waiting room to give a developmental age for the children and then, after they did a 72-hour exam, they were within a month or two of being correct. So, I was looking for day care providers or child care centers or

kindergarten teachers--I know you are not going out quite that far--are they different? Or, what do you think about these kids?

DR. WISNER: You mean collection of data about the kid that is as uncontaminated by maternal report as possible.

DR. GORMAN: Correct.

DR. WISNER: No. We have CBCL at age two, which is again a maternal report. We have a number of measures of maternal function, like maternal role function, maternal role gratification and completion of immunization rates in the first year that are more functional measures for the mom, but no totally independent--I mean, even the Bailey's would not be totally independent although it gets closer than some of the other things you are talking about.

But in the resubmission and competing continuation of this grant, we certainly are going to propose to go out to school age kids because that is really important.

DR. GORMAN: It is just that in this

particular population the contamination with disease diagnosis or potential disease diagnosis makes the data even harder to interpret for those outside the field.

DR. WISNER: There are a couple of things there. It is something that we can at least look at across the four groups because we have the occurrence of depression and drug all the way from pregnancy out to that 24-month time. So, we will have women with trait depression, that is, they have had it but they are well, commenting on these measures; women who are actively depressed, commenting; women who are normal controls and that mush group. What I think you are getting at is what is the validity of material that is observational about an infant or toddler if it is reported by someone who is depressed, whether it is state, that is right now, or whether it is potentially trait. So, it is more of a validity issue.

I think you are right, the way to really get at that--I am cringing because it is hard to

do, but the way to get at that is what we think about, say, blind observer ratings. Now, even a teacher isn't though because that teacher, knowing the parent, is going to be to some extent affected. It is a little more clean but still the validity issue is important. I mean, if you ask a teacher of a five year-old to fill out a CBCL, that teacher knows the family. I mean, it is a little more non-biased. The ability to comment on that child related to a class of 30 is probably more what we are after.

DR. CHESNEY: I have a suggestion for you, to hire Dr. Gorman as your consultant for your study!

DR. WISNER: Fabulous!

Discussion of Questions 2 and 3

DR. CHESNEY: Thank you very, very much for a rigorous drilling here. I think we need to move on to the questions. Dr. Iyasu is going to post those for us and maybe get us started on the first one.

DR. IYASU: We have two questions for you,

as usual, and we have subparts to those questions. The first question has to do with how we disseminate the information, the new label information to the public and prescribers. The second question deals with additional research that could eliminate some of the issues on neonatal toxicity and withdrawal.

I will read the first question: The FDA is proceeding with class labeling about neonatal toxicity/withdrawal syndrome related to in utero exposure to SSRI/SNRIs. Considering the risk/benefit of SSRI/SNRIs use in pregnancy with depression versus the risk/benefit to the fetus/newborn, how should this new information on the label be disseminated to child health practitioners and the public?

For your comments, here are the options that we have listed. Please discuss the following options: No further action is necessary. Label change is adequate.

A "Dear Healthcare Professional" letter.

Prescriber or healthcare professional

education through professional groups.

The last option is a public health advisory. After you have discussed this I will read the next question.

DR. CHESNEY: Could you just elaborate on the public health advisory? What would that involve?

DR. IYASU: Well, that would involve issuing a public health advisory. That means really an explanation of what the label change is and why we are doing it. It is usually issued by FDA and includes information about the rationale, the new information and is disseminated to the public and also put on the website, and also there is a paper that goes out. So, it is really a high-level dissemination so that everybody knows about this new label information.

DR. CHESNEY: Thank you. So, we should proceed with question number two and then you will come back with question number three. The issue is that the FDA is moving ahead with class labeling. That is a given. They are asking us for

information as to how the fact that the label is going to be changed should be disseminated to child health practitioners and the public, and they have given us four potential options. Dr. Nelson?

DR. NELSON: In trying to formulate an answer to which approach is best, I would start by framing it as a question of informed consent. What strikes me about this area is, as compared to a label which gives you data, you have a complex balancing within the decision-making of the pregnant woman between risks to herself, risks to the fetus and risks to the newborn. I think there has been a lot in the ethical literature about that in other areas.

So, in framing it as informed consent, then the question would be which of those actions would be most effective in providing information that could be useful within the informed consent process. I would be concerned if that were seen simply as providing information to the healthcare professional. Looking at the existing label with non-teratogenic effects and looking at the

pregnancy, it simply says tell your doctor if you get pregnant. Then, under the non-teratogenic effects it talks about what the physician should think about. But there is really nothing in here about the risks of untreated depression in pregnancy. I mean, there is nothing in here, as opposed to the articles, and there was some discussion of that, but nothing that I think you could give to a pregnant woman to say here is something that can help you and, in fact, if it helps here it probably helps the health professional think through this complex risk/benefit decision.

So, the question I would ask is could one develop information for the patient, much as Duragesic had, that could go through the kind of decision-making issues that would have to be addressed? That would be a very complex document. But I am not sure any of these four actions that are proposed actually would really get at the informed consent question which I think is at the heart of this.

DR. D. MURPHY: In a way, I think what you are telling us--and I would ask you all to comment on this, is that the information that we are putting in the label-- because, again, our labels have to try to at least raise this issue--is that that is not adequate for people to make a prescribing decision. So, you are proposing--and I am not quite sure whether you are saying it is not adequate for the physician or mostly for the patient--and you are proposing that we have in addition a patient insert on this issue that would have more information that would allow the patient and the physician to have a more detailed discussion. Is that correct?

DR. NELSON: Yes, I think it is correct. I think some of the comments that were made about women making decisions based on their response to coming off medication and whether they get sick quickly or get sick slowly, you are not going to put that in the label. It can't be put in the label. So, how you give people information to do that kind of balancing is the question. You can

certainly have the risks of the non-teratogenic effects in here but I can't imagine a sponsor wanting you to put in the risk of untreated depression in the label--

DR. D. MURPHY: Yes.

DR. NELSON: --for an antidepressant.

DR. D. MURPHY: Sandy Kweder, from the pregnancy labeling group is back in the audience. Sandy, would you like to make any comments on this area, and then I would like to go back to the Division and see what the Division might have to say too.

DR. KWEDER: Good afternoon. One of the things that we are in the process of is trying to revise the regulations for how drugs are labeled for use in pregnancy and lactation. One of our goals in that is to try and frame risk information. What I mean by that is try to include in labeling any information that would be relevant to take into account when considering the risk to the extent possible. In the version that we are working on of a new regulation, one of the things that we will be

asking companies to do in labeling is, to the extent possible, to include some information about the risk of the illness in pregnancy, of not treating the illness in pregnancy.

We have done this in several cases already. Even though we are quite a while away from a new regulation, we have been trying to incorporate that to the extent we can. A couple of examples where we have done it have been in drugs to treat and prevent malaria. Because the risk of malaria in pregnancy to the mother and fetus is extremely high and grave, we have incorporated that juxtaposed to any risk information. We have done it recently for some asthma medications. The risk of untreated asthma in pregnancy is discussed.

So, nothing is perfect and, you know, the unfortunate thing is sometimes we don't have data, although in this case I think there are some and it certainly could be done. One of the things that we know about this section of the label, unlike most, is that doctors read it. It is also often the only thing that they read and take into account when

considering whether to prescribe a medicine in pregnancy. We also know that patients read this section of the label. Pregnant women are a population that is very savvy and they look stuff up. One of the first things they find when they look things up when they are pregnant is the label.

So, even though the information, as you said, is for the prescriber, and the label itself is not necessarily the tool through which to communicate information to the patient, we have to take into account that they will read it and we need to take care in how we frame things in the label because it is likely to reach both prescriber and patient. Is that what you were looking for, Dianne?

DR. D. MURPHY: Yes. I think we always have to deal with that balance. Bob, did you want to say anything more about where the Division is?

DR. LEVIN: Sure. Dr. Nelson, I think one thing you are suggesting, and if this is the case I agree, is that the labeling currently doesn't address the risk/benefit as fully as one might like

and focuses more, obviously, on potential adverse events than it does on potential benefits of treatment.

Also, in general my sense is--at least in our Division we talk about this--that in labeling we try to stay away from micro-managing, dictating or strongly suggesting treatment. Even though in some cases we do, obviously, in dose administration, my sense is that people try to stay away from giving real definitive recommendations on exact treatment. So, it might relate to what you are saying. But I agree that it would be ideal to have something in the labeling that more carefully details the risks and benefits of treatment or not treating.

DR. CHESNEY: I think what we have heard from Dr. Kweder is that the agency already has experience in terms of putting information into label situations in which there is a very high risk to both the mother and the infant of doing one thing or another. So, they have had that kind of experience and we would assume it would be carried

over into this area. Dr. Wisner, you had your hand up?

DR. WISNER: I guess the way I think about this is the way that was mentioned, which is what do we want people to do? And, what we want them to do is recognize that things that happen to neonates born when moms take these drugs have to be considered in the context of that risk/benefit decision, which is more of an education issue.

The thing that makes me a little uneasy is that what to do is so unclear. I make the choice to offer the option to taper but as a researcher I sit here and say but I am cleaning my data about the outcomes for the babies about whether that intervention actually works, and I am cleaning the data about depression scores in the moms. So, I would like to have more to say to them, other than be aware.

Just as an aside, when Solomon called me about this and Sandy too, I actually put on a couple of graduate students to clean that data because I understand now the importance of getting

it out into the literature. But it seems to me I would like to have more meat in terms of telling them what to do once I get to the risk/benefit decision.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: Just a follow-up comment on the labeling experience that you have already had, I am thinking of it from the sponsor's point of view, and it is pretty clear that if you have malaria, in fact, listing the risks of untreated malaria drives individuals to realize the importance of getting treatment. That is very different than sharing the ambiguity about something that is so extensive in the population that you are then on it when you get pregnant and, in fact, given the variability in the diagnosis of depression, in many ways what you are trying to do is encourage people not to take the medication. So, I could imagine the discussion around the label would be framed very differently in depression than it would be perhaps in malaria and the other conditions. It sounds like you are going in the

direction that I encourage, but whether or not you would get there in this case, based on the other ones, I think is an open question.

DR. D. MURPHY: Bob will have to help us carry the message back.

DR. CHESNEY: Another consultant, along with Dr. Gorman, for Dr. Wisner. I think what we are all groping with is what you just mentioned, which is that we don't know what these manifestations represent and, therefore, we don't really know what to do about it, and I don't know that we can--in fact, I am sure can't solve that today, but I think what the FDA is asking us is what level of anxiety should we have, should they have in terms of how to at least let people know that this is a recognized phenomenon, even if we are not exactly sure what to do about it--if that is correct, I think that is where you wanted the focus to be.

Any comments about that? Do we want to go to the equivalent of a public health advisory or just let the process of label change move ahead, or

something in between? Dr. Hudak?

DR. HUDAK: Well, again, I struggle with exactly what all this information means for the baby. I mean, what we have heard so far I think is that some subset of babies have what appears to be a transient period of symptoms. We have no idea whether or not there are later-term persistent effects, and studies certainly need to be done on that.

I would say that even if you do get studies at two years of age that show that there is not an apparent effect, that doesn't guarantee that there is not an important long-term effect because in babies what we have been finding out is that we often have neurodevelopmental follow-up at a year or two years of age where it shows no difference between the two groups, whatever they are, but by the time you get to school age and look at function there are very significant things that are present that impact how those children can be taught.

I think here it is very difficult, without any data, to sort of have a huge public health

advisory. On the other hand, I would say that the information--I mean, this is relatively new and I don't think widely available information to target obstetricians and family practitioners who deliver mothers and those professionals that take care of newborns should know.

One of the important things--this is a trivial thing but one of the important things is you would think that a pediatrician who took care of a baby whose mother was treated with one of these drugs would know that the mother was treated with one of these drugs, but I will guarantee you that that doesn't happen. That is a shocking thing but in the hospital environment we have been working for years with medical record systems and obstetricians, and so forth, to let us know a simple thing, that is, is the mother Group E strep positive and, if so, did she get antibiotics and how long before she delivered did she get them because it impacts how we evaluate that baby and take care of that baby. And, we have just gotten to the point where we are successful but we do not

get prenatals; we do not get any information in the neonatal record in the hospital as to what medications the mother is on necessarily. That may be known but it is not available easily to the people taking care of the babies. I imagine in the office setting, Dr. Gorman, when you see a baby for the first time that information is even more closeted.

So, I think that one of the things in the advisory needs to be communication, that if mothers are on treatment for these things, rather than making it, you know, something that should be hidden, it should be something that is accessible and made known to the people who are taking care of the infants.

DR. CHESNEY: Can I ask a very pointed question? What is the downside of a public health advisory? I wonder if an upside wouldn't be in alerting everybody that this is a concern and much more research is needed. Would that, thereby, stimulate granting agencies to recognize that this is a very pronounced problem at this point in time

that we need to address? Would that be an upside? What are some recent examples that we could perhaps compare this to? If we have to come down on some side or another, I guess I would come down on that just to get the discussion started. What are the pros and cons of a public health advisory for something like this?

DR. D. MURPHY: We had all this at one time. For the health advisory I think in this situation the positive would be, yes, you would get it out to a large number of people. But the very potential downside is exactly what the committee has been discussing, which is what are we telling you to do? Not that we tell you at FDA what the practice of medicine is. That is not it. But do we have enough data to even tell you anything beyond the fact that this occurs?

Now, one could argue that that is a sufficient message but if you send out too many messages you lose the effect of the messages. So, I think that saying, very well articulated, this is what we know about it, you know, we know that it

occurs in certain situations; we can tell you what these are. From the FDA's point of view, it is, again, informing the physician who is prescribing this medicine so it is back to Dr. Nelson's point. You know, what else can we tell you about how to prescribe it or not prescribe it? That needs to be really put into some sort of context.

So, I think if you are going to do the advisory you have to be able to come up with a context that would allow people to make those risk/benefit assessments. I mean, has it always been true for every one of our advisories? No. As you know from some of our early SSRIs, we were criticized for some of the advice we gave there, which was just be aware. But we though it was important enough, there was enough concern that we went out--you know, we are still struggling with how much information we don't have but we thought it was important to get it out.

So, that is sort of what we are asking the committee. With this limited information should we do any of these other things at this time? Sandy

has worked at a lot of these with us.

DR. KWEDER: Good afternoon again. Yes, we have done a number of these and we try to be judicious in selecting simply because you can only do so many of these before people stop listening. Also, when we do issue them, usually it is because there is something that people can do. Some of the more recent ones that come to mind are risks of a particular drug that are new and that are potentially serious and immediate that would require stopping a medicine. Or, we have done them when a drug is being withdrawn from the market and we expect that clinicians need to know right away that there is a serious safety issue.

In the few cases where we have issued them when there is not something like that, as someone who takes a lot of the press calls, people are very confused when we don't have "and, therefore, you should do this." Both the professional groups and the lay public don't really understand why we do that. So, these things do have their pros and cons.

One of the things that we have learned is that it is very frustrating for practicing clinicians and professional groups when a public health advisory comes out and they aren't aware of the data. They understand it when it is something that is really critical with, you know, a major public health issue that is immediate but when there are nuances and there are data behind it that may be complicated they are frustrated when FDA comes out with something and they haven't had an opportunity to digest the data that underlie it and prepare themselves in their practice for what may end up being a deluge.

DR. CHESNEY: Just for the sake of argument, I was interested in the materials and the one thing that can be done is to observe these infants for a longer period of time for some of these findings. They said, for example, now with discharge within 24-48 hours maybe these infants need to be observed for a longer period of time. I realize that is trivial compared with what we would like to tell them to do but, again, just for the

sake or argument, there is something that could be done which is watch for these children because you might see some difficulty eating or all these different things. Dr. Hudak?

DR. HUDAK: No, I think that is a good point and that is why it is necessary for the physicians who treat the baby to know those things. The good news is that the trend is in the opposite direction now, that mothers are staying not 24 hours but more like 48 minimum, which is a good thing. The other thing that this would do is that even if the baby is okay at 48 hours, it would encourage the baby to be seen in early follow-up which would mean one or two days after discharge rather than two weeks, which is typical in many practices, especially the non-nursed baby.

DR. CHESNEY: I am going to stop talking right after this, but if we go back one step--professional education, I feel like that is a given. We have to do that through a whole variety of different societies and so on. But our next alternative is the "dear healthcare professional"

letter which is the sponsor's responsibility. And, I will stop talking and get some other input. Dr. Gorman?

DR. GORMAN: I think one of those has already arrived in my mail box. Being the good doctor that I am, I haven't read it yet. It is sitting on the pile of unopened mail but it does say a large pharmaceutical company and it says "open immediately, dear doctor" letter. So, there may be one of those already out there.

I am going to take the side of the obstetricians and psychiatrists for a moment and say that we are talking about a neonatal withdrawal syndrome but this decision has the potential for major negative impact on the mother. In the present state of information where we have what we presume to be an acute withdrawal phenomenon, I think the label is adequate as it is because if we try to change practice for obstetricians and psychiatrists that have negative adverse events on the moms when we have just an acute withdrawal syndrome for babies, pediatricians and

neonatologists should be able to handle an acute withdrawal syndrome.

Having said that, my background and my spotty career or checkered career or mosaic career, depending on which way you want to think about it, is lead. Lead is how I got interested in this whole field and there is an area where there is obviously an initial incident and then a long-term devastating neurological outcome. Like lead, this is so commonplace today, if 10 percent of pregnant women are going to be on these medications we will have a really hard time teasing this out if it doesn't get teased out earlier, meaning in 2004, '05 or '06 rather than in 2024 or '25 or '26.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I have a question but it would help me then frame how you would target the professional education. There are two options. I would assume that most of the overlap between depression and pregnancy are women who are on antidepressants becoming pregnant, as opposed to pregnant women getting depressed.

DR. WISNER: That is probably true but there are, in fact, many women who have a first episode of depression in pregnancy. So, there are both subgroups.

DR. NELSON: And if they have that in pregnancy, are there differences in terms of response to antidepressants?

DR. WISNER: It has never been studied systematically but from our long-term experience, no. Differences in side effects but not efficacy.

DR. NELSON: Because depending, I guess, on which approach you take when thinking about it, I mean, I am not sure I would advocate a "dear health professional" letter because if I got it, I mean, I would kind of look at it and say okay. But, you know, what would you say to someone who is prescribing antidepressants when they would counsel a woman, should she be thinking about becoming pregnant as one set of questions, and then what to do if she becomes pregnant. And then a whole other set of questions is then depression during pregnancy and the kinds of decision-making that

would be different and would be approached differently and would be complex in short-term/long-term issues.

So, I think, by default, you would end up in the third because the healthcare professional letter which a sponsor sends out I can't imagine could go into the kind of detail that you would need to tease out those issues, in particular since most of them would end up on the second page and people wouldn't read past the first paragraph or two. So, I think by default you end up in three. So, the question is, is there a way you can stimulate the third in a way that is productive?

My own bias is that I think a public health advisory--it doesn't sound like there is enough concrete information to where sending that out wouldn't send up an alarm and everybody says, well, what do I do about it? And, the answer is we don't know. That would strike me as crying wolf in a way that would undercut that process.

DR. CHESNEY: I hear what you are saying. On the other hand, SSRIs are such a hot button item

now. Other comments? Dr. O'Fallon?

DR. O'FALLON: We really have two patients here. We have the mother and we have the babe. We don't really know at this point how damaging this toxicity or withdrawal is. We truly don't have the data. So, this may be a horrible problem about to explode, I mean, down the line five years from now or it may not.

DR. WISNER: There are long-term follow-up studies of kids that have been exposed during pregnancy, particularly to fluoxetine and the tricyclics. By and large, the development, at least on fairly global but standard measures, has been indistinguishable between the groups. So, I don't think we are looking at something that is going to blow up and be very bad down the line at least on those major impacts. There is still a dis-ease about some more subtle, perhaps those neurobehavioral things that we are talking about, but I don't honestly think it is a major horrible thing.

DR. CHESNEY: I think that is critical

information. I don't believe I knew that. So, there have been extensive long-term follow-up studies of infants exposed to SSRIs in utero and those children are now without clear complication or problem?

DR. WISNER: That is correct.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: The point here is we have all been talking about giving the information out to the doctors and, you know, it is important. But you also have to give it to the mother. I mean, the mothers have to have this information given to them the best that they can have. You know, I don't know what our options are but that letter to the patient we saw earlier today, maybe something along those lines, or maybe the FDA could have a pregnancy website where they could keep the latest information about issues pertinent to pregnancy so if a woman gets pregnant and wants to do her homework she could go look up as much information and possibly that would at least help her. Because if she is depending on one of these doctors that is

so busy, and I understand because I work with them, they have never read it. They never read that advisory and she is not going to get the information either. There should be a way to get that information to the public directly.

DR. D. MURPHY: When you say patient letter, you are talking about the patient insert that we are proposing for the label?

DR. O'FALLON: Right.

DR. D. MURPHY: That would say in more detail to the mother about depression and treatment and just making her aware of the fact that this a risk. We know that there is a risk to the infant; we can say that as far as acute, manageable toxicity or adverse event. The question I think we are struggling with is--and that may be fine but then is there anything else to say? At this point I am hearing even though the Division is proposing that we have in there that your physician may want to taper your medication, we would then have to actually frame that in a way that would be more balanced about the limitations of information.

DR. O'FALLON: That is right.

DR. D. MURPHY: I mean, the point of a patient letter is that it gives you the ability to say more to balance it instead of just saying we don't know. There is that opportunity.

DR. O'FALLON: And like she just said, if they have some information--it may not be the highest quality because it may be voluntary information and all that, but if there is something there that says, "hey, look, we haven't seen all these long-term things" the mother could say, "well, you know, it won't be so awful for my baby if I stay on my medication"--that type of thing. Give them the information so that they can make an informed decision like he was talking about in terms of an informed consent.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: I agree very much with what you just said, but what I worry about is exactly what I saw in a case recently. I did a consultation on a patient who was very pregnant, who came in because she said, "you know, I went on

the web and I saw all this terrible stuff that happens to newborns if the mom is taking an antidepressant so I stopped my drug a month ago because what if I deliver early and maybe my baby will get those terrible things?" We had to hospitalize her because she was really quite depressed and suicidal and she went into labor, delivered and had to be transferred down to the maternity hospital. I have no question that all of that was way worse than to continue the drug.

So, if the information is in a context in which she is helped to value the traces, that makes sense, but delivered, you know, in a situation where, in fact, her treating physician wasn't very aware of the issues and she didn't have a lot of confidence, I just worry about the meta-message. When this organization says something it can pack a big wallop and that meta-message may lead to more negative outcomes than we hope, or the kind of negative outcomes that we don't want to happen.

DR. O'FALLON: But maybe they are going to go look at the website where it doesn't have any of

the nuances in it. So, I am suggesting that the FDA try to create a balanced message and point to the different issues so that they would have a halfway chance of knowing what they are doing.

DR. WISNER: Except that my point was somewhat different. That is, if it is an FDA message there is a meta-message that is separate from what the content says that packs a bigger wallop even if it is tempered. That was more my point.

DR. D. MURPHY: If FDA sends out a public health advisory, you are right, there is a big meta-message and you have to read a lot to be able to overcome that meta-message, which is the point of not sending out a whole lot of them because we want you to pay attention when we send them out, versus the other proposal I am hearing. I am just trying to make sure I am getting your perspective on this, versus the patient insert, which is another way "FDA says..." Are you still concerned about that meta-message that we would have a patient insert that went through this issue of

mothers on antidepressants and that there are these syndromes, but we don't know what the long-term effects are? We have some evidence at least in certain situations that there aren't that we know of at this point or have been able to identify, and that this is a decision you need to balance against the importance of maintaining your health during this process. I mean, you are concerned that even for the additional--because something is going to go in the label because we have this information and we have to tell people.

I think what is being brought forth is that there is a concern that that alone may not be balanced enough, and is there another way to balance it without making it worse, and is the patient insert that way versus--I think I am hearing we don't want to send out an FDA notice but is there another way?

DR. CHESNEY: What I am hearing are three things. One is that there will be a label change. The second is that we should educate. I think that is a given. Then, the third, which is the issue

now is whether, Dr. Wisner, you have concerns that just by putting in a patient insert or an enhanced patient insert would frighten women, without any black boxes or anything, just a more informational patient insert?

DR. WISNER: Actually, I was responding more and I think agreeing with the negative feelings about the advisory as a major message. You know, I guess as you were talking what I kept thinking about is what was raised before, that women will find out about this if they are industrious anyway, and if we take the meta-message liability away, which I think would happen with the advisory, and it is a balanced presentation, that sounds more reasonable because at least it is a trusted source. If the directive is to say here is information we think you need as you consider your choices, that makes sense to me.

DR. CHESNEY: In the interest of moving on because we still have another question, is there anybody on the committee that would not agree with an enriched patient insert, enhanced education of

physicians and then the label change that is in process? Does everybody agree to that? Dr. Gorman?

DR. GORMAN: The only part of the enhanced label that I saw was in the dosing and administration and I still have reservations about where it prescribes a course of action for physicians which is to taper these doses. I think that is a leap of faith that we don't have information for.

It says when treating a pregnant woman with these drugs carefully consider potential risk and benefit. Then, physicians may consider altering or revising or rethinking these treatments during pregnancy as information becomes available that will give the physician alternatives. The only alternative they put in here is tapering and then it gets that imprimatur of that is the way to go. I don't think we have any data to say that that is the way to go. That is the only reservation I have about the proposed label change.

DR. CHESNEY: Thank you. Dr. Iyasu, do

you want to give us question number three?

DR. IYASU: The second question deals with research. I will just read it. BPCA does not provide a mechanism for issuing a written request to study drug therapies for pregnant women. There are no population-based estimates of SSRI or SNRI exposure data in pregnant women and there are no systematically collected data on neonatal outcomes in infants exposed to these drugs. Furthermore, determining causality for neonatal reactions is challenging as the role of drug discontinuation, direct toxicity (example serotonin syndrome) and/or other drug/substance exposure during pregnancy is often unclear.

Is there a need for further research to evaluate and characterize the neonatal effects of in utero exposure to SSRI/SNRIs? If your answer is yes, in your discussion of research options, please discuss feasibility and potential sponsors for each option. I think you have answered the first question already.

DR. CHESNEY: Does anybody feel that we

know everything that we need to know?

[Laughter]

Thank you. Moving on then?

DR. IYASU: Here are the options that we have for you for discussion, and think about feasibility and potential sponsors from these approaches.

DR. CHESNEY: And we are always interested in more options.

DR. IYASU: The first option is to continue evaluating/monitoring postmarketing adverse event reports, like what we do with the Office of Drug Safety.

Conduct some population-based prospective study of pregnancy exposed to antidepressants and assess neonatal outcomes.

Another option is to conduct a retrospective study of neonatal withdrawal syndrome or serotonin toxicity.

The last option is conducting a randomized, controlled trial of treatment of maternal depression. As a subpart to this

question, if yes, what research questions should be addressed by the trial?

DR. CHESNEY: Probably we can already x-out the first option because you will continue to monitor postmarketing adverse events.

DR. D. MURPHY: I think one of the things that that was meant to try to say is that there is a difference between the routine monitoring or saying we are going to follow up, and we want to make sure that when we tell you that we are just going to do routine monitoring that means that we are going to then be bringing it back again. Of course, like many of the things today we really didn't think we needed to bring back to you but this is really that question in a way, do you want us to just to continue versus just have the routine path of reporting process?

DR. CHESNEY: I understand. In other words, with an emphasis on further research, are we content with that or do we want you to continue to look at this internally and bring us additional feedback each meeting?

DR. D. MURPHY: It could be simply that we will continue to look at it a year from now and if we don't see anything we won't come back to you if we don't have any new information, but clearly if we did, we would. I mean, you would be putting this as a task for us, meaning Pediatrics, to follow-up with you versus we are not following up. If we report to you 1-year post-exclusivity and there is nothing there, we do no longer follow-up with you.

DR. CHESNEY: It is a form of ongoing research for you all, if you will, and you are not required to do that; we would be asking you to do that. Comments? Dr. Nelson?

DR. NELSON: I guess I have three. The first is that I would be interested in Sam's comments on whether a registry requirement for industry for women who become pregnant or are pregnant and they get placed on the medications, whether that would facilitate data collection and also meet some of the problems behind the voluntary system of adverse events.

The second two I think would be fine, although I would modify the retrospective and talk about case control, and I would advocate that something like that ought to be NIH funded as opposed to industry funded.

The reason for that is that I get nervous, particularly when I look at number four and think about the impact of an industry-sponsored trial--which I presume you could only get them to do if there was money on the table to be earned by doing it--in a setting where there is under-funding of basic care for mental health and the potential for undue influence on women even going into the trial, and the complexities of even designing an ethical trial under those circumstances. I think it could be done but I would prefer it then to be done without the sort of recruitment drive that industry-funded research creates even if that recruitment is carried out appropriately. I mean, mental health is so under-funded the undue influence to then go into that trial, even if their own risk assessment independently might not to be

on antidepressants, I think could be potentially large.

DR. CHESNEY: Thank you.

DR. MALDONADO: I think actually the FDA has experience with registries. When I was at the agency in antivirals we asked companies to do that and I remember that one of the first registries was for acyclovir in pregnancy and also AZT. Unfortunately, those registries--please correct me if I am wrong--never yielded any of the goals that they were created for. I am sure that Sandy knows that very well. So, basically, over the years they have not been very good at giving data. They basically give extemporaneous reports to an 800 number by clinicians or by women exposed and they didn't yield the results that we wanted.

DR. CHESNEY: Thank you. Dr. Cragan?

DR. CRAGAN: I have actually been on the scientific advisory committees of four of those registries that are sponsored by industry. They are very similar in methods but the usual one is that the outcomes are obtained. There is active

attempt to contact whoever reported the pregnancy originally to the registry, and most of the times that is the obstetrician; occasionally it is a pharmacist or a neurologist or some other specialist. They are contacted to find out the outcome of the infant. So, it is somewhat whatever the obstetrician knows about the outcome or if they take the extra step to contact the pediatrician and find out.

But I think in this kind of behavioral type of symptoms, withdrawal versus toxicity and such, you really need to get to hard, objective data by the person who is caring for the child and not just the first day in a delivery room. So, that method I think is not well suited for this type of outcome.

Now, there is one registry, the anti-epileptic registry, that is multiple company sponsored and they give a grant to someone in a university setting who actually administered the registry, and the mother enrolls herself and they get informed consent to contact the pediatrician

and attempt to get copies of hospital records, and such. So, it is possible; there is one registry that does that better but I think this kind of outcome is not well suited to that design in general.

DR. CHESNEY: Could you comment on what design would be good, specifically with respect to bullet number two?

DR. CRAGAN: What comes to mind is the National Children's Study which is a population-based enrollment, a longitudinal study of children and they do have work group on drugs and they have a group on newborn outcomes I think. I would make sure that these kinds of issues will be covered in what they are addressing. I think they will be automatically but presumably SSRIs and antidepressants in general are a common enough exposure in the population that you really may be able to get some good data from that.

The other things that come to mind that have an existing structure that you might be able to tap on--one is the teratology information

services, the one in California particularly that Christina Chambers heads or is part of. They are set up to interview mothers about exposures. They have several studies where they follow infants out to a year. They have physicians who travel around in California to examine infants. I think with some funding and some support they would probably be able to take that on for a longer term. It depends on how many you have.

Our division funds a number of state-based population-based birth defect surveillance programs and those are geared toward malformations. But some of those, the ones in California, the one in Texas, do have abstractors that go out to hospitals and look for abstract information about children with specific conditions. Again, with some extra support or funding some of those might be able to broaden those to look for symptoms noted in the newborn that then could be followed up to look for exposure. Those are the thoughts that come to mind.

DR. CHESNEY: Other suggestions or

comments? Dr. O'Fallon?

DR. O'FALLON: You know, I think that retrospective studies are the ones that can get done the fastest and probably provide the most bang for the buck, at the beginning anyway. But the problem with them is they do depend on data that was or was not recorded so you have interesting biases that show up, but they still are the greatest bang for the buck and, at least in the beginning, give us some information. It would probably have to be validated through something like a prospective study forward in time if it looks like there is something going on.

DR. CHESNEY: I was struck in reading the articles and here today that we don't really know what we are looking for in the newborn. I mean, there may be two totally different syndromes, one being the behavioral teratogenicity and the other being the toxicity/withdrawal. We don't even have good definitions for what we are looking for if we were to go retrospective. I just kept thinking this would be so perfect for somebody that, you

know, would actually get in and examine the infants and develop some kind of scale for evaluation. Dr. Gorman, I think you had your hand up.

DR. GORMAN: After listening to the AERS disclaimer for the last three years, it strikes me that the process we follow for identifying off-label drugs for study at NIH might be a useful analogy to start looking at for AERS signals that are picked up. They get a signal in AERS. It says there may be a toxicity that has previously been unrecognized. You use some group to rank them in terms of their significance and find a way through NIH to fund them through whatever mechanism. It struck me as incredibly serendipitous that there is an RO1 trial going on today that is trying to answer the question that we are being faced with. I would like to make that less serendipitous.

DR. CHESNEY: Dr. Luban?

DR. LUBAN: There certainly are two NIH-sponsored groups that look into pharmacologic trials that PBRUs, and certainly the neonatal network, which is Maternal and Child Health-funded,

is another resource. It almost seems like you need to get all these people to sit down in one room together and talk to one another. I would imagine that between that you could get the measurements that I would be most interested in looking at because the PBRUs have very extensive drug testing methodologies available to them and the neonatal network certainly has a broad base of diffuse neonates from different socioeconomic groups that are from across the United States.

DR. CHESNEY: Maybe I could hazard a response to your first bullet. I partly feel like you have done your job and we don't see you as a research agency. On the other hand, given that it may take some time for some of these other programs to get up and running, and hopefully they will fairly quickly, maybe it would be useful for us to have this on the agenda for a year to have you come back and say here is what we have found since last year and, again, I just put that on the table for others on the committee to comment on. Dr. Nelson, you always have a comment to my comments.

DR. NELSON: Well, I was thinking that the data look like it needed to be updated. If I recall, it was 2001 cleaned and then 2001 to 2004 uncleaned. So, at the very least, an update of the 2004 data cleaned would probably make sense. So, I guess I am in agreement that that might be a useful thing to do and then present.

DR. CHESNEY: Thank you. We agree on that. Does anybody disagree with that?

[No response]

That is number one. Number two, population-based prospective studies, I think we all feel that that is absolutely important and essential through whatever mechanism we can come up with.

Retrospective studies--there are some out there now. They have alerted us to the problem. I don't know how much more information they could give us because we don't know what to look for now, let alone what to look for retrospectively. I am just free-associating and then I will let other people comment.

A randomized, controlled trial of treatment of maternal depression and what research questions should be addressed--that is much more difficult. Dr. Wisner?

DR. WISNER: If what you mean is a drug-placebo, controlled study during pregnancy, it wouldn't be funded by NIH. One of the possibilities is a drug-other treatment control, and there are investigators who have tried to compare drug treatment versus psychotherapy and have submitted such studies but for a whole number of methodological and ethical reasons they have not been funded by NIMH.

What we are doing is a study of light therapy. We have done two pilot studies and hope to present enough evidence that it is an effective treatment to do a light therapy versus drug treatment when then could potentially give us the chance to look at drug versus another active treatment on the kinds of neonatal outcomes that we have been talking about today.

DR. CHESNEY: What do we know about

neonatal outcomes of women who had severe depression before we had effective drugs? Do we know anything about those neonates? How they behaved?

DR. WISNER: Other than being described as irritable and difficult to console--you mean longer-term outcomes?

DR. CHESNEY: No, just the immediate, just the effects of the maternal depression without any therapy. They were irritable, difficult to console?

DR. WISNER: Yes, and can have long-term growth and certainly socioemotional difficulties. In Lynne Singer's data set in which she looked at women who had abused various substances in pregnancy, the motor and more physical effects on kids long term could be related to drug use, but the socioemotional development was pretty highly correlated with maternal depression score, which is kind of interesting. The effects on development are pretty devastating.

DR. CHESNEY: Fascinating. What research

question should be addressed by the trial? Shall we continue to pursue that part of bullet number four?

DR. D. MURPHY: I think we have enough here to work with.

DR. CHESNEY: I am hearing no's all around me. I hope you could hear that. Thank you, everybody for getting us through all of that. I think, unless Tom is signaling me something else, we need to move on now to Dr. Iyasu's presentation on an update on congenital eye malformations in infants.

Update on Congenital Eye Malformations in Infants

DR. IYASU: Good afternoon again. This will not take a very long time and you have the break after that.

I am going to discuss congenital eye malformations reported through AERS with the maternal use of antidepressants during pregnancy. First I would like to acknowledge Kate Phelan from the Office of Drug Safety for performing the primary review of adverse event reports. I think

Kate is still here.

To provide you with some background, during the February, 2003 meeting of this committee we reported a case report of a potential eye malformation related to the use of citalopram during pregnancy. Namely, it was a patient with ptosis, eye muscle paresis and nystagmus. At that time an expanded review of citalopram and several other antidepressants for potential reports of eye malformations were under review. The review has been completed and today's talk is an update of congenital eye malformations for citalopram and its enantiomer, escitalopram and several other newer antidepressants.

In March, 2002 the WHO Upsala Monitoring Center of Drug Safety published three possible reports of congenital eye malformations with the use of citalopram during pregnancy. Two of these reports were congenital optic nerve hypoplasia. Both were from Sweden. The third was a report of a non-specific eye malformation from Great Britain. All were exposed to citalopram during the first

trimester. The publication of this report triggered an FDA review of the AERS database.

First I will just give you some background again about this drug. I will discuss relevant labeling for the drug products included in this current review. Citalopram is labeled as a pregnancy category C drug. In rat embryo or fetal development studies teratogenic effects have been reported at maternally toxic doses, and this included decreased embryo or fetal growth, decreased survival and increased incidence of cardiovascular/skeletal defects. However, this did not include any teratogenic effects on the eye.

Fluoxetine, flovoxamine, paroxetine, sertraline and venlafaxine are labeled as pregnancy category C drugs. No teratogenic effects have been seen with these drugs, except decreased pup survival in rats. Like all antidepressants, the label also recommends use of these drug products during pregnancy only if the benefit outweighs the risk to the fetus.

The other drug that was reviewed was

bupropion which is labeled as a pregnancy category B drug. No teratogenic effects in rat studies have been reported.

The last medication is desipramine which has no pregnancy category on the label but does carry a warning about use in pregnancy, like antidepressants, and reproductive studies are reported to be inconclusive.

Now on to the search strategy of the AERS database, the Office of Drug Safety searched the AERS database for reports of "eye disorders, congenital" in relation to citalopram, escitalopram and the other drugs that I mentioned before.

The AERS search results for citalopram revealed that there were 5 unduplicated pediatric eye malformations. One was a U.S. case; 4 were international reports. Only one congenital optic nerve hypoplasia, reported in the WHO bulletin, was found in the AERS database. There were no adverse event reports for escitalopram.

Of the 5 reports that are in the AERS

database, one was a congenital optic nerve hypoplasia and there were other medications also used concomitantly during pregnancy, cefuroxime and nitrofurantoin for urinary tract infection about the fifth month of pregnancy.

The second case was a non-specific eye malformation, also with multiple medications were used concomitantly during pregnancy.

The third case is the one we reported last February, which was a congenital ptosis and nystagmus. The report does not indicate any concomitant medication use.

The fourth case is bilateral retinal coloboma, right hydronephrosis, respiratory distress syndrome with collapsed lung. There were no other medications except multivitamins.

The last case was downward deviation of gaze without paralysis. In the case report there were no concomitant medications. No other neurologic or increase in pressure was noted in this patient.

Looking at the other search results, for

bupropion there were 2 cases, one with lacrimal duct obstruction and another case of eyelid malformation. Fluoxetine had 2 cases, optic nerve anomaly and congenital lacrimal passage anomaly. For paroxetine there were 2 reports, retinopathy and congenital cataract. For Sertraline there were 3 reports. One was an eye deformity which was non-specific; an anomaly of the orbit; and then lacrimal passage anomaly. Desipramine, fluvoxamine and venlafaxine did not reveal any case reports.

In conclusion, these adverse event reports were reviewed extensively by the Office of Drug Safety and also by the review division, as well as the ophthalmology group at FDA. The conclusion is that the report of congenital eye malformations does not constitute a recognizable pattern that could be attributed to the use of citalopram or any of the other antidepressants during pregnancy. There were too few cases to make any significant attribution or association with its use during pregnancy, and there were also several concomitant medications.

Therefore, we will continue, as was mentioned before, with monitoring of the AERS for any additional cases of eye malformations with these medications.

DR. CHESNEY: Thank you. Any technical questions for Dr. Iyasu?

[No response]

Open Public Hearing

Thank you very much. We do have one speaker for the open public hearing today and I do have something I have to read before that. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you

may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our speaker is Dr. Philip Sandy Zeskind, who has provided us with a set of his slides in our packet. Also, Tom tells me, one of his papers is in the blue book material we received before coming to the meeting. Dr. Zeskind?

DR. ZESKIND: Thank you very much. While Tom is coming up to rescue me, I am not funded by any drug companies. There is no conflict of interest there. In my role as director of neurodevelopmental research in my hospital, they

are supporting my transportation here.

I have a series of comments and I am going to try and whip through this pretty quickly. After hearing the discussion, some of the issues that are embedded in this presentation directly address some of the questions that you are asking about what kinds of questions should be asked and what kinds of research methods should be done.

This is in reference to an article that I published in the journal Pediatrics in February of 2004. I will whip through the stuff that is obvious, that there is a lot of depression. Depression in and of itself, as Dr. Wisner said, does have debilitating effects. Serotonin is a neurotransmitter that is going to affect development. In my view, it is not whether it affects development but how much and in what ways. That, to me, is a given as someone who studies prenatal development.

Unfortunately, the way these questions have been answered in the past is by using measures such as birth weight, gestational age and physical

anomalies. Quite honestly, in my view, these are the measures that Sparta used to see if a baby was healthy 3,000 years ago and I think that, as a field of research, we have moved on way beyond that yet we are not applying it to some of these important questions that we have in front of us today.

For the study that we did, the issues that are relevant for us, especially if you are talking about doing retrospective studies and big population-based studies--all infants in this study were full birth weight. Except for one infant, they were all full term, and no infants had any physical anomalies. There were absolutely no differences between the SSRI-exposed and the non-exposed infants. It is a small sample, yet it was an intensively studied sample. If anybody went back to the medical records on these infants, they would find "no effects of SSRI exposure." That is the bottom line.

What we found, through methods that are described in the paper, is quite a list of

neurobehavioral differences in the prenatal SSRI-exposed babies They showed incredible amounts of tremulousness that was not picked up by the attending physicians; increased startles or some call them arousals. There was also independent motor activity besides those. The whole sleep-state architecture of the infant was totally disrupted. We sat and we watched these babies sleep and recorded blinded measures of state regulation in a way that we have developed over 30 years and others have used as part of standard newborn exams. We measured increased REM sleep; rigid state organization and depressed range of states. Normal babies should get up and cry. These babies are functionally, physiologically, behaviorally depressed.

We have also worked out a way of spectrum analyzing the infants' heart rate variability to look at oscillations in the heart rate. What we found is that the oscillations in heart rate over time are totally messed up, just to put it colloquially. They are not rhythmic. The

parasympathetic and sympathetic nervous system is disrupted seriously.

Importantly, all these measures have been previously used to detect effects of prenatal drug exposure or differentiate high risk infants in the past. These are not new measures. They have been used to assess cocaine-exposed infants, cigarette-exposed infants, alcohol-exposed infants, prenatal malnutrition, etc. They are the same kinds of behaviors.

We also found, as far as neurodevelopmental effects, a lower gestational age by one week even within a full-term sample. Again, going back to medical records which can't use NICU admissions as a measure, yet, there was seemingly an effect on gestational age.

As far as whether these have effects on subsequent development, I want to address this because this came up and Dr. Wisner answered it very nicely, that is, the long-term studies of SSRI exposure have focused on the equivalent of using birth weight an physical anomalies of the newborn.

Doing standard IQ tests at 2 years of age is not a way of measuring long-term effects, and that is what has been used, standard IQ tests and language development tests. They will not detect effects of SSRI exposure. The cocaine literature, the cigarette smoking literature knows this already. They have moved on from that kind of analysis. Now what people look at is socioemotional regulation, how people handle emotional issues, regulation of arousal, those kinds of things.

I will say one more thing with that, the measures that we have found, these neurobehavioral measures in my own work and others' work have been predictive of subsequent differences in development. I don't think we can say that there aren't differences at this point. We still need, of course, better research to look at it directly.

I will say also that since I published that article I have received a plethora of letters, unsolicited emails and letters from parents saying, "my God, I'm glad someone finally said this because my baby, at 2 years of age, is having these motor

tremors and my doctor says it looks normal, but there's something not right about my child." I have a list of emails and letters from parents. Again, that is a biased sample, self-selected, however, we need to throw that into the hopper here.

I really enjoyed listening to the discussion. I don't know if we should just call this withdrawal syndrome. We heard whether this is serotonin toxicity. Serotonin is the precursor for synaptic development. I don't know how being bathed in extra serotonin for nine months during gestation would not have some kind of serious long-term detrimental effect. It just escapes me.

My conclusions are that what we have found is that prenatal exposure to SARIS during pregnancy disrupts neurobehavioral development. I think we have clear evidence of that. I don't think that birth weight, pre-term birth, NICU admission and physical anomalies are sufficient measures of the effects, and I think that if we continue to do that we will be missing the boat. Number three, there

may be neurotoxic effects; it may not just be withdrawal. I think number four is obvious.

In conclusion, I think when we were asking here what should we do about this, I think it is a question of balance. As Dr. Wisner said, depression during pregnancy is a serious problem in and of itself. For me, talking to the patients that I examine, SSRIs have been given out pretty much like M&Ms during pregnancy. I think it is a question of balance and concern. "Oh, you're feeling a little bit down? Here, have this," I do believe that characterizes some of the administration of this drug.

So, we don't want to throw the baby out with the bath water with this, but I don't think it is safe for us to conclude, well, don't worry; it is only a transient effect. It is only withdrawal. The baby will get over it or there are no effects because the baby is full birth weight and full term. I will stop there and thank you very much.

DR. CHESNEY: Thank you very much. We really appreciate your perspective of many years of

having looked at this very issue that, obviously, many of us are coming at from a much less detailed background. So, we really appreciate your input. Are there any questions of Dr. Zeskind? Dr. Gorman and then Dr. Wisner.

DR. GORMAN: SSRIs have now been out in the population for ten years. I assume pregnant women start taking them whether they know they are pregnant or not near the beginning. What epidemic are we seeing today, in your opinion, that has been predicated on this use? And, it doesn't have to be an epidemic of such, you know, is this why all the patients in my practice use Game Boys--

[Laughter]

DR. ZESKIND: You joke--

DR. GORMAN: I am not joking.

DR. ZESKIND: We are talking about emotional regulation. You know, one of the long-term effects, now that we know about prenatal cigarette exposure for example, is some very nice research that shows it is attention deficit. Where did that come from? I don't know what the epidemic

is, but I do know, as you said and it is not an exaggeration; I run a child clinic at my hospital and there are a lot of children with regulation disorders that are associated with things that moms take during pregnancy, including subclinical effects of alcohol, cigarettes, SSRIs. I think we have a lot of children. Where is all the depression coming from that makes the headlines of Newsweek magazine for bipolar disorder? We are creating children that just, by the amount of it, appear as "normal" in a statistical sense.

That is the best answer I can give and I think it is a very good question. But I don't think if we give the kid IQ tests and they appear normal, then we should conclude there is no effect on develop.

DR. CHESNEY: Dr. Wisner?

DR. WISNER: Sandy, I wonder in your application of the wonderful measures you have developed, you have looked at the SSRI cases but, as I recall, you have a parallel literature on the effects of depression as well. Right? I mean,

moms who are depressed give birth independent of SSRIs. Is there a difference on those outcomes?

DR. ZESKIND: That is a great question, Kathy. From my clinical experience, the effects of depression are different than the effects of SSRI exposure. The study would have, of course, benefited greatly by having an untreated depressed group. I mean, that is obviously the next question that needs to be answered so I know the limitation of the study in that sense. But these do not look like infants of depressed moms; they look like a different kind of issue.

DR. WISNER: And just to add to that, Sandy has a wonderful cry analytic procedure that is being done with RR1 so that at birth and 2 weeks the cries of all kids in those groups will go to Sandy for analysis.

DR. ZESKIND: What we do with that is we spectrum analyze the cries. This is something we have been developing over 30 years. By spectrum analyzing the cry and looking at the 4-minute frequencies you can actually tell if there is a

problem with the brain stem. I am very sure, based on some of the stuff we have already received, in collaboration with others and my own work, that these babies have the kinds of cries, cry thresholds and sounds that are evidence of damage.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: Just to be pesky, threshold effect or non-threshold effect dose response, and is it uniform across babies or are there babies who are spared and babies who are dramatically affected?

DR. ZESKIND: That is another good question. I can't answer that. That is not my area of expertise. I believe Dr. Oberlander--he is over on the West Coast of Canada--has been looking at differences in genetic populations with different cultural groups and how they metabolize the drug. There may be differences in metabolic activity that may have an effect. My study cannot address the dose response or whether an one SSRI is worse than another, that kind of stuff.

DR. CHESNEY: Thank you again very much

for taking the time to come and be with us.

DR. ZESKIND: Thank you for having me.

DR. CHESNEY: Tom is asking whether we want to take a break, and my thought is that a 5-7-minute break isn't really going to impact traffic and it may impact traffic to the men's and ladies' room. So, if is all right with everybody, I would like to take a 7-minute break. Plan to be back here at 3:45. At that time, Dr. Maldonado also wants to give a response to some of the issues raised this morning, briefly, before we move on. Thank you.

[Brief recess]

DR. CHESNEY: Dr. Maldonado had asked if he could spend just a few minutes responding to some of the issues that were raised this morning that involved pharmaceutical companies. He has promised he will be brief but they are important and I think it is important for him to enlighten us.

DR. MALDONADO: Thank you, Dr. Chesney. I know we talked a little bit about formulations and

I will be brief on this. That is an issue where, unfortunately, the science has not evolved as rapidly as in other parts of pharmaceutical aspects. The reason is that basically there are two very good solvents for a lot of the products, especially in liquid. One is water and the other is alcohols, and there are limitations with alcohols. A lot of the new drugs are not very soluble in water. So, even when I was still at the agency, I remember a sponsor trying 200 formulations and failing in every one of them. So, the science, unfortunately, is not very conducive to producing formulations sometimes.

The other thing is that we talked a little bit about negative studies. That might have actually a negative connotation. Negative studies are not necessarily unsafe; they just fail to demonstrate what they thought they were going to demonstrate, and in Phase 1, those are exploratory studies many times. I am glad that Dr. Murphy clarified that within BPCA those studies are becoming public and published, if not in journals,

at least the BPCA requires that the FDA make them public. So, there is not the veil that there used to be. This is the first time that actually industry has the incentive to send so-called negative studies to the FDA. Many of those studies were never sent before because they knew they were not going to be reviewed anyway.

But the most important thing that I want you to consider, the committee to consider and even the people from FDA--and I have to be very careful because I don't want you to perceive that I am trying to create a negative impact on how you do business. For example, today we saw several drugs in which the pediatric use is very minimal, 0.1 percent, 0.2 percent in some of them. So, most of the drugs are used in adults. After the meeting in the morning I inquired of one of the reviewers how is that different, how is the adverse event profile different in pediatrics than it is in adults. I was told it is the same.

Now, we are talking about changing the labels and focusing on the pediatric part. So, I

think we shouldn't do that because we are creating a perception of liability in pediatrics. If the adverse events are similar in adults, let's do it because of what is happening globally. I can tell you, I am an advocate for pediatric studies in my company. Otherwise, when we go back in front of the people who hold the wallet of the company, there is going to be some reluctance to approve pediatric studies because they are going to be perceived as being a liability. As you see here, I mean it is a no-brainer, if the companies only sell 0.1 percent of the drug in pediatrics or 0.2 percent, not even 1.0 percent--actually, I had a lawyer ask me at one of the labeling meetings why are we doing this to ourselves? I said, no we are not doing this to ourselves. We are providing this information for kids. So, this is the connotation.

So, if there are particular things for pediatrics, frame it on pediatrics but if it is not particular to pediatrics, then let's not frame it in pediatrics. Let's say, okay, these things--for example the abuse of some of the drugs, happen

actually more in bigger absolute numbers in the general adult population. So, that way we don't create a perception that there is something wrong with the pediatric drug development or pediatric use of these drugs because many times that is not the case. Thank you very much for the opportunity.

DR. D. MURPHY: I think, Sam, we have to find for the committee your presentation on what companies think about when they go through the process of trying to develop drugs for pediatrics. I think that it is a very useful process for the committee to be aware of.

DR. CHESNEY: On the next committee, of which we may not be members, we will get to hear your presentation. Dr. Shirley Murphy is going to talk to us about the Pediatric Research Equity Act.

Pediatric Research Equity Act

DR. S. MURPHY: We have heard today about what Dr. Gorman and the American Academy of Pediatrics did to really lobby to get this into legislation. In your packet you have the law. It is a long way from the law to what it actually

means and how you interpret it, and what I am going to do today is just give you a very top-line overview of how we are starting to interpret this law at the FDA.

It really takes a whole team to interpret the law, and on this team have been Terry Kwizenzi, Grace Karmuz, Rosemary Addy and Rosemary Roberts. It is evolving. It is like medicine, it almost takes a case-by-case. You look at an application and you see if it triggers PREA. You discuss it, why it does; whey it doesn't. So, it takes a while for precedent to be developed, just like in BPCA with the written request.

But I will give you a very quick overview of PREA, what it means, how it compares to the Rule and really how we are interpreting at the FDA. The Pediatric Research Equity Act has lovingly been called PREA, and is known throughout the FDA and through the pharmaceutical world too as PREA. So, it rapidly got a nickname.

It became law, as you know, on December 3, 2003 when it was signed by the President. The

legislation mimics the Pediatric Rule with some changes. It required pediatric studies of certain drugs and biological products unless they are waived or deferred. It is retroactive to all applications back to April 1, 1999, and that was when applications started to be triggered by the Rule. So, what happens is instead of just starting the date it was approved, it makes sure that certain applications didn't fall through the cracks so nobody got an "out of jail" free card with this.

PREA is not applicable to drugs with orphan designations or orphan applications. That is very different, as you will see, from BPCA. There is a guidance under development. Initially we had hoped that this guidance would be available to hand out to you but it is not quite baked yet. It, very importantly, establishes the pediatric advisory committee.

How does PREA compare to the Rule? It is actually quite similar. PREA is legislation so it is a law. So, thank you very much, American Academy of Pediatrics and everyone who worked so

hard on this. The Rule was a regulation and, as you know, the courts enjoined its enforcement.

PREA does not specify meetings at appropriate times, although we anticipate that the guidance will give some guidance about this. The Rule said you should have a pre-IND meeting and discuss pediatric plans. That wasn't in PREA. It is retroactive and it does establish the advisory committee.

Well, PREA is the return of the stick and BPCA remains the carrot. You know, why do companies do studies when there is such a small percentage of the patients that are taking the drug? Well, it is for the billion dollars that you make on the six months. It is not for the 0.1 percent of the kids that may take that drug. And, BPCA remains a very successful carrot.

These studies are voluntary in BPCA. They include orphan drugs and orphan indications, where PREA does not include orphan drugs and orphan indications. Now, BPCA is wide. It is just huge wide. It covers the entire moiety. So, if you

have a corticosteroid, for instance, like fluticasone, the written request may be for the lung, the nose and the skin, all of those indications. PREA is very, very narrow. The studies are limited to the drug and the indication that is under development. So, that is very, very different.

Now, a pediatric assessment is required for applications, or applications trigger PREA when there is a new ingredient. So, say, a combination of Tylenol and a muscle relaxant wanted to add caffeine in, that would trigger PREA. A new indication, say, a skin steroid wanted to go for an indication of eczema; a new dosage form, something goes from a liquid to a chewable, dispersable tablet; a new dosing regimen goes from 4 times a day to 2 times a day; or a new route of administration, it goes from an IV administration to a patch. So, these are the things that trigger PREA and require the company to have a pediatric plan and do pediatric assessments.

A pediatric assessment--and pediatric

assessment is probably interchangeable with pediatric studies--it has to be data adequate to assess the safety and effectiveness of the drug or the biologic product and data to support dosing and administration for each of the relevant pediatric subpopulations.

Just like with drug development in general, effectiveness can be extrapolated from adequate and well-controlled studies in adults, and then can be supplemented, just like we do in BPCA and the written request. Where there are gaps, it can be supplemented with safety and PK/PD data in children. You can extrapolate from one age group to another where appropriate. So, you might be able to extrapolate from an adolescent down to a child of, say, 6 but it would be a big gap to go from adolescents to neonates.

Now, I mentioned that there could be deferrals and there could be waivers. A deferral is granted when the drug or biologic product is ready for approval in adults and the pediatric studies aren't completed yet. You cannot hold up

access of medication for adults under PREA so you go ahead and approve it and then you would have then you would have the adult [sic] studies come in a year or two later. Or, the FDA believes that additional safety or effectiveness data that is necessary before this drug is studied in children. Some sponsors will come in very eagerly at a pre-IND meeting and want to start study in children when adults haven't been studied and the FDA can say wait, let's get some adult data, or it can even go up to approval and say let's get it on the market a while and see what happens before we subject children to it. This is really with a new molecular entity most often. But these deferrals are tracked in a database at the FDA as Phase 4 commitments so they don't get lost.

What about waivers? Well a full waiver, meaning you don't have to do pediatric studies at all, are granted when a condition doesn't occur in children. Prostate cancer would be an example of that. Or, necessary studies are impossible or highly impractical, and these are probably some

cases we will have to go through to see what this exactly means. Or, strong evidence suggesting a drug or biologic would be ineffective or unsafe. Or, a drug or biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.

A partial waiver can be granted when there is a subset of kids that can't be studied. That might be neonates. Or, reasonable attempts to produce a pediatric formulation necessary for that age group has failed, and that gets to what Sam was saying.

But there is a labeling requirement. If a full or partial waiver is granted because there is evidence that the drug or the biologic would ineffective or unsafe, the information then has to be placed in the label.

These are the drugs that I was talking about that are new, new applications, new ingredients, new formulations, new chemical entities. What about already marketed drugs, drugs

that are already out there on the market? Can they be triggered by PREA? This had the same stipulation under the Rule, but the FDA never invoked it and it is a very, very long, laborious process under PREA in which the FDA has to notify the company, give them a chance to come in and have a meeting. Then the FDA writes a written request. Then the sponsor declines it. Then the written request is referred to the NIH Foundation and, if there is no money there, then the sponsor is required to do the studies. And, if the sponsor doesn't do the studies the drug can be misbranded. In that are lots and lots of meeting periods and time periods. So, it would take over a year to go through this. But, as I said, it was never invoked with the Rule but it is there as, I guess, the heavy part of the stick if it is really needed.

PREA establishes, like Dianne talked today, very importantly, a full pediatric advisory committee at the Office of the Commissioner with very broad responsibilities that go across foods, devices and biologics and lots of issues that go

across the FDA. The advisory committee will continue to have the adverse event reporting, and labeling dispute resolutions will also be heard. I have to say, you know, we have gone almost to the line of having to bring a labeling dispute resolution to the committee but, somehow, just the threat of, "well, we're going to take it to the advisory committee," gets those things resolved in-house so I guess it is another form of a stick. Subpart D referrals that Dianne has talked to you about will also be part of the advisory committee.

In summary, we feel that PREA and BPCA, just like BPCA and the Rule, really go hand-in-hand to give us new pediatric information for labeling. Thank you. Any questions?

DR. CHESNEY: Dr. Santana?

DR. SANTANA: So, under PREA the likely scenario, and I will speak from the oncology point of view, is that most drugs in oncology are not developed for kids; they are developed for the common adult cancers, prostate, breast and so on. So, in the developmental process of those drugs if

the sponsor knows already that they are going to develop the drug for prostate and breast, then there will never be pediatric studies. Right? Because those indications are not part of what they ultimately want to develop their drug for. So, PREA will not help us be able to study those drugs effectively in children. Am I correct?

DR. S. MURPHY: Well, for that specific indication--it is indication specific. So, if they are coming in for a prostate cancer indication, yes, it wouldn't. It would probably be waived. But if they start to broaden out into solid tumors that would occur in children or hematologic tumors that would occur in children, then that indication would trigger PREA.

DR. D. MURPHY: I think, Victor, you are getting at the struggle that we are aware of, and one of the reasons that there was that forum that the Academy called a number of years ago is because it was recognized that the Rule just isn't going to work as well where you don't have similar diseases between adults and kids. I am not talking about

extrapolation but just talking about, you know, you can get an indication for pneumonia for adults and kids. But where you don't have that link you are not going to be able to use this hook. That is why the exclusivity process was reevaluated as to how it can most effectively be utilized for cancer development for children. That is why there is a special guidance out on how products that are being developed for cancer therapies in kids could get exclusivity at a stage that is less clear as where they are going to go than in other products. That was a particular focus of that guidance.

DR. S. MURPHY: And I think exclusivity has worked extremely well in oncology, which we saw this morning. By doing really Phase 1 and Phase 2 studies, without doing Phase 3 companies do get exclusivity.

DR. SANTANA: The exclusivity only applies to marketed drugs. Am I correct?

DR. S. MURPHY: Well, it can be planned premarketing. Design the studies and plan them--

DR. D. MURPHY: Right.

DR. S. MURPHY: --way before. In fact, it is included in the forecasting for products now as they come out that they are going to get exclusivity and how much money they are going to make.

DR. GORMAN: One of the hopes that some of us expressed during the creation of PREA was that as drugs go through Phase 1 testing in adults, and oncology drugs would be included in this, and they are tested for mechanism of action, if the mechanism of action is shared it might become clear where pharmaceutical companies might go with the development of agents, and that would be an opportunity to initiate pediatric studies. It may not be as effective as we hope because of the limitations of PREA, which is for targeted indication and it may not be there, but it will alert the agency, as well as the pediatric research community, that these agents are coming down the pike and have potential pediatric utilization.

DR. CHESNEY: I think Dr. Nelson commented on this, but I am intrigued that the companies can

do Phase 1 and 2 studies with preparations that can't be used commercially. I realize it is very hard to develop those. We have heard that over and over again. Dr. Spielberg used to talk about that all the time. But does the company have to be actively working on trying to get the product into a commercially usable preparation at the same time that they are doing Phase 1 and 2 studies?

DR. S. MURPHY: Well, I think it all depends on the product. A lot of the verbiage in the law talks about the severity of the illness, the existence of other therapies, the need basically and the number of patients affected, as to how early the pediatric plan would come in and be accepted and go into effect. So, I think it is really, like I said, almost like medicine. We are seeing this already because Grace and Rosemary are the repository of all the questions in the FDA about PREA. They come in case by case and we are actually having to decide is this good; is this bad.

I think the pendulum, you know, we don't

want that when things are added to drugs, especially generic drugs and it triggers PREA. We don't want children studied with things that are unsafe, that have AERS reports coming in, that are probably never used in kids. So, we have to be really careful because it is a balance.

DR. CHESNEY: Thank you very much, Dr. Murphy. Finally, Dr. Nelson is going to give us an overview of the Institute of Medicine report, of which we have a copy although I think it hasn't been published yet--"Ethical Conduct of Clinical Research Involving Children."

Overview of Institute of Medicine Report,
"Ethical Conduct of Clinical Research
Involving Children"

DR. NELSON: Thank you and, given the hour and time, I am going to try and go through this quickly. I think all of you have copies of the slides and I would comment the full report.

What I would like to do--you know, we say you shouldn't look at the trees and miss the forest. In this case I want to point out some

trees and, you know, you can look at the full report for the forest. So, let me run through this fairly quickly.

This just lists the study committee, and Dick Behrman did an admirable job chairing it.

The study process--you see on the slide, in terms of number of committee meetings and public discussions and forums. It was publicly released on March 25th but I don't think it is yet in a form you can actually purchase and hold in your hand at this point though it is available on the Internet.

The issue I think fundamentally--and this is from Dick Behrman's preface--is that we are trying to balance providing benefit but, yet, making sure that in the process of providing benefit we are not inappropriately exposing children to risk. That is really the purpose of the regulations that guide our research process, to try and balance the appropriateness of the benefit and risk that is involved.

The charge to the committee was specifically focused on clinical research. This

lists the specific topics that you can look in the report for. The only comment that I want to make here is that these topics were mandated by the Best Pharmaceuticals for Children Act. The report, if it went outside those topics, in fact, couldn't include it because it would be struck. This was mandated by Congress and if the committee wanted to talk about something that wasn't on that list, it really couldn't put it in there. So if you don't see it, that is why it is not there.

Three broad things, first, good research is important for the health of children. It is pretty obvious but we wanted to strike that theme at the beginning of the report.

The second is that protecting children is part of human subject protection overall. There has been a fair amount of criticism and concern about the overall system. To the extent that you want to protect children you need to look at that overall system was our second broad theme.

The third broad theme was that the effective implementation in terms of both

protection and, I would argue, also the conduct of research is appropriate expertise. I will come back to that towards the end in some of the comments. But, basically, appropriate expertise in the design, review and conduct of such research. I don't think anybody who has been part of the discussion on this committee over the last five years would disagree with any one of those themes.

Now, the summary statement was that the committee felt that the regulations were by and large appropriate. But the problem with it is that there is insufficient guidance about the interpretation of those regulations. It is difficult to get data about that. I mean, you look at the Adverse Event Reporting System--try and get data about the IRB system, it is worse, believe it or not. It is worse. There is nothing out there. And, there is a lot of variability in the application and interpretation.

The feeling was you are not going to reduce this variability by trying to narrow down the regulations themselves, which really means

guidance. When you think about it, it is much like PREA. You have the regulations themselves at a certain general level, then you have to have guidance that implements that down to the case level. You are not going to solve the problem by going back to the regulations and changing them; what you need is better guidance.

In the spirit of that, the recommendation of the report was an attempt to look at some of those areas where guidance is necessary. I am going to run through these five areas quickly, just highlighting some of the trees, if you will, rather than the forest.

One of the issues that has been discussed over the years is the interpretation of minimal risk. In pediatrics it is important. If it is minimal risk research you are eased of certain restrictions and the balancing of risk and benefit is very different. Well, does minimal risk refer to the normal, healthy, average child on the street or does it refer to the child with leukemia? Every single commission, including the national

commission originally and the Institute of Medicine report has said this should refer basically--here is the definition, by the way, which is 45 CFR 46.102. I apologize, I think it is 21 CFR 54.102 but I could be mistaken.

The committee as well said that you should interpret minimal risk in relationship to the normal experiences of healthy, average, normal children. So, when you are looking at the definition of minimal risk, this has an impact on how IRBs would review the research. I won't go through the rest.

Now, the second category, which is in the FDA 50.53, which is minor increase over minimal risk, basically this is to be slightly more than minimal risk. That doesn't really tell you much but where this becomes important is if you want to do this kind of research--and often single-dose PK studies are approved by IRBs under this minor increase over minimal risk--you then get into condition because this particular category of research is restricted to research where a child

has a particular condition.

So, where I think this becomes important for our discussion is how do you decide whether a child has a condition or not. This is how the Institute of Medicine committee approached this. It should be interpreted--and this is one of the trees I want to talk about--it should be interpreted as referring to a specific or a set of specific physical, psychological, neurodevelopmental, or social characteristics--we had a lot of discussion about that word "social." Should it be in there? Should it not? What are the issues, etc.--that an established body of scientific evidence--and those who wanted it in, kept it there but the issue is what is the evidence. If you want to use the social characteristic what is the evidence that that is, in fact, tied to something that would negatively affect children's health and well being or increase their risk of developing a health problem in the future?

So, the emphasis here is on evidence and

on risk of development. For example, we talked about fenfluramine study in New York and the issue of whether or not you could consider being the sibling of a child who is incarcerated as a condition. That is not in the report but that was part of our discussion.

Now, personally, in looking back at this consensus statement, I think there are some ambiguities in it that would merit perhaps revisiting by the next edition of the committee. Here susceptibility to the disease I think does imply this notion of risk but it is tied to this notion of benefit in a way that doesn't really capture condition in the same way that the Institute of Medicine reported, in my view, in the same way the regulations tried to capture it. So, I think this statement that is up on the web melds risk of condition and benefit together in a way that is ambiguous and not as helpful as it could be, looking back now four years later. So, I think it would make sense to revisit this particular statement at some future time.

The committee does call for the need for the development of guidance and I think that is fairly straightforward. I might just say that there is a potential mechanism for this. The Secretary's Advisory Committee on Human Research Protections does have a pediatric working group which could be one locus for that discussion, and then having guidance work its way up through SACHRP, which is the Secretary's advisory committee, and then work with FDA and OHRP, and I think there may well be a process under way to look at that.

Another tree is what is called component analysis of risk. For research that offers benefit, the argument here is that if you have a procedure that doesn't offer benefit as part of it--let's say a bone marrow aspirate where the oncologist clearly says this does not offer any clinical benefit to that child--within the pediatric regulations you are supposed to judge the appropriateness of that procedure against its risk, minimal risk or minor increase over minimal risk,

as opposed to the benefit of other things that may be in that protocol, the chemotherapy. The risk and benefit of the interventions that offer the possibility of benefit are evaluated on their own merits, and then the risks of procedures that don't offer the prospect of direct benefit need to be restricted to minimal risk or a minor increase over minimal risk. That is called the component analysis of risk.

Otherwise, what you could do is take a very risky non-beneficial procedure, toss it in and offset it with all sorts of other benefits that are totally unrelated to that procedure and that is not felt to be appropriate. So, it raises an interesting question about choice of control groups. This is what the Institute of Medicine report says, for research involving children and a placebo control group to be approved by an IRB under federal regulations, either the balance of potential harms and benefits for children in the placebo control arm must be as favorable as those for children receiving the active, standard

treatment--that is simply restating the conditions of 50.52 which is the regulation.

Or, the potential harms to which children in the placebo control arm would be exposed are no more than minimal or involve only a minor increase over minimal risk. So, what that is saying is if you are removing the potential benefit from that placebo group, then the risk that they are exposed to because of the removal of that benefit needs to fit within the minimal risk or the minor increase over minimal risk.

That then raises the question about whether one of my favorite documents, ICH-E10, control of control group, how you should interpret that in light of pediatrics. We had a discussion of this on the committee, probably in 1999, at this point, and one or my favorite quotes is from Bob Temple saying that he doesn't think E-10 dealt with pediatrics because the E-10 did not apply to children because it assumed as the ethical basis for withholding effective treatment informed consent. Look back at the transcript. I will tell

you where it is. I use it all the time when I talk about E-10. I think it is an open question.

The issue of the threshold, death or irreversible morbidity--I would propose to you the absence of that may not be the same as minimal risk or minor increase over minimal risk. It probably isn't. So, I think that is an open area that would have to be addressed in the ethics. So, that is another tree.

Parental permission and child assent--this is a drum that I think ethicists are continuing to hit, the notion that the FDA does not allow a waiver of parental permission for conducting pediatric research, and specifically said they would not adopt the same waiver that is found in the HHS regulations. The report says that is not a good idea; we think they should, in fact, be the same regulation.

The notion of harmonization is part of that component, that these two regulations ought to be harmonized. The one point that is not harmonized is, in fact, the waiver under 46.408(c).

A controversial issue, but the report said that should be harmonized. Will it be? Who knows?

Payments--this is an opportunity to say something good about industry. It says that people should be compensated for injury during trials. I will point out that in most of my experience industry trials do offer that kind of compensation; other trials do not generally. It does talk about investigator payments where it says investigators and staff should be compensated for the costs associated with conducting research. However, finders fees and those kinds of kickbacks, if you will, to individuals referring subjects are unethical and should not be permitted. So, this is another tree.

Now, there is a PhARMA principle for conduct of clinical trials which does, I think, say something similar, that payment to clinical investigators is appropriate if it is reasonable for the work to be done; that you can, in fact, provide additional payment if there is more work to recruitment of subjects. You could read this as

precluding finders fees but it doesn't come out and say that clearly. I would interpret it as precluding that. Just as an aside, so would James Sheehan, the Associate U.S. Attorney of the Eastern District of Pennsylvania, who often has looked at industry-sponsored research who says that there is no law prohibiting payment to doctors for recruiting study subjects but a jury would find the practice wrong. Even in the absence of an expressed statutory prohibition on finder fees, they are problematic. I think most industry protocols do not include finders fees, in my experience, and I think most sponsors would interpret PhARMA's principle as excluding those but they are still out there.

Regulatory compliance--there is a need for data. We probably know more about what is going on in the FDA arena and to some extent in the NIH arena, but we have no idea what is going on in pediatric research in other arenas in terms of the distribution of protocols among minimal risk, minor increase over minimal risk, what is happening with

investigator-sponsored, single institution, locally funded--we have no idea what is going on in that area. It would be helpful to know what is happening in terms of development of guidance. So, that was one of the recommendations, to get better data.

Finally, responsible conduct of research, which I interpret as systems improvements, the first is something that I think has been brought up. It was brought up by the original national commission and again by the Institute of Medicine, that federal law should require all clinical research to be governed by the same set of rules. The way it is worded is conducted under the oversight of a formal program for protecting human participants in research. In other words, you have the FDA and industry sponsored research; you have NIH and its funded research. But if you are not going to submit any of the data to the FDA or if you are not funded by the NIH and you are not working in an institution that would require you to be obedient to those rules, you can carry research

out in your basement and whether you are breaking the law or not is a separate question.

I might point out that there is a draft Bill that I believe Sen. Kennedy--I don't know if it is officially coming out in a draft but I read about this in a BNA medical policy report, where he wants to provide statutory authority for OHRP to, in fact, issue rules that would apply a common rule to all research, and to require all greater than minimal risk research to gain approval from an accredited IRB, effective by those two dates. Whether this will happen or not--open question. But that is at least one attempt to move that along.

The need for IRB expertise--I think this is one thing where IRBs, particularly small community IRBs, may struggle with. I would propose that this could be something that the FDA audit procedure could, in fact, look at if they wanted to. IRBs reviewing pediatric protocols should have adequate expertise in child healthcare and research. At least three individuals with such

expertise present and voting, and among the pediatric clinical care research, psychosocial aspects of child and adolescent healthcare and research, and then ethics of research involving children.

Where did we get this list of three? Well, if you look at ICH-E11, at the end it says there should be adequate expertise on an IRB in these three areas, but it doesn't translate that to three people. We had a lot of discussion about this. Is one enough? Is five too many? We just decided to say you should have three because often if you are on a general IRB with only one pediatrician it is very easy for that voice to be drowned out. I think there are many IRBs that might struggle with this particular requirement. We also say they should consult with other child healthcare experts, parents, children, etc., relevant family and community perspectives.

It goes on and actually you could say potentially it would impact the pediatric advisory committee. The Institute of Medicine report

advises that standing pediatric advisory committees and pediatric IRBs, but standing pediatric advisory committees include at least one non-scientific, unaffiliated member who can represent explicitly the perspectives of parents and children.

I would propose this is not quite the same as a consumer perspective. The argument here was that this is very much a sort of participant standpoint perspective as far as those who would potentially be the subjects of this kind of research, which would be very different than a consumer perspective. So, that is one of those recommendations.

Multicenter studies in terms of coordination was another recommendation. Here is another guidance. This is another tree I would like to call your attention to. Ideally, there would be coordinated guidance among NIH, FDA, OHRP and the like, and that doesn't currently exist. Let me give you one example that I came upon when I was reviewing the NIH guidance on the inclusion of children in research for another talk.

You heard earlier today that the FDA does not require sponsors to do efficacy studies if, in fact, you can extrapolate data from the adult to children. The ethical argument is that it is really unnecessary to expose children to the risk of that research if, in fact, the efficacy data can be extrapolated and you would only need PK data or safety data. I think that has been a fairly consistent approach over the last decade. But if you look at the NIH guidance on the inclusion of children, it actually says if the disease is the same you can include children and you don't even need to include enough children to do a meaningful subgroup analysis. So, it is the opposite and I think the FDA approach is right; I think the NIH approach is wrong. In fact, you shouldn't include children in the research unless you can have meaningful data about them as a population. It raises the same issue as the inclusion of women so it is a broader issue than that, but if you look at that guidance, it is the exact opposite.

So, I think that is something that ought

to be discussed between the two, and I might point out there was recently an RFA for inclusion of adolescents in sleep studies but then a proposal failed to get past what would be equivalent of a 50.54 review because the review panel and then the OHRP and the Secretary agreed that it was unethical to do the study in adolescents even though the RFA specifically asked for adolescents to be included.

Finally, 50.54 which was alluded to. Here I think again the FDA has a leg up on the process. It has a federally mandated public, accessible advisory committee where, if there is a 50.54 application that the sponsor then pursues and doesn't take off the table because they don't want the publicity, and that is a whole separate question, there is now a venue for that to happen which is open and publicly accessible. To date, that has not been available. To date, all of the reviews that have happened within OHRP have been done non-publicly by individuals offering opinions individually to the OHRP, which then correlated it all and went through that process.

There is a proposal that, in fact, that will be done publicly but OHRP can't establish a FACA committee so it will be a public, non-FACA process. If you can imagine, all of us, after we have our discussion, we leave the room, write our individual reports and we send them in to the office and then they try to collate that. That would be the equivalent. Here now at least there is a process that the FDA has where they can do that if such request comes up. I know there are discussions about how to coordinate that if there is a coordinated product that would be both NIH reviewed and FDA regulated.

So, I have kind of given you a whirlwind tour. Hopefully, you can see the forest but I wanted to point out where I see some trees that are of interest and the impact of this report potentially on FDA activities and the like, and in may ways, I hope in a positive sense, where there are some things that are being done well and some things that could be done better.

Again to remind you of the three-part

theme, clinical research is essential to improve the health of future children; a robust system is necessary for protecting child research participants; and effective protection requires expertise in child health at all stages of the design, review and conduct of such research. I hope that hasn't been too fast.

DR. CHESNEY: Outstanding. Any technical questions for Dr. Nelson? Dr. Luban?

DR. LUBAN: I don't know if you would define this as technical, but could you flesh out a little bit more some of the discussion on the multicenter studies? That appears to be, at least at our institution, just one of the most difficult problems to deal with, particularly when they are NIH-sponsored and large and excessively multi-institutional. DR. NELSON: I guess the committee felt since the institute process is meant to be evidence-based, and there are a lot of models out there in terms of independent IRBs that are often used by industry; central IRBs that are used by cooperative groups--I know there is a National

Cancer Institute initiative that is primarily in adults; there are a lot of initiatives out there--the feeling was that right now there is not good data to say which of those models is best. Part of that was also recognition that many institutions are very reluctant to hand over authority or responsibility for some of that decision-making. So, one of the obstacles to centralization is often local concerns about liability. Basically, the report runs through some of those issues and suggests that we just need more work done in sorting out what is the best way to conduct those multicenter studies. I have my own bias about that, but we didn't feel there was any clear winner in all of that to be able to say, from an evidence perspective, what is the best approach.

DR. CHESNEY: Local concerns about liability.

DR. GORMAN: Just to reengage the discussion on minimal risk, which average, healthy, normal children were you planning on using? Would that be country dependent or the traditional

suburban child in east Philadelphia or west Philadelphia?

DR. NELSON: You know, if you look at the report, the way I would answer that is one of the principles that I think has been under-discussed in research ethics is justice. What we are really talking about is under what conditions is it appropriate to expose a child to increased risk. Is one of those conditions that you happen to live in inner city Baltimore in lead-affected housing? Well, maybe in one protocol the answer is yes and in another protocol the answer is no. So, figuring out the notion of condition requires both evidence and then I think an understanding of the risk within that. With average, healthy, normal children the intent was to not use what would be considered research irrelevant characteristics to justify increased risk exposure. You know, if you were going to do non-lead related research you wouldn't use the risk of living in Baltimore as a justification for going into that population to do something riskier than you wouldn't do in the

suburb that you live in, for example, maybe. So, that would have to be the same.

On the other hand, if you define the condition, then there might be a justification for a protocol that would have an increased risk exposure in that population. So, that is part of the balancing that we went through. So, average, normal, healthy--I don't think we defined it but, on the other hand, since it is not defined at all I think the first step is to at least agree that that is what we are talking about. Right now you could define as minimal risk, although most IRBs don't, a child who has leukemia, if you wanted to, in terms of their daily experience. I don't think IRBs do that but they could.

DR. CHESNEY: Thank you very much. I think Dr. Buckman had a comment that she wanted to make in response to Dr. Maldonado's comments.

DR. BUCKMAN: Sorry, you probably thought you had finished hearing from me today. Just very briefly, I just wanted to bring up one point of clarification. As you know, the FDA is all about

the details. It is just responding to a comment that was made a little bit earlier and maybe a concern that was raised to me regarding adverse events in the pediatric population versus the adult population for the Duragesic patch, and whether there were similarities or differences, and I wanted to give the exact information because I didn't want it to go into the record without it being very clear.

DR. CHESNEY: Do I need to recuse myself from listening to this?

DR. BUCKMAN: I don't think so. No questions; this is just a point of clarification. The top 20 reported adverse events in the adult population were compared to the pediatric population for that 1-year post-exclusivity period for Duragesic. Of the events that were captured in the adult population, there were 4 unique events that were captured in the pediatric population that were not seen in the top 20 for the adults. I just want to read what those were: cardiac arrest; respiratory arrest; self-medication; and anxious

parent. Those were not captured in the top 20 adverse events for the adult population.

Now, I cannot say whether below the top 20 those adverse events were also captured in the adult population, but I just wanted to give that as a point of clarification.

DR. CHESNEY: Thank you.

DR. SANTANA: So, besides the message that there were some differences, the underlying message is that when you look at pediatric adverse events for these drugs you also look at the adverse event reporting for adults and do a backside comparison.

DR. BUCKMAN: Right, right, we try to. You know, we look for similarities and differences. I don't want to go on the record making a global statement that they are the same or that they are different, but there are some similarities and there may be some differences as well.

DR. MALDONADO: I wasn't focusing on that particular drug because I heard the same thing for Effexor. So it is in general. I mean, I said don't frame it in pediatrics if it is not only a

pediatric problem; just frame it generally because otherwise people will focus and say this is a pediatric liability issue. It is general. That is all.

DR. BUCKMAN: The point is well taken.

DR. SANTANA: Yes, it is, but we did see a couple of examples of the drugs that were reviewed this morning in which they were very similar and no issues were made of that. I remember at least two of the oncology drugs in which the profiles were very different and no further issues were created because of that analysis.

DR. BUCKMAN: Thank you.

DR. CHESNEY: Well, thank you, all, very, very much. Tom tells me that the vans to take anybody wherever they want to go are outside. I don't know what to say except thank you, all, again.

DR. D. MURPHY: Thank you, all.

[Whereupon, at 4:42 p.m., the proceedings were adjourned.]

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