UNITED STATES OF AMERICA

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

PEDIATRIC ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

FRIDAY
NOVEMBER 18, 2005

The Advisory Committee met in the ballroom of the Washington-North Hilton, 620 Perry Parkway, Gaithersburg, Maryland, at 8:00 a.m., Dr. Robert Nelson, Chair, presiding.

PRESENT:

ROBERT W. NELSON, M.D., Ph.D.	Chair
ANGELA DIAZ, M.D, M.P.H.	Member
MICHAEL E. FANT, M.D., Ph.D.	Member
MELISSA M. HUDSON, M.D.	Member
THOMAS B. NEWMAN, M.D., M.P.H.	Member
JUDITH R. O'FALLON, Ph.D.	Member
MARSHA D. RAPPLEY, M.D.	Member
DEBORAH L. DOKKEN, MPA	Patient-Family Representative
ELIZABETH GAROFALO	Industry Representative
PAULA KNUDSEN	Consumer Representative
JAN N. JOHANNESSEN, Ph.D.	Executive Secretary

PRESENT: (continued)

JANET ENGLUND, M.D.	Consultant
DAVID K. SHAY, M.D., M.P.H.	Consultant
ROBERT WARD, M.D.	Consultant

ALSO PRESENT:

SUZIE McCUNE, M.D.,	Division of Pediatric Drug Development
LARRY GRYLACK, M.D.	Division of Pediatric Drug Development
SOLOMON IYASU, M.D.	Office of Pediatric Therapeutics
DIANNE MURPHY, M.D.	Office of Pediatric Therapeutics
MELISSA TRUFFA, R.Ph.	Division of Drug Risk Evaluation
DEBRA BIRNKRANT, M.D.	Division of Antiviral Products
LINDA LEWIS, M.D.	Division of Antiviral Products
ANNE TRONTELL, M.D.,MPH	U.S. Public Health Service
DAVID SHAY, M.D.,MPH	Centers for Disease Control and Prevention

I N D E X

INDEX (continued):

P R O C E E D I N G S

Time: 8:11 a.m.

CHAIRMAN NELSON: I would like to call the meeting to order. I guess we want to start with the confidentiality statement. Then we will do introductions.

EXEC. SEC. JOHANNESSEN: Good morning. The following announcement addresses the issue of conflict of interest with regard to the discussion of a report by the agency on adverse event reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act for Anagrelide, Carboplatin, Fluconazole, Irinotecan, Oseltamivir, Rofecoxib, Sodium Ferric Gluconate Complex, and Sumatriptan, 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 Food and Drug Administration present no potential for a conflict of

interest at this meeting.

In the event that the discussions involve any other products or firms no 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 note that Dr. Robert Ward, Dr. David Shay, and Dr. Janet Englund are participating in the meeting as voting consultants and that Paula Knudson is participating as the Acting Voting Consumer Representative.

We would also like to note that Dr. Elizabeth Garofalo has been invited to participate as an Industry Representative, acting on behalf of regulated industry. Dr. Garafalo is employed by Pfizer.

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.

CHAIRMAN NELSON: Thank you, Jan. So why don't we go around the table and introduce ourselves and, if we could start, I gather, over to my right.

DR. LEWIS: I am Linda Lewis. I am an antiviral reviewer in the Division of Antivirals.

DR. BIRNKRANT: Debra Birnkrant, Director, Division of Antiviral Products.

DR. IYASU: I am Solomon Iyasu. I am the Acting Deputy Director for Division of Pediatric Drug Development.

DR. MURPHY: I am Dianne Murphy. I am the Office Director for the Office of Pediatric Therapeutics, FDA.

DR. JOHANN-LIANG: Rosemary Johann-Liang, Deputy for the Division of Drug Risk Evaluation, Office of Drug Safety.

DR. TRONTELL: Anne Trontell, Deputy Director of the Office of Drug Safety in FDA.

DR. WARD: I am Bob Ward, neonatologist and clinical pharmacologist from the University of Utah.

MEMBER FANT: I am Michael Fant. I am a

neonatologist and biochemist at the University of Texas Health Science Center at Houston.

MEMBER NEWMAN: Tom Newman, a general pediatrician and professor of epidemiology and biostatistics at UC-SF, member of the Committee.

CHAIRMAN NELSON: Robert Nelson. I am an associate professor of anesthesiology and critical care at the Children's Hospital, Philadelphia, and at the University of Pennsylvania.

EXEC. SEC. JOHANNESSEN: I am Jan Johannessen. I am the Executive Secretary of the Pediatric Advisory Committee.

MEMBER KNUDSON: And I am Paula Knudson, the NIRB Administrator from the University of Texas Health Science Center, Houston.

MEMBER DOKKEN: I am Deborah Dokken, the patient-family representative on the Pediatric Advisory Committee.

MEMBER HUDSON: I am Melissa Hudson. I am a pediatric hematologist-oncologist from St. Jude Children's Research Hospital in Memphis, Tennessee.

MEMBER RAPPLEY: Marsha Rappley,

Developmental and Behavioral Pediatrics from Michigan State University.

DR. ENGLUND: Janet Englund from the Department of Pediatric Infectious Diseases at Seattle Children's Hospital, University of Washington, and Fred Hutchison Cancer Research Center in Seattle.

MEMBER GAROFALO: Elizabeth Garofalo. I am a pediatric neurologist and the Industry Rep, and I work for Pfizer.

CHAIRMAN NELSON: Thank you. Dianne, do you want to give us the overview?

DR. MURPHY: Thank you. First of all, I wanted to thank the Committee for their marathon participation over this past week. You arrived in the summer, and you are going to leave in the winter, and we really do recognize, as I said yesterday, the tremendous benefit you provide to the agency, and appreciate your participation over these past four days.

Today we are -- I am going to provide a quick overview of the agenda, and also wish to take some time to recognize the contributions of our

Japanese colleagues.

We are going to begin with our usual review of products that have been studied under the exclusivity provisions of the Best Pharmaceuticals for Children Act, and we report on the adverse events and safety reporting that has occurred during that year.

We will begin with Dr. Suzie McCune and Dr. Larry Grylack -- each of them will introduce a subsequent person to you in a little bit more detail -- who will review the products that are listed here. I am not going to repeat them all. They are in your handout.

We will then have a break, and Melissa Truffa will be presenting the ODS review, Office of Drug Safety review, for Tamiflu.

We then are going to have Dr. Linda Lewis present to you the clinical trial and literature review involving Tamiflu.

Then we have Dr. Joseph Hoffman from Hoffman La Roche, who will be presenting for the sponsor an executive summary of their comment on Tamiflu.

Then at the end, we will have Dr. David Shay from the CDC, who is going to provide you all an overview of influenza surveillance data in the U.S. At that point then, we will turn the Committee back over to you all for discussion and input and your response to our proposed questions.

In this review, which you have noted in your packet, the predominant report -- predominant number of reports were received from Japan, and today you will hear a bit about why we think that occurred. But we would like to take a moment to tell you that our colleagues at the Japanese regulatory agency, the Ministry for Health-Labor-Welfare, have been very helpful. We have been in fairly frequent discussion and had exchange of information with them.

So I am going to now -- how shall we say? -- mutilate these names. I apologize beforehand to the Japanese: Dr. Toshiro Nakagaki who is the Director of Safety Division, Pharmaceutical -- and they put the word Food in there -- Pharmaceutical and Food Safety Bureau; Dr. Noriatsu Kono, who is the Deputy Director of the same division; Mr. Tatsuo

Kurokawa, who is Councillor, again with the Ministry of Health, Labor and Welfare; also from the Pharmaceuticals and Medical Device Agency, Dr. Osamu Doi, who is the Senior Executive at that agency; and from the National Center for Child Health and Development in Japan, Dr. Hidefumi Nakamura, who is the Director of the Division of Clinical Research at the National Children's Medical Center.

They have tried to provide us not only information from the regulatory perspective, but also provide us information on the practice of medicine and the approach to care of influenza in Japan.

As I said, we will conclude the day by asking the Committee to address these three questions. We are actually beginning it by telling you what we are recommending, and then asking you, do you concur with this approach.

For the first series of products that we will be presenting, we are recommending that we return to routine surveillance for those products, and we ask the Committee's concurrence or comments for that.

Then we are telling you that we are

proposing that we continue to monitor pediatric adverse events that are being reported for Tamiflu and return to this Committee with an additional report in the next two years. Do you agree with this, and do you have any additional comments?

We are also saying the FDA is proposing additional information for the Tamiflu labeling regarding serious skin reactions. After hearing the discussion today, do you agree? Does the Advisory Committee agree with this approach?

So that is a quick overview of what we are asking you to do today and, if we are successful and do as good a job as we have done over the last three days, you will actually solve all of our questions and be out of here on time. Thank you very much.

CHAIRMAN NELSON: Thank you, Dianne.

DR. MURPHY: Oh, I failed to introduce Dr. Iyasu. Dr. Iyasu is a pediatrician, a medical epidemiologist, who previously worked at the Center for Disease Control, and will be providing our overview of the safety review, which many on this Committee have heard a number of times, but we do have

some new members who we really feel it is important for him to do this for you and make sure that everybody is beginning at the same place. So, thank you, Solomon.

DR. IYASU: Thank you, Dianne. Good morning. I am going to make some comments on the safety report --

CHAIRMAN NELSON: Just before you get started, let me note that our wayward member has now been released from the elevator. We are here safely.

DR. O'FALLON; What a ride.

CHAIRMAN NELSON: Thank you. Sorry.

DR. IYASU: I am going to make some comments on the reporting that we've been doing since the report of 2003. We have done 42 drug product reviews so far, and at the end of the day we will have done 50 of these products that have been approved for exclusivity.

These reviews are mandated by Congress under the Best Pharmaceuticals for Children Act under Section 17 where it specifies that the adverse events reported for the one year following the exclusivity

granting would be referred to the Pediatric Advisory Committee for their review, and such reports are to be referred to the Committee by the Office of Pediatric Therapeutics.

That activity has resulted, as I said, in now 50 reviews being completed, and today you will hear reports for eight products.

I wanted to give you a little bit for the benefit of some of the members who have not been part of this Committee before what you will be reviewing and what the safety reviews are based on.

Most of the reviews are based on the adverse event reports that are submitted to the agency through the passive surveillance system, and this database is the AERS database, which was started in 1969, and by now has more than 2 million reports in the database, and these reports contain adverse event reactions that may be related to drug or therapeutic biologic agents.

The exception is not contain any reports related to vaccines, because vaccines have their own adverse event reporting system.

Just to characterize the kind of reports that we get, as I say, they are voluntary and spontaneous reports, and the type of reporters varies from health care professionals to consumers and patients, but I should say that most of the reports are -- over 90 percent of them actually come from manufacturers, because they are required as part of the post-marketing reporting regulations, and this will include also foreign and domestic reports.

There is a clear definition of what an adverse event is or an adverse drug experience is by the regulations. It is an adverse event associated with the use of a drug, whether or not considered drug related.

So attribution to a drug is not essential for reporting, and this may include accidental or intentional overdose or drug adverse events that occur from the abuse or drug withdrawal or failure of expected pharmacologic action or drug being ineffective.

Also there is a definition of what an unexpected or unlabeled adverse drug experience is.

It is defined as any event not listed in the current labeling for the drug product, including events that may be symptomatically and pathophysiologically related to a labeled event, but deferred because of greater similarity or specificity. An example is hepatic necrosis versus hepatitis.

There is also a regulatory definition of what a serious adverse event is: Any event occurring at any dose that resulted in any of the following outcomes. So it is really defined by the outcomes, and the outcomes may vary from a death to a life threatening adverse event or an adverse experience that resulted in hospitalization or prolongation of hospitalization or persistent or significant disability or incapacity or a congenital anomaly or birth defect. Therefore, these outcomes are defined in the regulations.

Part of what we do at the FDA, because these reports come without any attribution to a drug, they are simple reports that come in spontaneously into the agency, we do do a careful analysis or causality assessment.

Some of the factors that are considered in that causality assessment are listed on this slide, important being, of course, the temporal relationship of an event to the drug, that the exposure occurs before the reported event.

Other factors that we look for in the reports is whether there is information about de-challenge or re-challenge, de-challenge being defined as whether an ADE subsides when the drug is discontinued or the same event reoccurs when the drug is readministered to the patient, and when we see also a dose-response relationship, meaning an increase in frequency or severity of an event of interest with changes in dose.

We also look at issues related to what we know about the biologic plausibility of the event and the drug interaction. We look at preclinical studies from animals that may provide us some information about causality. We also look for laboratory evidence of an expected or unexpected pharmacologic effect.

We also look at prior knowledge about whether what we see with a particular drug is a class

effect, and that would help us also in assessing whether an event is related to a drug or not.

Other very difficult issues that we deal with are whether the underlying disease and concomitant medications would really confound the causality assessment, and it makes it very difficult often to distinguish between a drug effect and the underlying disease, especially when the manifestations of the disease are similar to what you would expect with a drug effect.

I just have to mention that there are some serious limitations to the databases that we normally look at for post-marketing reports, and there are also strengths, being that this database includes all U.S. marketed drugs. We get worldwide reporting on many of these medications.

It is very simple, in a sense, and very inexpensive, because they are spontaneous reports, processing of those reports and, therefore, a very useful tool, and also it provides a very early detection system for serious signals which are rare, especially rare signals like anaphylaxis or liver

failure, aplastic anemia and things of that nature.

The limitations are serious. There is underreporting of adverse events. It may vary from drug to drug or over time. Most of what we get in terms of reports are really a nonrandom sample of an unknown universe of adverse events that may occur with any medication intake.

The quality and the completeness of reports also varies, depending on where the reports are coming from and who reports them. Often they are very poor, and based on these reports it is very difficult to do estimates of event rates or risk, or really measuring risk of an adverse event.

The numerator is uncertain, because of underreporting and variable quality. The denominator in terms of who is at risk, who is taking the medications, is again very difficult. Often it has to be estimated, virtually impossible for really getting national estimates for inpatient drug exposures or often they are developed through access to outpatient clinics where medications are usually given for oncologic drug products, for example, and very little

data on OTC products.

In terms of the materials you will be reviewing today, primarily the focus is on pediatric adverse event reports during the one-year period. So, really, the reports that you get in your package include the Office of Drug Safety assessment of the post-exclusivity adverse event review.

We also provide you in your package and in the presentations the pediatric drug use data, so that is a measurement of the frequency of use of this medication in the pediatric population, sort of a surrogate measure for the exposure.

We have better data on outpatient drug use frequencies projected nationally, most of them from IMS or from pharmacy benefit organizations. The inpatient use data currently do not have an ability to project nationally. We do have data from pediatric hospitals and nonpediatric hospitals as well, which you will hear about in subsequent presentations, also in your packets in detail.

In addition to these primary reviews, we have also the summaries of the clinical and

pharmacology-toxicology reviews and exclusivity studies. That would be summarized in some of the presentations where it is appropriate. Otherwise, you have all those materials in the package also for your review. It is also publicly available on the FDA website.

We also provide you the drug product label and the published literature pertinent to the issue at hand, and also the sponsor's materials, presentations when they become available.

So continuing the conversation we started maybe two years before, we try to make it more efficient in terms of your time here. We have briefer reports when we find no new sector signals or safety concern for any product. We normally provided a whole package of materials and background material, but in terms of the presentation we do very brief report, and we ask you for your comments and concurrence that we have no safety concern raised by the reviews.

Standard presentations are sort of a little more fuller presentation where we really don't have any unlabeled new safety concern, but we have

encountered some labeled serious adverse events that may benefit from a public discussion or they are not very well known -- the example is Cipro -- or there has been some recent interest, public interest, in the drug where we felt that it would be beneficial to discuss them, giving more sort of in the presentations.

In that presentations really where we felt that there are maybe possible safety concerns or the reported adverse events warrant further review, and we have done that before with fentanyl transdermal system where we felt that there was a suspected safety concern, and that will be where we do an in-depth presentation.

Then the other type of presentation we have done, and we will continue to do at the entire Advisory Committee meeting where -- or session dedicated to drug or class-specific safety concern, which you participated in for the SSRIs before and where we will be doing one for ADHD drugs in the spring next year.

So in that sense, I will -- You know, in

terms of the presentations that we will be doing today, bringing presentations for most of the products listed on this slide. We will do a lot more for Fluconazole because of the level of interest in -- the type of events that we have seen in the AERS reports, some serious reports, mostly labeled, but probably felt that this would be beneficial to discuss at the Committee level and getting input.

We are going to do an in-depth presentation for Tamiflu, because we felt that the reports warranted further review because of the unusual nature, mostly coming from one country, Japan. We will do the one-year post-exclusivity adverse event review, and the drug is reviewed here in detail, and the summary of materials from our interactions with the Japanese regulatory agencies.

Then we will do more of the summaries of the literature and pediatric and trial review, a presentation that will be done by the Division of Antivirals; also from CDC, just a little more. I think that will be beneficial to discuss in terms of influenza surveillance in the U.S., and with a focus

on pediatrics. Then there will be a presentation from the sponsor.

Finally, at the end of the day -- we have to get you out by 1:30. You have had a very busy two to three days, some of you, and the Committee discussion will be where we will discuss some of these very important questions regarding Tamiflu.

With that, I want to acknowledge the contributions of the Division of Pediatric Drug Development. Several medical officers are involved in the review: The Office of Drug Safety, specifically the DDRE and DSRCS; the Office of New Drugs, especially the Division of Antivirals who have been very integral to this review process, and the Office of Pediatric Therapeutics under whose auspices these Advisory Committee meetings are hosted. Thank you.

CHAIRMAN NELSON: Thank you, Solomon. Let me ask if there is anyone in the audience who would like to speak in the open public hearing portion of the meeting. Hearing and seeing none, we need to take a short break. I've been told we will be moving the podium. I guess it's in the way of the cameras.

So we will be moving that to the side. So we will take a five-minute pause, and then we will restart our agenda.

(Whereupon, the foregoing matter went off the record at 8:38 a.m. and went back on the record at 8:43 a.m.)

CHAIRMAN NELSON: We have, I think, three new people at the front table that we should also introduce. Why don't we do that? I think we have had three new people join us, one from the elevator. We'll let you guess who it is. Why don't we start over with David, if you want to just introduce yourself, and then Angela and then Judith.

DR. SHAY: Thanks. Good morning. I am David Shay from the Influenza Branch at CDC.

MEMBER. DIAZ: Angela Diaz, Department of Pediatrics and Community Medicine, Mount Sinai School of Medicine, and Director of Adolescent Health.

MEMBER O'FALLON: Judith O'Fallon, biostatistics, Emeritus Professor of Statistics at the Mayo Clinic, and recently released from the elevator.

CHAIRMAN NELSON: Reminds me of the old

song, "The Man Who Never Returned" on the MTA in Boston.

Susan, let me introduce you. A neonatologist whose previous experience included academic neonatal practice at Johns Hopkins and Childrens National Medical Center, she received her Master's degree in education and has worked on computer-based education models for pediatrics, and she is going to present, I guess, the first four drugs, which I think Jan did a wonderful job pronouncing. So I won't do it again.

DR. McCUNE: Thank you, Dr. Nelson. Ladies and gentlemen of the Committee, thank you very much. I just want to acknowledge that I do have a Master's in education technology, and I want to apologize for the wordy slides, but I am not clever enough yet to figure out how to turn them into creative slides, but I am working on that.

As Dr. Iyasu pointed out -- and I just wanted to make sure everyone can hear me okay, and I just wanted to be in profile. That's why we had to change everything here. As Dr. Iyasu mentioned, I

really do abbreviated presentations of the one-year post-exclusivity safety monitoring for the four drugs that you mentioned, and the first drug that we are going to talk about is Sumatriptan.

The background information on the drug is: This is Sumatriptan nasal spray, trade name Imitrex. Its therapeutic category is that it is a selective 5-hydroxytryptamine receptor agonist. The sponsor for Imitrex is GlaxoSmithKline.

The indication is for the acute treatment of migraine attacks with or without aura in adults, and it is not recommended for use in patients under 18 years of age. The original market approval was August 26, 1997, and pediatric exclusivity was granted on February 18, 2004.

For each of the drugs that I am going to discuss, I am going to give you some information that was added to the label based on the trials for exclusivity. For Sumatriptan nasal spray, the information that was added to the label are that there were two controlled clinical trials of 12-17-year-old patients with an N of 1248. Adverse events were

similar to those reported for adults, but the studies did not establish efficacy compared to placebo.

In terms of use of Sumatriptan nasal spray in the one-year post-exclusivity period, pediatric patients accounted for less than five percent, which was 3100 to 3500 approximately) of all paid prescription claims for Imitrex nasal spray from March 2002 to February 2005.

In terms of the adverse event reporting in the one-year post-exclusivity period, there were six unduplicated pediatric adverse event reports. None of these reports were serious or life threatening.

So in summary, for Sumatriptan nasal spray there were no new concerning unlabeled safety signals identified in the pediatric adverse events reported through AERS in the one-year post-exclusivity period.

This then completes the one-year post-exclusivity adverse event reporting as mandated by the Best Pharmaceuticals for Children Act. The FDA recommends routine monitoring of adverse events for sumatriptan in all populations, and wishes to know if the Advisory Committee concurs.

I think I will put up the acknowledgements for all the people that were very helpful from both the Division of Safety and also the Review Division and, while I have that up, I will answer any questions that you have about sumatriptan nasal spray.

CHAIRMAN NELSON: Do you want us to take action on each individual drug or just, when we get to the end of the seven, we will just consider it as a group?

DR. MURPHY: We were going to ask you to consider them as a group.

CHAIRMAN NELSON: So why don't we just see if there's any clarifying questions and pause for a moment, but if not, we will run through the other reports.

DR. McCUNE: All right. The second drug that we are going to talk about for the one-year post-exclusivity adverse event review is Irinotecan.

In terms of background information, irinotecan hydrochloride injection, trade name Camptosar, is an antineoplastic agent. This drug is sponsored by Pfizer.

The indication for irinotecan is a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. Effectiveness in pediatric patients has not been established.

The original market approval was June 14, 1996. Pediatric exclusivity was granted on March 10, 2004.

In terms of pediatric information that was added to the label: PK information, including clearance and AUC, were added, and adverse event data from the exclusivity studies were added to the label. This includes statements about pediatric adverse events in the exclusivity trials that included neutropenia, diarrhea, dehydration, hypokalemia, hyponatremia, and infection. It also includes information that accrual to the single agent irinotecan phase -- there was a single agent phase and also a combined phase -- was halted due to the high rate of progressive disease 1928.6 percent) and the early deaths (14 percent).

In terms of use information, this is very difficult to obtain, since the data resources available to the agency do not capture the use of irinotecan and other antineoplastic agents that are given in the outpatient clinic setting. For this drug, that represents approximately 75 percent of its use.

In terms of a premier database, this revealed that pediatric use was noted in 16 percent or 205 discharges in which irinotecan was billed between 10 of 2002 and 9 of 2004.

In terms of the safety and adverse event reporting for the one-year post-exclusivity period, there were nine pediatric adverse event reports, of which four were unduplicated.

There were two deaths. Those two deaths include a patient with Wilms' tumor that progressed and a patient with paraneoplastic meningoencephalitis that was associated with the patient's underlying diagnosis of neuroblastoma.

So in summary for irinotecan hydrochloride, there were no new unexpected safety

signals identified in pediatric adverse event reported through the AERS system in the one-year post-exclusivity period.

This then completes the one-year post-exclusivity adverse event reporting as mandated by BPCA, and FDA recommends routine monitoring of adverse events for irinotecan in all populations, and asks for the Advisory Committee's concurrence.

In terms of acknowledgements, once again I would like to acknowledge the Office of Drug Safety and the Review Division, and I would like to open it up for any clarifying questions.

CHAIRMAN NELSON: Seeing none, let's go.

DR. McCUNE: The third drug that I am going to review is carboplatin. Carboplatin aqueous solution, trade name Paraplatin injection, is also an antineoplastic agent. The sponsor for Paraplatin is Bristol-Myers Squibb Company.

The indication for Paraplatin is for initial and secondary treatment of advanced ovarian carcinoma. Safety and effectiveness in pediatric patients have not been established. The original

market approval was March 3, 1989. Pediatric exclusivity was granted on April 30, 2004.

In terms of new information added to the label, there was no new information added to the label based on the exclusivity trials. The adverse events in the exclusivity trials were similar to those of adults and were similar to those that were already labeled. So the label was unchanged.

IN terms of use information, as I discussed with the previous drug use, use information is very difficult to obtain, because the data resources available to the agency do not capture the use of carboplatin, which is given in the outpatient clinic setting, and this for carboplatin represents approximately 60 percent of its use.

In terms of the Premier database analysis, this revealed pediatric use in 2.9 to 4 percent of discharges, for a total of 168, in which carboplatin was billed between January of 2004 and December of 2004.

In terms of the adverse event reports in the one-year post-exclusivity period, there were 43

pediatric adverse event reports, of which 36 were unduplicated. Most of these events are currently labeled or would not be unexpected in association with the disease or the concomitant medications that the patients were receiving.

Of note, there were four deaths, nine life threatening events, and six events that required hospitalization. In terms of the deaths, two of the deaths were related to disease progression. One death was in a patient who had an arrest during stem cell infusion. Carboplatin had been used for bone marrow conditioning prior to the stem cell transfusion, and one death due to acute myocarditis that was possibly related to ifosphamide or infection.

In terms of those 36 unduplicated reports, there were a couple of unlabeled events that warranted further analysis. Portal vein thrombosis was noted in two children who were no multiple additional chemotherapeutic agents, and there was one case of blindness secondary to eye swelling and optic nerve atrophy in a patient with bilateral retinoblastoma who received subtenon carboplatin, cryotherapy and

systemic chemotherapy.

In terms of evaluating the importance of these two, portal vein thrombosis has been associated with use of dactinomycin in the literature, and also based on an ODS consult in July of 2005 with vincristine.

Having noted this, off-patent Written Requests were issued in 2004 to evaluate the safety issue, particularly related to hepatic disease and hepatic veno-occlusive disease for both dactinomycin and vincristine, and that study is currently in progress through NCI and COG.

So in summary for carboplatin aqueous solution, most of the adverse events, with the exception of hepatic veno-occlusive disease and blindness, reported in the one-year post-exclusivity period are currently labeled or would not be unexpected in association with the disease or the concomitant treatments received by the patients.

This then completes the one-year post-exclusivity adverse event reporting as mandated by BPCA. The FDA recommends routine monitoring of

adverse events for carboplatin in all populations, and wishes the Advisory Committee's concurrence.

Once again, I want to acknowledge the Office of Drug Safety and the Review Division, and while I have those up, we will take any clarifying questions.

CHAIRMAN NELSON: Bob?

DR. WARD: Susan, have you had any access to COG data about their adverse event profiles? This is an area of pediatric medicine where we really do have comprehensive enrollment of children in carefully monitored trials, and it would seem to me that it would be helpful for the FDA to use their data, if possible.

DR. McCUNE: That is exactly why we wrote these off-patent Written Requests and worked with NCI to design them to get the safety data from these databases, and actually they have put together a tremendous program, and they are doing both PK and safety for these drugs that are currently in trials, particularly focusing on dactinomycin and vincristine, and particularly related to veno-occlusive disease in

these -- especially in the younger kids.

Yes, ma'am?

MEMBER KNUDSEN: In one of the reports that were submitted about this drug in the Executive Summary, it says that you had found the analysis performed by the sponsor inconclusive and suggested that discarding of data from analysis is discouraged.

What's been happening?

DR. McCUNE: I'm not sure I know exactly what you are -- Is this the review of the exclusivity trials? Oh, okay. I don't know the status from the perspective of the Review Division.

I know that the Review Division discussed long and hard about what information to put in the label, based on these trials, and felt that, while the information was not conclusive enough to establish efficacy or even to include the PK data because of some issues related to drug dosage and patient enrollment, that they also felt that it was not significantly negative enough to put negative data in to discourage it being studied. But I don't know right now what the status of the drug in the Review

Division is or in terms of COG and their approach to studying this drug.

CHAIRMAN NELSON: Tom?

MEMBER NEWMAN: I have the same concern, and I think maybe we need another time or another agenda item to discuss this. But the Executive Summary that studies use to establish exclusivity really raised concerns about what kind of studies need to be done to get exclusivity and what the quality is and whether they really need to have any value at all.

The recommendation to the sponsors that they discourage discarding data and they look at prior studies to be able to tell what they are doing -- They say the differences are inconclusive due to small sample size, N equals 5. You know, I think we at some point should look at what studies are being done, and is there any quality standard to allow the exclusivity, or else not put the stuff in our packets, because it just is troubling to read.

DR. McCUNE: I know that the Review Division felt, when the written reports were issued -- They certainly felt that what they had asked for was

going to give additional information. This particular drug was studied in combination, and so part of the problem was differentiating the single drug from the combination drug, and then when it came down to looking at CNS versus non-CNS tumors, wound up with really a number of different types of tumors. I think that that made the analysis difficult, but I hate to speak for the Review Division. But I recognize that, when there are small numbers, it becomes an issue.

CHAIRMAN NELSON: Getting into that topic would take us far afield, and having read a fair number of those reports, I think sometimes those are legitimate questions, but there is also an evolution over time in terms of the Written Request, etcetera. So that's as much a moving target.

DR. MURPHY: I just wanted to respond to Tom's comment, in that the whole arena of what types of trials should be done for exclusivity, because of the nature of the cancer trials and the nature of the small numbers, it has been extensively discussed with COG, and actually there is a guidance out on what kind of approach we need for pediatric exclusivity; because

it is a real issue, but people have thought a lot about it.

Yes, there are concerns, and it's nice to know the committee reads all these in detail, but it is not because people aren't thinking about it and trying to deal with it.

CHAIRMAN NELSON: Thank you. Proceed.

DR. McCUNE: Finally, I am going to present the post-exclusivity review of rofecoxib. The background information for rofecoxib, for Vioxx, the trade name Vioxx, is that it is a nonsteroidal anti-inflammatory COX-2 inhibitor. The sponsor for this drug was Merck.

The pediatric indication based on the exclusivity trials was the relief of signs and symptoms of pauciarticular and polyarticular course JRA in patients greater than two years of age and greater than or equal to 10 kilograms.

The original market approval was May 20, 1999. Pediatric exclusivity was granted in February of 2004. The pediatric indication was approved on August 19, 2004, and the drug was withdrawn from the

market on September 30, 2004.

In terms of the use information, of the nearly 20 million prescriptions dispensed in 2003, approximately 220,000, or 2.2 percent, were dispensed for pediatric patients.

In terms of the adverse event reports during the post-exclusivity period, which amounted to a seven-month review, was that there were 9,626 reports of all ages, including 1,049 deaths. During that period of time there were 19 pediatric reports, 16 of which were unduplicated, including three deaths.

I am going to talk to you about those three deaths. These were all foreign reports. The first was an adolescent with a salt wasting syndrome who died after receiving treatment with rofecoxib for 18 months. Post-mortem showed aspiration, pulmonary emphysema, bleeding underneath the pulmonary pleura, significant enlargement of the heart, with no evidence of MI. Infection and myocarditis could not be ruled out.

The second case was a pre-adolescent with JRA who was on rofecoxib 25 mg who died five months

after treatment, and the complaint was chest tightness. The other medications that the patient was on were methotrexate, Chinese traditional medicine, and spiruline, which is an herbal product.

The final death was an expected fetal death following an elective abortion. The examination of the fetus did not reveal any pathologic findings. The mother was on rofecoxib for an unspecified indication.

So in summary for rofecoxib, there were no new concerning unlabeled safety signals identified in the pediatric adverse events reported through AERS in the post-exclusivity period.

This completes the one-year post-exclusivity adverse event reporting as mandated by the Best Pharmaceuticals for Children Act, and no further monitoring is necessary, as the drug has been withdrawn from the market.

Once again, I would like to thank members of the Office of Drug Safety and the Review Division with help with this review, and I open it up for any clarifying comments.

CHAIRMAN NELSON: Thank you, Susan.

DR. McCUNE: Thank you very much.

Finally now, it is my privilege to introduce another neonatologist. We are going to take over the world. Dr. Larry Grylack is a pediatrician and a neonatologist who practiced neonatal medicine at Columbia Hospital for Women in Washington, D.C. for a number of years.

His clinical interests are high risk infant development assessment and infant apnea, and he has participated in clinical research and teaching. Larry.

DR. GRYLACK: Thank you, Suzie. It is a privilege for me to work with Suzie, and along with Doctors Ward and Fant, you know, we give testimony to the fact that we can talk about patients who are older than the one-month phase.

There's been a slight change in the order of presentation. We will start with fluconazole. First of all, I would like to mention that Dr. Hari Sachs performed most of the preparation for this slide presentation, but she is wearing one of her other hats

this week. She is attending the American Academy of Pediatrics' Committee on Drugs in Chicago, meeting in Chicago.

I was thinking of lip synching, but most of you have seen Hari and I before, and heard us. So that wouldn't work, and I'm sure there is a Federal regulation against lip synching. So I'll proceed with the presentation.

Diflucan is an antifungal drug manufactured -- sponsored by Pfizer. It was approved in January of 1990 and was granted pediatric exclusivity in January of 2004, based on studies done in pediatric patients with tinea capitis. Fluconazole is a selective inhibitor of a fungal cytochrome pathway.

Fluconazole is indicated for the treatment of Candida and cryptococcal infections and for prophylaxis against Candidiasis in bone marrow transplant patients greater than six months of age.

Doses are listed here for children, with a specific recommendation for dosing interval in the treatment of preterm neonates.

In response to a Written Request, two efficacy and safety studies were performed in pediatric patients with tinea capitis, comparing fluconazole to standard doses of Griseofulvin. Fluconazole treatment was not superior to Griseofulvin. Efficacy was not established, and no labeling change was made. No abnormal cardiac events were described in these trials.

In addition to the clinical studies performed for exclusivity, an animal cardiac study was performed to characterize fluconazole's effect on the QTc interval. This two-week trial in male beagles reaffirmed the potential for increased QTc intervals,

diazole antifungal drug products.

The label carries a bolded warning regarding potentially fatal hepatic toxicity. The precaution section details the class effect of azoles on the QT interval and the need to avoid the drug use in patients at risk for pro-arrhythmic events.

Prescribers and patients are cautioned to weigh the higher incidence of adverse events due to Diflucan compared to topical intravaginal anti-yeast

products. Multiple drug interactions are also described in the label.

Fluconazole is characterized as pregnancy Category C, and I have defined on this slide what that actually means.

At high doses -- that is, 20 to 60 times the typical doses in humans -- embryo lethality in rats increased, and fetal anomalies such as wavy ribs, cleft palate, and abnormal craniofacial ossification occurred. There are no well controlled studies in the human, but there are case reports of congenital anomalies from multiple or single dose treatment in the literature.

Regarding usage, fluconazole products are dispensed commonly, with over 11 million tablets, suspension or generic products, sold annually. While the majority of the outpatient prescriptions for all products are for adults, infants, particularly in the one to two-year age range, accounted for almost three-quarters of the outpatient prescription for fluconazole oral suspension, amounting to over 300,000 prescriptions. Pediatricians and family practitioners

were the top prescribers of the suspension.

Now during the one-year post-exclusivity period, pediatric patients accounted for less than seven percent of the total 400 total adverse event reports. There were 29 total, and 19 unduplicated pediatric reports.

Serious adverse events, including deaths, did occur. However, all of the serious adverse events may be associated with the patient's illness or concomitant medications or are addressed by labeling.

The 19 unduplicated spontaneous pediatric adverse event reports included four fatalities. Two of the deaths occurred in children who were receiving intravenous multi-dose therapy for suspected or confirmed systemic fungal infections. Their deaths may have been related to their underlying illnesses or concomitant medications associated with similar toxicities to fluconazole.

Two neonatal fatalities were reported to be associated with single-dose therapy and maternal exposure. One of these was a stillborn infant with a congenital anomaly who was remotely exposed to the

drug six months prior to conception.

The breast-fed infant with sudden unexpected death died one day after single dose treatment in the mother. Death was described as asphyxia and sudden infant death syndrome in the case report, but an autopsy was not performed. Labeling for fluconazole includes potential transmission of the drug into breast milk.

There 15 patients with non-fatal adverse events reported during the one-year post-exclusivity period. These adverse events are broken down on this slide into seven categories, and five of these adverse events were associated with single dose or short term therapy -- that is, less than three days duration. Most of the 10 adverse events associated with multiple dose therapy were potentially confounded by the presence of underlying illness in addition to the fungal infection and/or concomitant medications.

Three nonfatal events were associated with maternal exposure. A genital urinary anomaly was associated with rather remote exposure to fluconazole, given the half-life of fluconazole of about 30 hours.

The second was a skeletal anomaly which has been described in animals. The third patient had microcephaly and ophthalmic abnormalities.

These anomalies may have resulted from congenital infection or first trimester concomitant therapies, as well as exposure to fluconazole.

So in summary, the number of pediatric adverse events reports were small compared with those in adults, which parallels the use patterns. Most of the adverse event reports were potentially confounded by concomitant illness and/or medications. No new safety concerns were identified.

Pursuant to the one-year post-exclusivity adverse event review, the FDA recommends routine monitoring of adverse events for fluconazole in all populations. We are asking whether the Advisory Committee concurs with this recommendation.

Finally, I would like to acknowledge all of the individuals who participated in this review, and we have Dr. Nikhar from the Division of Dermatology and Dental Drug Products actually in the audience, and I thank her for being here. I am not

sure in the interim whether others have walked into the room from the Office of New Drugs.

Any clarifying questions on the presentation?

CHAIRMAN NELSON: Go ahead.

DR. GRYLACK: I will proceed, if there are no questions. Yes, ma'am?

DR. ENGLUND: The question I have is to what age is this exclusivity down to? What is the minimum age? You have given us data down to one year. It's used, as you know, sometimes all the way down to zero day. So --

DR. GRYLACK: Well, you know, as you saw, the dosing has been described into the preterm. So the dose being the same, but the intervals being different in that population. So, certainly, there is information in the label about patients even down to the newborn range.

MEMBER KNUDSEN: Dr. Grylack, tell me the upper age limit. Are women -- I mean girls who have reached menarche also included? But on the children, I saw 12 years. I didn't see any reports over that

unless I skipped it.

DR. GRYLACK: Yes. It is indicated for adults and children greater than six months of age in the label. That's what the label says in terms of the indication. However, there is further information, as I mentioned, about patients below six months of age in terms of dosing. But that's what the indication reads. So it includes patients all the way up the scale in terms of age.

CHAIRMAN NELSON: Okay. Proceed.

DR. GRYLACK: Thank you. The next presentation will be about anagrelide. Again, Dr. Sachs contributed heavily to this slide presentation, and the trade name for this product is Agrylin.

It is a platelet reducing agent. The sponsor is Shire, and it is indicated for the treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, in order to reduce the platelet count and thrombosis as well as ameliorate symptoms.

Market approval and exclusivity dates are listed on the slide.

We get to the summary quickly. This is an abbreviated presentation, and the pediatric exclusivity studies performed with anagrelide resulted in labeling describing pharmacokinetic and clinical study results.

Pediatric use equals 0.2 to 0.3 percent of all prescriptions for this drug. No pediatric adverse events were reported during the one-year post-exclusivity period.

Pursuant to this finding, the FDA recommends routine monitoring of adverse events for anagrelide in all populations, and asks whether the Advisory Committee agrees.

Again, our acknowledgement and our appreciation to all of these individuals. Dr. Min Lu, in particular, here is in the audience, I know, and we thank her and her colleagues, and the Office of Drug Safety, of course.

CHAIRMAN NELSON: We do have one question.

DR. GRYLACK: Yes, ma'am?

MEMBER O'FALLON: From the statistician, of course. I think I figured out that you had 245.

Was that it? That's the estimated number of prescriptions. Is that correct? I saw that somewhere, because I got a nice little number here.

DR. GRYLACK: I have the usage report here.

MEMBER O'FALLON: I mean, it is not included in your slide, and this just brings me to -- This always bothers me. If we had only a handful of prescriptions during that year, I wonder if we've gained enough information in that small number to really be able to tell whether this is safe in kids. That's my -- It's a principle here.

CHAIRMAN NELSON: What I might suggest is, after the next presentation, I was going to ask someone to describe what routine surveillance is before we make a decision about fostering that. I think that might answer your question. Routine surveillance doesn't mean that we just stop surveilling. So there, obviously, is an opportunity.

DR. GRYLACK: But you are correct in that 245. I verified that in usage report. Thank you.

All right, moving on to the third drug.

Did this all by myself, and this is -- We are going to talk about sodium ferric gluconate complex in sucrose injection, and that is the full name of the drug.

The trade name is Ferrlecit, and it is a hematinic compound indicated for the treatment of iron deficiency anemia in adult and pediatric patients greater than or equal to six years of age who are undergoing chronic hemodialysis or receiving supplemental epoetin therapy.

Somewhere along the line, the extra i got dropped out of erythropoietin when it was changed to epoetin. Just a serendipitous observation I have made.

The drug was approved in 1999 and received pediatric exclusivity in 2004.

Labeling changes resulted from the exclusivity studies, citing safety and effectiveness in pediatric patients six to 15 years of age, while indicating that no studies were done in children less than six years of age.

Information on dosing, pharmacokinetic parameters and adverse events are also included in the

label. The adverse event profile in pediatric patients six to 15 years of age is similar to that reported in metals.

Regarding usage, the inpatient use ranged from about 11,500 to almost 14,000 discharges during the years 2003 to 2004 for all ages. Less than one percent of usage occurred in pediatric patients, however. There was no outpatient usage data available to the FDA.

In summary, there was one labeled pediatric adverse event since exclusivity. Subsequent to the completion of the one-year post-exclusivity monitoring of adverse events for gluconate complex in sucrose injection.

The FDA recommends routine monitoring for this drug. Does the Advisory Committee agree?

Again, we have acknowledgements for the Office of Drug Safety, as well as the Office of New Drugs. Again, Dr. Min Lu is here with us today from the Office of New Drugs.

Thank you for your attention on these three presentations. It has been a privilege, again,

to report to this Committee.

CHAIRMAN NELSON: Thank you. I would like to suggest before we take action on the question of routine surveillance for these seven compounds, for the benefit of the new members of the Committee, if someone would like to just simply describe what routine surveillance means, so that we understand and it isn't returning to a lack of attention to adverse events.

DR. MURPHY: Sure. I just want to say, just briefly, that for the pediatric mandated review, you have the exclusivity being granted, and then there is a one-year period where the safety evaluators for that drug will go and look at the AERS reports during that one year, and then report to you. But over and beyond the daily, there is routine surveillance of all post-marketed drugs.

Those AERS reports are coming into the Office of Drug Safety. In particular, in the Division of Drug Risk Evaluation, their safety status is assigned to the drug groups, and for serious and unexpected reports that are coming into the inbox,

those are screened pretty much on a daily basis.

So I do want to reassure you that after this report doesn't mean it is over, that there is continuous surveillance. Dr. Trontell wants to add to that.

DR. TRONTELL: I just wanted to reinforce Dr. Johann-Liang's point, which is that we are doing intensive surveillance on a daily basis. BPCA specifies a systematic review for a specified time period, but routine surveillance that would come after a meeting such as this would include the daily review of the serious and unexpected adverse events by our safety evaluators.

The accumulation of one or more cases, particularly if they meet many of the criteria that Dr. Iyasu described, could trigger yet another systematic review and update of the information, and that has no time period. We are doing this on, again, a daily basis.

MEMBER O'FALLON: My question is, though -- I know that you are picking up all the reports. That's not the issue. The issue is whether you are

looking at the number -- at the denominator. That one you, obviously, have to go look for. That is, obviously, something that you have to work at getting the information, and that is what I meant.

So you see one come in. If the denominator is small, it is more important than if the denominator is large, and that's all I was asking.

DR. JOHANN-LIANG: I do want to also say the routine surveillance goes on. The reports are coming in, but let's say there is a concern about a signal. We have a whole division, Division of Surveillance, and they do provide -- We would ask for usage information at that time, to try to put the whole story together. It's not just the reports in isolation, obviously. So we do recognize it.

CHAIRMAN NELSON: Bob and then Marsha.

DR. WARD: Let me just try. The areas of concern are where the reports are quite limited at this time. So in essence, the numerator would trigger all by itself, I think, a review at that point, because we have those with no adverse events reported.

CHAIRMAN NELSON: Marsha.

MEMBER RAPPLEY: I'm new to the Committee. So there are lots of things I don't understand. But if the regular routine surveillance is adequate, then why do we have a period of exclusivity, and why is there special attention to pediatric safety issues, and is the burden to the manufacturer so great to continue this special reporting that, when we have circumstances where either we don't have enough numbers, where we have confounding type of conditions, that we can't really make a decision about the safety, why not continue it?

CHAIRMAN NELSON: I'm sure the FDA may want to respond, although I need to give a first attempt at the answer.

When the exclusivity was renewed in the BPCA back in -- 2001? -- '02, in that law was a specific mandate for review of this data within a year after granting exclusivity by this Committee. Basically, the surveillance is routine, is happening all the time. The only difference is that, unless there was a new concern that was raised during that surveillance, it would not return to this Committee.

MEMBER RAPPLEY: So it's only the scrutiny of the Committee that's different?

CHAIRMAN NELSON: Correct. And the report that's generated -- there is more activity around it, but it is not as if the surveillance stops, and reporting this, I think Solomon mentioned, on the part of the sponsors is mandatory of all adverse events throughout the time, before, after. So there is no real burden on the sponsor that is different.

You could argue the burden is on the Office of the Pediatric Therapeutics in putting together these specific reports, in addition to the monitoring that is ongoing through their normal activity within the Office of Drug Safety. Is that fair?

DR. WARD: The philosophical underpinnings were that BPCA would lead to increased exposure of children to medications and that, with that, came a responsibility to carefully monitor for whether there was an adverse event that is unanticipated and not replicative of the experience in adults.

CHAIRMAN NELSON: It is certainly within

our purview if we thought there was something in any of these reports that would suggest coming back to us, as we may see in the next one. We always have that -- We can always exercise that discretion. I think Dianne wanted to say something.

DR. MURPHY: I think that the points that you are really important in that there is routine surveillance, as has been described. Sponsors, you know, I hope, religiously turn in their adverse event reports as they are supposed to. The agency gets them. The agency looks at them for the serious ones.

I think that the -- and the theory behind needing additional focus on pediatric safety with all the new activities that have been going on has been explained.

I think what the process does do is it, in essence, puts everybody on alert, if you will, that this product is going to come up for review and that there is going to be transparency and a focus on what is going on, so that you have an additional -- You do have an additional burden, and there is no question about that, within the agency; and the Office of Drug

Safety does generate, as you saw, significant analysis and report.

We have to bring together not just Office of Drug Safety but the Review Division that reviews this, the Division of Pediatrics. All these people need to look at this.

One needs to weigh, which is another one of those risk-benefits, that something that we think is worthwhile. Out of this process -- we are now up to 50 -- we have had a number of events which have either independently identified an issue or have been in parallel with activities going on within the Division and the Office of Drug Safety that have been pediatric-specific and have required greater attention.

So that, I think, is a summary of why we do it, how we do it, and what benefit we think it provides.

CHAIRMAN NELSON: If we are going to -- I might add, there has been a considerable evolution over time of the, I would say, sophistication of the analysis and reports. When this first started out a

number of years ago, we had no denominators.

So if you recall, there's been a lot of discussion about those reports, and there's been a lot of effort in getting that kind of information. So there's been an evolution even of this abbreviated, extended and middle report.

So this is -- What you are seeing now is -- and I'm sure it will continue to evolve -- is part of a process that started a number of years ago.

DR. MURPHY: I do want to say that - Skip, thank you -- that we are learning, and we are trying to improve as we go along. One of the options, though, I also want to point out: The Committee has occasionally said just this: We don't have enough data; we want you to come back.

CHAIRMAN NELSON: Angela, then Elizabeth.

MEMBER DIAZ: When a medication is withdrawn from the market like Vioxx was, what are the implications for the surveillance? Does that change? What do we do at that point?

DR. MURPHY: Well, if a report comes in and it is serious, they look at it. But it is not on

the market. So, theoretically, people shouldn't be taking it.

CHAIRMAN NELSON: Someone has a stash in their closet, I bet.

DR. JOHANN-LIANG: There is one thing that I do want to clarify. The AERS reporting system, as was mentioned earlier, is a voluntary, spontaneous reporting, although there are requirements with certain regulatory actions from the sponsors.

So for the most part, if it is reported to us, we look at it. We do not go out and solicit surveillance. This is an interesting point, because as we discuss Tamiflu later, you will see that there are different types of reporting. Surveillance is routine. Monitoring -- that's built into the regulatory systems of different countries, but in the U.S., you know, if there is a case of Vioxx that comes in, we will look at it, but we are not going to go out there and solicit that type of surveillance.

CHAIRMAN NELSON: Elizabeth.

MEMBER GAROFALO: I thought I would just add that, of course, the companies were looking at the

safety data on an ongoing basis as well, but this one-year review does bring more focus. We would have sales information, but we also don't know, unless we go out and solicit, what the use is necessarily in pediatrics versus adults, and the pediatric PHRMA committee has been very interested in making these the most beneficial reviews that we can.

So I think it is useful all the way around, because we are doing this work as well, but it brings a special focus to pediatrics. We might know within our individual company what is going on, but we don't know other companies' information. So there's a chance to look across all of the drugs that are being used in children. So we think it's a good thing, too.

DR. JOHANN-LIANG: That's a very important point. Just to add to that, you know, we are looking at these reviews by mandate one drug at a time, but often what -- you know, just looking back, just trying to do some metrics of what has happened is that it often does bring up an issue where multiple drugs are involved, and looking at it from the perspective of the children.

So that is very -- That is something that goes beyond the routine surveillance.

CHAIRMAN NELSON: What I would like to suggest is that we take action at least on the first question about these seven drugs. I am sure, when we get to the further discussion, we may have other points to make about more general issues around surveillance, particularly the differences between the United States and Japan, which may come up in discussion.

So what I would like to do is, I guess the first question is that the FDA is recommending a return to routine surveillance, which we have heard is still considerable surveillance, for seven of the products that have been presented to us, and is asking if we concur with that recommendation.

So I guess from a voting procedure point, Dianne, can we just take it for a show of hands? Is that appropriate, or do we have to go around the room?

DR. MURPHY: I think a show of hands, unless there was some contentious issue.

CHAIRMAN NELSON: Okay. We will find out

when I ask for a show of hands. So I guess the question would be: All those in favor of returning to routine surveillance for the seven drugs that have been presented to us, if you could just raise your hands, and I will make note. Anyone disagree with that?

Paula was out of the room. So let me reframe the question.

MEMBER KNUDSEN: Please. Thank you.

CHAIRMAN NELSON: All right. We will ask again. So the question is, all those who are in support of the FDA's recommendation that the seven drugs that we have had presented are returned to routine surveillance, raise your hand. And make sure you take it down now.

Then those who disagree with that? So it shows that the Committee is unanimous in agreeing that these can be returned to routine surveillance. Thank you.

Now what I would like to do, in looking at the timing, is it would be a little bit too early for a break, and we have about an hour between now and

when the break was scheduled. So I am hoping we can get in the first two presentations before the break. Is that doable? The first two reports -- would that be fine, Dianne?

DR. MURPHY: We are counting on you keeping this moving, Skip.

CHAIRMAN NELSON: All right. We will start with the one-year post-exclusivity adverse event reports from Ms. Truffa, and we will take a break in between the next presentation and the sponsor's presentation, just so people know when they can get their coffee.

MS. TRUFFA: Good morning. I am Melissa Truffa, and I am a Safety Evaluator Team Leader with the Division of Drug Risk Evaluation within the Office of Drug Safety and, as stated, I will be presenting the topic of the one-year post-exclusivity review of the adverse events for Tamiflu (oseltamivir).

My presentation this morning will include a brief overview of the background and regulatory history, a few slides on the Tamiflu drug use, and then the majority of my topic this morning I will

spend on the AERS adverse reports for oseltamivir during the post-exclusivity period, which is defined as March 22, 2004 to March 22, 2005, and within that talk I will focus on three main topics of interest, which are the pediatric deaths and the most commonly reported adverse events during the post-exclusivity period, which are the serious skin reactions and the CNS effects.

As you will see as I start to go through the presentation, the vast majority of the reports that we have received during this post-exclusivity period were from Japan. So I am going to do a brief summary of what we have learned about the Japanese experience with Tamiflu.

Then I will conclude with a few summary points before Dr. Lewis completes her review today.

Tamiflu, or oseltamivir, comes in two types of -- sorry, technical problem -- user. Okay. Tamiflu comes in two types of dosage forms, which are oral capsules and oral suspension. It is one of two drugs in the therapeutic class of neuraminidase inhibitors. Its sponsor if Roche U.S.

Pharmaceuticals.

It is indicated for the treatment of influenza in adults and pediatrics one year and older, and for the prophylaxis of influenza in adults and pediatrics greater than 13 years.

You will see that it was originally approved, the Tamiflu capsules, in October of 1999, and its indication was treatment of influenza in adults. About a year later in November of 2000, it received a prophylaxis indication, and that was in adults and pediatrics 13 years of age and older.

About a month later, the Tamiflu suspension was approved, and that received an indication for the treatment of influenza in adults and pediatrics greater than one. You will note that there is a pending application with the Division of Antiviral Products for an indication of prophylaxis of influenza, and that would be in pediatrics 1 -12 years. As stated, its pediatric exclusivity was granted March 22, 2004.

Next I will talk about the drug usage data, and the source for the outpatient prescriptions

is Verispan. Verispan measures retail dispensing of prescriptions. Prescriptions are captured from a sample of approximately 51,000 pharmacies throughout the U.S.

The pharmacies in the database account for nearly all retail pharmacies, and represent approximately 55 percent of retail prescriptions dispensed nationwide.

I would also like to note that this does not include Internet or mail order sales.

We've talked a lot about numerators and denominators this morning, and I would just like to reiterate that this data is really being presented to kind of put the context of the use in Tamiflu into some kind of contact in relation the discussion of the safety.

These data cannot be used as a denominator to calculate incident rates versus the U.S. reports of safety data, and I just wanted to say that again, because I think it is an important point.

The first graph here I will walk you through is Tamiflu prescriptions dispensed by retail

pharmacies for all ages by flu season. As you will note, each bar or interval represents or captures one year of data, and we are defining that data as from July to June in order to capture an entire flu season.

So, for example, the first bar captures data from the July 1999 to June 2000. For the first four years of marketing Tamiflu was pretty consistent with its use, ranging between approximately 600,000 and 800,000 prescriptions for the 2000, 2001, 2002 and 2003 seasons.

In 2004 you will note that there was a pretty dramatic increase in use, to about 1.5 million prescriptions, and that's pretty much double what we had seen in the previous four years. Then in the 2005 season we saw we had another slight increase to about 1.8 million. Again, this is in all ages.

You may ask about the current flu season, which is just starting, because it's just November. So we don't have any data for 2005 or 2006. And I did want to make one more comment that is right there in the footnote. There is a total of approximately 6.3 million prescriptions for Tamiflu from marketing until

June of 2005.

The next slide stratifies the number of Tamiflu outpatient prescriptions by age. You will see that we only have three years on here, 2003, 2004, and 2005. That's because that is the only data that we have available to us.

In 2003 approximately 40 percent of the use was in pediatrics, and we are defining that as children age zero to 16. For that year in 2003, there was about 600,000 prescriptions overall, and about 200,000 or a little over 200,000 were in pediatrics.

In the next year, in 2004 and 2005 you will see that there was an increase in use to 1.5 and 1.8 million prescriptions, but the actual percentage in pediatrics went down, and you will see it ranged between 25 and 28 percent for those two years.

While the percentage of the overall use went down, the actual outpatient prescriptions written did go up to about 400,000, which is double of what it was the previous year. And I think this is obvious. The majority of the use, over 60 percent of it, is in adults.

Next we will move on to the review of the adverse events reports for Tamiflu in FDA's Adverse Event Reporting System, or AERS. This table includes raw counts of AERS events for Tamiflu from the AERS database from approval until April 22, 2005, which is the end of the post-exclusivity period.

Again, it should be noted, as has been said already multiple times this morning, that these cases represent -- noted that in some cases the reported clinical data in these reports is incomplete, and there is no certainty that the drugs caused the reported reaction.

Again, the reaction -- they actually have been due to underlying disease process were never a coincidental factor. Further, these data are generated using computer printouts, and some of the numbers may reflect duplicates.

I also wanted to note, the first line says "all ages," and that includes ages where age was not specified or ages with a null value.

The next line is adults, and then the final line is divided by pediatrics ages zero to 16.

You can't really add up the numbers, and I want people to know that, because some people will look at this and say the numbers don't add up. The reason they don't add up is because there are reports in the first slide when no age was specified.

I did want you to focus in onto the last row, and that's the one where we look at pediatrics. You will note that all the reports were serious that we received in the AERS database, and you will also note that a small percentage of them, 28 of 190, are U.S. reports, and that none of the death reports that we received were from the United States.

This next table is set up the same way as the previous table, but this focuses on the raw counts of adverse events from the post-exclusivity period. Again, I just want you to focus in on the last row with pediatrics, and you will note that all the reports that we received were serious by definition of their outcome, and that six of them were from the U.S. and that there were eight reported deaths during this period, but none of those were for the U.S.

Now I will spend probably the greatest

proportion of the morning taking a closer look at the pediatric adverse reports for Tamiflu received during the post-exclusivity period.

There were a total of 75 unduplicated AERS reports, and you will see the location or the source of them. Sixty-nine of them were from Japan. Five of them were from the United States, and one was a Canadian report.

All deaths, all eight deaths all are from Japan. Of the 67 non-fatal reports, 32 of them were classified as CNS effect reports. Twelve were skin or hypersensitivity reports, and then there was a multitude of other events, GI, musculoskeletal, abnormal lab values, vascular, infections, hypothermia, cardiac and overdose.

The first topic that I am going to go into more detail is the pediatric deaths. Because we had received eight deaths, we went back and looked at all of the deaths in the AERS database, and there is a total of 12 of them and, as I have said more than once this morning, eight of them were reported in the one-year post-exclusivity period.

There were 10 males, two females. The mean age was about four and a half years. The age range was from two to 14.

If you look at the current Tamiflu labeling, you will note that death is not mentioned and that there were no deaths in the clinical trials.

The source of the pediatric reports: All 12, again, are from Japan. I just wanted -- When we received eight in one flu season, that was kind of concerning to us. So we went back and actually looked at when the events occurred.

Eight were reported in 2004-2005, but you will note that four of those actually occurred in 2002-2003, and were just reported to us later, basically due to lag reporting time. You will note that the 2002-2003 season had five reported deaths, and 2004-2005 had four, and the other three were in multiple other flue seasons.

The four reports of "sudden death" from the 2002-2003 flue season are from a Japanese newspaper article. It was one reporter, and it was concerning children that died suddenly in their sleep

who were also on oseltamivir at the time of their death.

Since there are a relatively small number of reports, death reports, I will go into more detail with each of the 12 reports. For ease of presentation, I have chosen to break these into two very broad categories.

One of them is reports of sudden death and cardiopulmonary arrest. There are six of those in that particular group, and I have grouped those because I felt that they were similar.

The next ones that I grouped were pediatric deaths with confounding factors and limited information, and I should say that, even though the ones in the sudden death and cardiopulmonary are grouped differently, there is still limited information in many of these reports.

The first full reports are from that Japanese newspaper article, and there were actually very few details provided in these particular -- the AERS narrative text for these.

It should be noted that these Japanese

reports were all translated to English before they were sent to FDA. I don't know if you have had an opportunity to look in your packet and reading them. Some of them can be very difficult because of the translation just to understand, I think, the nuances of it, because they are translated from Japanese to English.

From these four reports from this Japanese article, there were two two-year-olds and two three-year-olds. Two were described as healthy, and two were described as having a history of asthma. All had influenza, and the report describes them as dying suddenly in their sleep one to two days after starting Tamiflu.

Two of the cases included a statement about autopsy results, and they stated that there was pulmonary and brain edema in one and pulmonary edema in another one. Pretty much what you are seeing on this slide is pretty much all the information we have about these deaths.

The next two -- and I am just going to read these. This is basically a two-year-old male

with influenza and mild pseudo-croup, developed difficulty breathing, and was taken to the hospital. En route, he suffered cardiopulmonary arrest and died. Encephalopathy and myocarditis were suspected. The patient had received one dose of Tamiflu before being taken to the hospital. No autopsies were performed.

In the final report in this category, you have a four-year-old female who was described as being in good general condition, was diagnosed with a fever and influenza. She received one dose of Tamiflu and complained of notable cold feeling and pain in limbs, and about 15 minutes later she developed cardiopulmonary arrest and died.

Again, there is really not a lot more information than you are seeing in this about these reports.

The next category has the final six reports, and these are ones that I classified as pediatric deaths with confounding factors and limited information.

The first one is a two-year-old male with multiple medical problems was diagnosed with influenza

and suffered cardiopulmonary arrest with pulmonary and brain edema three days after starting Tamiflu. He died of sepsis over two months later.

This one is confounded, because he had some co-morbidities, and also he died off Tamiflu. So causality sometimes could be difficult in relating it back to the use.

The next one is a three-year-old male who was hospitalized in the ICU with encephalopathy. he developed encephalopathy due to influenza and was in a coma, and then was hospitalized. An influenza test was positive.

He was admitted to the hospital, and he was diagnosed with influenza. So Tamiflu and amantadine were started after admission to the hospital. The patient died six weeks later of pneumonia.

A four-year-old male with a fever and suspected influenza suffered cardiopulmonary arrest and anaphylactic shock, and became brain dead. He died two months later. There was no autopsy.

The next patient is a five-year-old female

who started Tamiflu and a cephalosporin antibiotic, and the next day developed asphyxiation and vomiting. The antibiotic was stopped, and three days later Tamiflu was stopped, died of asphyxiation on an unknown date.

A nine-year-old patient with mental retardation, cerebral palsy, and methylmalonic acidemia (often with serious acidosis) was diagnosed with fever and influenza. Patient developed acute pancreatitis with cardiopulmonary arrest and died four days after starting Tamiflu.

Also Tamiflu was stopped when the patient developed acute pancreatitis. The patient then experienced the cardiopulmonary arrest. The reporter suspected the pancreatitis was due to the patient's underlying conditions.

The final report that I wanted to go over is from a 14-year-old male, and I know there's been some media reports around two particular pediatric deaths in Japanese patients, and this is one of them. The other one is actually in a 17-year-old adult patient, because we define pediatrics as zero to 16.

So I just wanted to make that clear.

The initial report in this 14-year-old stated that a male with influenza "took one dose of Tamiflu" and took his life within an hour. We received follow-up information from Roche that updated the report to state that the 14-year-old male with influenza took one dose of Tamiflu, and in two hours fell off the ninth floor of his apartment building. He died of hemorrhagic shock five hours later. No autopsy was performed.

At his clinic visit earlier in the day, he had shown no disturbances of consciousness or mental disorders, and the report stated that there were no witnesses to the circumstances of his fall.

Finally, I will just do a few summary reports on what my conclusions were after my review of these 12 pediatric deaths.

Co-morbidities and confounding factors are in many of the cases, as I've previously stated. There was limited and missing data in a majority of the cases, making it difficult to assess cause of death.

Issues with translated reports and access to follow-up information make interpreting these foreign reports very challenging. At this time, based on the available data, it is difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths.

Next I will discuss the 12 reports of pediatric skin and hypersensitivity reactions that were received during the post-exclusivity period.

There were four males and eight females. The mean age was six, range 2 to 14 years. The outcomes were three hospitalizations, one life threatening, and eight medically significant.

Again, 11 of the 12 were from Japan, and one was from the U.S. The type of reactions that we saw in these 12 reports were Stevens-Johnson Syndrome, Stevens-Johnson Syndrome with toxic epidermal necrolysis, anaphylaxis and anaphylactoid reactions, erythema multiforme, urticaria, and eczema.

If you look at the current Tamiflu labeling for serious skin and hypersensitivity reactions, you will note in the adverse reactions

section it lists dermatitis under Treatment Studies in Pediatric Patients.

Also in the Observed During Clinical Practice section under General, it lists rash, swelling of the face and tongue and TEN.

The summary of my review of these pediatric reports: The majority of the Stevens-Johnson, TEN and EM cases were confounded by concomitant medicine. What I mean by this is a lot of other medicines were started at the same time as Tamiflu which also have skin or hypersensitivity reactions associated with them. So that made assessing causality to one particular drug difficult.

Three additional cases had limited information that we received in the report to really do an adequate assessment of the adverse event. However, there were four notable cases that could possibly be due to oseltamivir.

There was one of Stevens-Johnson Syndrome, one of anaphylaxis, one of urticaria from the post-marketing exclusivity period.

Four cases is not a lot, and some of the

events have already been recognized and labeled for Tamiflu. However, these cases and cases identified from a review of adverse events from the 2004-2005 flu season prompted the Office of Drug Safety to further investigate all serious skin and hypersensitivity reactions in the AERS database.

Before I go on, I do want to say that this slide is different than the slide that you actually had, and this will kind of get to my point that we are still really looking at these reports in the Office of Drug Safety. So that's why this slide was updated.

These are just really -- These aren't duplicate reports, but these are reports that we are still in the process of assessing them for causality, but I did want to give you just a brief view of where we are with that review.

You will note that again this is divided by age. You can't add up the numbers, as I said before. For serious skin, there are 43 for all ages, 24 for adults and 16 for pediatrics, and seven of these reports are U.S. reports.

For the anaphylaxis, this is where these

reports include where any type of anaphylactic symptom was reported to us. There's 110. Thirty-six are the U.S. Eighty are in adults, and 18 are in pediatrics. For those two reactions, I added them up for the deaths, and there are -- deaths reported, not associated with just reported.

There are 11 deaths. Two are U.S. Ten are in adults, and you will note that there is one in pediatrics, and that was included in the 12 pediatric death cases that I discussed earlier. It was the four-year-old with anaphylactic shock as a reported event.

Next I am going to go on to the pediatric CNS events, and there are 32 of those from the post-exclusivity period. Twenty are males. Twelve are females. Mean age is eight. Range is five months to 15 years. Outcome was hospitalization in 12 cases, life threatening in two, disability in one, and 17 were medically significant. On the same thing, 31 of these are from Japan, and one of them is from the U.S.

If you look at the relevant Tamiflu labeling for CNS events, you will find in the Observed

During Clinical Practice section of the label under Neurology or Neurologic, it lists seizures and confusion.

Again for ease of presentation, I have placed these 32 CNS events into general categories. All the patients who experienced these 32 were being treated for influenza, and there may be some overlap in the CNS effects within the categories, but I tried to capture the major event in each case for these general categories.

We all can recognize that, because these patients were being treated for flu or suspected flu, influenza, fever, dehydration, can all cause CNS effects such as convulsion, somnolence and delirium. So some of these can be seen as part of the underlying disease that is being treated. However, what we found particularly interesting about these cases was the last bullet point, these abnormal behaviors, and there were six that I put into this category.

I am going to go through and just give you a little bit -- in the next slide, a little bit of a flavor for what these reports said, because they were

unusual, and they were striking to us, and they caught our attention. So they really needed to be looked at a little bit further.

From the six cases of abnormal behavior, I looked at the narratives, and what I did is tried to just take out some of the behavior that we found to be unusual. These are verbatim. These are all Japanese reports. So the English is not perfect. So please excuse that.

In the first case -- and again, I think I said that all of these children had influenza or suspected influenza. In the first case it stated that the patient, hours after the second dose of oseltamivir, jumped from the second floor of his house. His lower body was deep in snow. He got out of the snow and rang the doorbell and entered his house. He repeatedly said, "I am no half asleep" and went back to his room and slept. He remembered the incident, but did not know why he jumped.

In the second report, the patient complained he was suffering from an "abnormal look" and jumped from the upstairs window of his house.

In the third case, the patient experienced hallucinations and showed abnormal behavior. He seemed frightened by something and rushed out into the street. He was stopped by his mother. So he did not come to any type of harm.

When we finished our review of these pediatric reports from the post-exclusivity period, we actually had more questions than answers, because all of the deaths in the CNS reports of abnormal behavior were originating from one source, or Japan. We took a series of steps to try and look at this, because we couldn't really have answers, and we didn't know how this differential reporting was going to relate to a U.S. population.

So right after we finished the report and a few months prior to this Advisory Committee, we took steps to address this differential reports and the adverse events. We established a working group with representatives from the Office of Drug Safety, the Office of New Drugs, the Office of Counterterrorism and Pediatrics, and the Office of Commissioners, which is the Office of Pediatric Therapeutics.

We went on to request additional information from Roche about all of these reports, particularly the death, the serious skin and the CNS effects. We obtained a copy, a copy of the English version of the Japanese product labeling for oseltamivir. Because all of these events were coming out of Japan, we wanted to know if they knew about the reports, had they evaluated them, had they labeled them.

Finally, as Dr. Murphy mentioned this morning, we formally contacted the Japanese Ministry of Health, Labor and Welfare for additional information. I know Dr. Murphy said this, but I wanted to reiterate publicly a thank you to our colleagues at the Japanese Ministry for their gracious and timely response to our inquiries. Their input was a tremendous help in starting to understand the Japanese experience with Tamiflu, and to try and put these events into perspective with regard to the U.S. population.

This is going to be a summary of some of the FDA inquiries that we asked the Japanese

regulators. We asked them: Have there been reports in pediatric patients of deaths, CNS toxicity or serious skin/hypersensitivity reactions with the use in Japan?

We were not even sure if they were receiving the same reports as us, and that was of interest. Are they labeled events, as I mentioned?

Are there differences in the manifestation of influenza in Japanese patients, especially regarding CNS or neurological effects? Could these adverse events be due to drug, influenza -- I mean, excuse me -- be due to disease or drug or maybe perhaps a combination of both?

We asked how Tamiflu was prescribed to pediatric patients in japan. Was it prescribed at different doses? Was it higher or lower? Was it used off label, etcetera?

How are adverse events reported in Japan? We thought that that was an important question, because we know how they are in this country, but there were so many reports coming in. So we were interested in how their system was set up.

The final question we asked: What is the usage data of Tamiflu in Japan? We had heard some informal information that there was increase of use of Tamiflu with the Japanese, and we wondered, could this be resulting in a potential early safety signal that has not yet been seen in the U.S. pediatric patients; because as you will see, there is a tremendous use of oseltamivir in Japan compared to the U.S. we have seen in the last few years in U.S. pediatric patients.

Again, this is just a brief overview of some of the responses the Japanese gave us to the prior inquiries.

In Japan's Tamiflu label, shock, anaphylactoid/serious skin reactions, and psychoneurological symptoms are labeled under their section labeled call PRECAUTIONS/Adverse Reactions/Clinically significant adverse reactions.

So these events had been seen and recognized in Japan, and put into their label.

Influenza-associated encephalopathy has been a concern in Japan for over a decade. Dr. Lewis will go into more detail with that in her talk, and

then I am sure Dr. Shay will touch on that point, too.

There is widespread use of test kits for detecting influenza, and the awareness to treat influenza especially early is great in Japan. They let us know about these kids with even symptoms. They go right into the clinic. They are diagnosed right there, and they are given prescriptions. So it is a widespread use and recognition of influenza, basically because of the encephalopathy that they had been seeing for over a decade.

We also found out there the mass media reports of positive effects of Tamiflu when it was first approved in Japan, and it continued. It is interesting, and this is a quote, that we heard from one of our Japanese colleagues, "We love Tamiflu in Japan." So I thought that was interesting.

The next thing I am going to talk about is their post-marketing surveillance. Just to give a little bit of an overview of their post-marketing surveillance, there is increased surveillance in Japan for all drugs six months after approval of a new drug or a new indication.

In July of 2004 there was an approval of Tamiflu for the prophylaxis of influenza triggering one of these periods of increased surveillance, and this just happened to coincide with the post-exclusivity period for Tamiflu, which was -- July 2004 was the previous flu season.

There is also increased or active solicitation in Japan. They send out solicitations to greater than 70,000 clinical institutions on soliciting them to send in reports about adverse events. There was also a retrospective study in Japan in 2003 and 2004 to evaluate CNS effects in infants, defined as less than one year of age.

What they saw from this report is that they did not see a difference in the neuropsych events in Tamiflu patients compared to others.

There was also a prospective study in this same population, which was completed in November of this year, and the preliminary results also did not see an increase in neuropsychiatric events in infants receiving Tamiflu compared to others not receiving Tamiflu.

Finally, I just wanted to put a bullet point up there about use. Tamiflu is readily available in japan, as I have stated, resulting in tremendous use compared to the U.S. I defined these as prescription sales, and I will say to Roche that they provided this information. So if there is any clarifications, I apologize for that.

I also apologize -- in the slides, I left off the "n" in Hoffman.

So prescriptions for 2001 to 2002 for all ages: You will see that the use in Japan was 24.5 million prescriptions versus 6.5 million in the U.S. When we break these down and we look at prescriptions for 2001 to 2005 in children less than 16 years, the use in japan is 11.6 million versus about 900,000 in the U.S. So there is a lot of use compared to use in this country.

Finally, I will do a couple of summary points. U.S. adverse reports do not show deaths or comparable CNS effects in the pediatric age group, as seen in the Japanese data.

Serious skin/hypersensitivity reactions

for both adults and pediatric patients are still under review of the Office of Drug Safety.

CDER will continue to closely monitor all serious adverse event reports for oseltamivir.

In the previous flu season, we had a real concern with the shortage of the vaccine, and we felt that in the shortage of the vaccine in the 2004-2005 flu season that there may be an increased use of antivirals.

So we tried to be proactive in having pretty routinely every two weeks meetings with CDC to evaluate any adverse reports that we were receiving. We felt that this was a good exercise, and FDA will continue to meet with CDC for the next flue season to discuss serious U.S. adverse events with antivirals to treat influenza.

I did want to acknowledge Evelyne Edwards particularly, because she did a lot of the work on the actual consult, the BPCA consult, and Rosemary Johann-Liang and David Moeny who provided me with the use data.

I didn't know if you wanted to do

questions now or wait.

CHAIRMAN NELSON: Wait.

MS. TRUFFA: Wait? Okay.

CHAIRMAN NELSON: Yes, I would like the Committee to make note of any questions, because I think it is important for us to get all of the information on the table before we get into questions and discussion, as some of our questions might be answered by subsequent presentations. I would like to have that perspective.

So we will go on to Dr. Lewis' presentation, and after that take our break, which I suspect will be later than 10:30, given the number of slides I counted, but whenever is fine.

DR. LEWIS: I can talk very fast.

CHAIRMAN NELSON: I think it's important to not go too fast.

DR. LEWIS: I am from the South. So I can't talk as fast as Ms. Truffa can.

My name is Linda Lewis. I am a Medical Officer and the primary clinical reviewer for Tamiflu in the Division of Antiviral Products at the FDA.

The Division of Antivirals, as you have just heard, has been working closely with the Office of Drug Safety in monitoring the safety of Tamiflu in not only children but in all age groups.

After the ODS compiled the BPCA summary of safety events, we were asked to look at a reevaluation of the pediatric clinical data available for Tamiflu. In the next 25 minutes I will describe how the Review Division, in collaboration with ODS, the Division of Pediatric Drug Development, and the Office of Pediatric Therapeutics evaluated these events from a clinical perspective.

First, I will give a brief recap of the ODS BPCA safety consult and some possible explanations that we discussed for the unusual pattern of adverse events.

Then for each of the topics of interest, pediatric deaths, neuropsychiatric adverse events, and serious skin reactions, I will walk you through our re-analysis of the pediatric data from the available clinical trials that were submitted both for the original approval of Tamiflu and some that have been

submitted since that time.

Then I will give a brief review of the pertinent scientific literature related to the manifestations of influenza in children. I will summarize with the FDA's conclusions about these events.

As you just heard from Ms. Truffa, the ODS reviewed the Adverse Event Reporting System database for cases of adverse events in pediatric patients over the year following granting pediatric exclusivity. A total of 12 deaths have been reported in pediatric patients receiving Tamiflu since its approval.

The review of deaths covered the entire use period and not just the BPCA review period. All pediatric deaths were reported as from Japan.

A total of 75 pediatric adverse events, which includes the death, were found in the database during the review period from March 2004 to april of 2005. sixty-nine of these reports were from Japan. Five were from the U.S., and one was from Canada.

The neuropsychiatric events and serious skin reactions were the most common and the most

concerning to all of us in the clinical realm.

This pattern of deaths and adverse events, reported almost entirely from Japan, was unusual for us. The FDA receives adverse event reports from all over the world, and usually reports are very similar from one reporting country to the other in the types of events that are reported.

Because of this, we had a number of discussions of these cases and explored several possible explanations for this pattern of pediatric deaths and adverse events among Japanese children.

Could this reflect a difference in the absorption, distribution, metabolism, or elimination of Tamiflu in Japanese children leading to a different PK profile in that population? Specifically, could it lead to increased drug levels?

I will tell you that there is no clinical pharmacology data from either the japanese or the U.S. literature to support this hypothesis, and I won't expand on that any further.

Also, could this be a difference in the dose or the indications for use of Tamiflu in Japan?

We know that the drug product is the same in Japan and the U.S.., and dosing recommendations for Tamiflu are very similar in the Japanese label and the U.S. label. Tamiflu is approved for similar indications in both countries. So this is unlikely to provide us with an explanation for these events.

Could these events represent a difference in reporting of adverse events in Japan? As you have heard, we have some evidence that the reporting of adverse events during the time period that coincided with our BPCA review was more intensive in Japan than it was in the United States.

What I will spend most of my time discussing is the next question that we came up with. Could these adverse events represent a difference in the manifestations of influenza in Japanese children that are not in the ready armamentarium of events that are seen by pediatricians in the United States?

Finally, could these adverse events indicate a safety signal associated with the use of Tamiflu in children because of the greater use of the drug in this population?

I will focus my presentation really on our efforts to tease out whether these reports really symbolize an effect of the drug itself or are more likely related to the disease process of influenza.

As you know, post-marketing adverse events can be very difficult to interpret. You saw some of the verbatim events that we get in our AERS reports. Even when they are not translated from another language, they are frequently very sketchy and difficult to interpret.

In part, this is because the reports are uncontrolled. There is no comparison group, and there is often no way to separate use of the drug from the underlying condition.

In order to evaluate rates of adverse events in a more controlled way, I reevaluated the pediatric safety data from all of the available clinical trials with Tamiflu that had been conducted in the U.S., Canada, Europe and South America. These studies have been submitted to the FDA for complete review.

This review included reanalysis of two

randomized pediatric influenza treatment studies that supported the approval of Tamiflu suspension submitted back in 2000. Of these, let me describe these studies in brief.

Study WV15758 was a study comparing Tamiflu to placebo in otherwise health pediatric patients 1 to 12 years of age. These patients all had a clinical diagnosis of influenza. Virologic studies confirmed influenza in about 65 percent of the patients enrolled.

Patients received Tamiflu at 2 mg per kilogram twice daily for five days. In this study, 342 patients received Tamiflu, and 353 received placebo.

Studies WV15759 and 15871 were actually two identical studies that were conducted in northern and southern hemispheres following flu seasons. These studies compared Tamiflu to placebo for the treatment of influenza in pediatric patients 6-12 years of age with clinical influenza and known underlying asthma.

The dose of Tamiflu was the same, 1 mg per kilo twice daily for five days, and in this study 170

patients received Tamiflu, and 164 received placebo.

We haven't really focused on efficacy in discussing these studies, but I will say that in both of these studies use of Tamiflu shortened the duration of flu symptoms by about 1 1/2 days compared to placebo, and this is what led to the efficacy indication for the drug in this country.

In addition, we have recently received a household transmission study submitted to extend the prophylaxis indication to children 1-12 years of age. This study is currently under review, but it does provide additional pediatric data.

Study WV16193 was a study which enrolled ill index cases with influenza and their households. All index cases were treated with Tamiflu at the standard approved doses, and their household contacts were randomized as units to receive either Tamiflu prophylaxis once a day for 10 days or no prophylaxis and treatment if they became ill.

One hundred thirty-eight households received Tamiflu once daily, and 139 households received no prophylaxis. This actually added up to a

total of 1104 active subjects in this study. Of those, 534 patients were between 1 and 18 years of age, 181 as index cases who were all treated, and 353 who were contacts randomized to either prophylaxis or no prophylaxis.

Additionally, as part of this supplement, Roche was asked to provide updated post-marketing safety data for all serious hepatic, renal, skin, and neurologic adverse events in all ages, and this data is still currently under review.

The electronic study datasets were reviewed for the adverse events of interest, using selection criteria from the MEDRA Medical Dictionary preferred term and by body systems.

Adverse events were included from both the dosing period and the post-dosing follow-up to include all possible adverse events. All neurologic and psychiatric adverse events were selected and compiled, and all determatologic and hypersensitivity events were selected and compiled.

Since the prophylaxis study included patients of all ages, we selected patients from 1 to

18 years of age, and patients who received both Tamiflu prophylaxis and treatment were pooled.

I'll just make a comment, that while I used the more inclusive age of 1 to 18 years to look at pediatric patients, as Ms. Truffa indicated, the BPCA age criteria is up to 16. So this is a little more inclusive and, being a pediatrician, I naturally gravitate toward having more patients rather than less.

All studies were evaluated separately -- and then the data were pooled. In these studies and what I will be showing you is the integrated safety review -- all patients receiving Tamiflu were compared to all those who received either placebo or no treatment.

First, I evaluated the occurrence of deaths in the pediatric patients. In looking at the clinical trials, this was relatively easy, as there were no pediatric deaths reported in any of the treatment or prophylaxis trials of Tamiflu submitted to the FDA. This includes that there were no deaths in adolescents who were enrolled in the adult studies.

The case summaries of the 12 post-marketing AERS death reports, as you have heard, were quite variable in the level of detail provided and confounded by other conditions and use of other medications. Consequently, it is very difficult to assign causality in these cases.

What we do know about influenza in children is that young children have known higher morbidity and mortality with influenza.

A study published in 2000 by Neuzil and colleagues enrolled a number of children in the Tennessee Medicaid program. This was a very large epidemiologic study. They identified excess rates of hospitalization, particularly in children less than one year of age, and excess number of deaths from cardiopulmonary conditions during the flu season.

Just to provide a little additional context, in the MMWR the CDC reported 152 influenza associated deaths during the 2003-2004 flue season in patients less than 18 years of age in the United States.

I think you will hear a little bit more

about the mortality surveillance in the U.S. from Dr. Shay a little bit later.

Now I would like to summarize our review of the neuropsychiatric adverse events. This slide shows the results of the integrated analysis of neuropsychiatric adverse events from all of the available pediatric clinical trials of Tamiflu.

As I said, the neuropsychiatric adverse events in all patients who received Tamiflu were combined and are seen in this column. All of the adverse events that were seen in patients who received placebo or who were not treated in the prophylaxis study are combined in this column.

As you can see there are a variety of neuropsychiatric adverse events reported in these studies, and I will remind you that most of these patients had influenza as part of their presenting symptoms. By far, the most common symptom was headache, occurring in four percent of the patients who received Tamiflu, and five percent of those who received placebo who were not treated.

Events such as confusion, hallucination,

mood swings, and nightmares were seen in very small numbers of patients in both treatment groups. Overall, 44 of 903 Tamiflu recipients, or five percent, experienced some neuropsychiatric adverse event. Forty-five of 660 patients who did not receive Tamiflu experienced an adverse neurologic event.

Most of these events were considered non-serious and, therefore, there are very few details about the individual events. There were a few events that I thought a little additional information.

In the pediatric influenza treatment trial, there was one neurologic adverse event that was reported as a serious adverse event. This involved a nine-year-old male patient with confirmed influenza B who was hospitalized on study Day Two. He was described as having viral encephalitis with no other description of his symptoms.

The event was considered moderate in severity and unrelated to study drug. The event resolved without sequelae over 16 days. This patient had, in fact, received placebo.

In the prophylaxis trials, two adolescents

were reported to have psychiatric events. An 18-year-old male contact was reported to have a psychological disorder noted to be present about one month prior to the study. The event was considered mild and did not require specific treatment, but was not further described.

This event was considered unrelated to study drug. The patient had received Tamiflu prophylaxis and did not acquire influenza.

Lastly, a 17-year-old female index case was reported to have a nervous breakdown, and this event was reported as a serious adverse event. She received Tamiflu for her influenza at standard doses. She was hospitalized on study Day Five for this event, and was noted at that time to have a history of depression.

The event was considered severe, but she was not given other specific treatment, and the event resolved. She was discharged from the hospital after two days, and referred for counseling.

In addition to reviewing the comparative clinical trials data, we also searched the pediatric

literature to review possible neurologic manifestations of influenza.

This literature search documented increased reports of influenza-associated encephalitis and encephalopathy, mostly originating from Japan, beginning in the 1990s before the approval of Tamiflu.

These reports in Japan prompted a nationwide surveillance effort for encephalitis and encephalopathy. They also promoted both medical community and public education efforts regarding the neurologic complications of influenza.

One of the most detailed reviews of influenza-associated encephalitis or encephalopathy was published by Dr. Morishima and his colleagues in Japan. This was a retrospective study of the 1998-1999 flu season, again prior to the approval of Tamiflu.

This study was conducted as a national survey, sending questionnaires to every local health care center in Japan. This was an extraordinarily complex effort on the part of this Japanese group.

They used as their definition of

encephalitis and encephalopathy a clinical definition requiring altered consciousness or loss of consciousness. Diagnosis of influenza was based on positive culture, antigen test, PCR, or increased hemagglutination inhibition titers.

Of the 217 responses they got to their survey, 148 cases met their definition of encephalopathy with documented influenza, and I will remind you that this is a survey of a single flu season.

Dr. Morishima's review described a typical course of influenza associated encephalitis and encephalopathy. It describes the sudden onset of high fever, seizures, altered consciousness, and sometimes with rapid progression to coma within one to two days of flu symptoms.

Very few of the patients in this series had Reye's syndrome. Only four percent exhibited the metabolic and liver enzyme abnormalities typical Reye's.

Eight-eight percent of their cases were associated with influenza A, and, interestingly, it

was H3N2 that was circulating widely in Japan during that flu season.

CSF findings in these patients, when available, were frequently normal. Brain imaging was suggestive of cerebral edema and localized areas of low density. Some patients exhibited bilateral symmetric thalamic low density lesions that are characteristic of acute necrotizing encephalopathy, an entity that has been described both with flu and other viral illnesses in the past.

In this series there was a very high mortality of 32 percent and very high rates of disability. Twenty-eight percent of patients in this series had some sequelae, and nine percent had severe sequelae.

Not all of the reports from the Japanese literature of neurologic complications of influenza and so severe. There are also reports in the literature of milder syndromes with descriptions of abnormal behavior, hallucinations and delirium.

There is no accepted explanation for the apparent difference in the rate or pattern of neurologic complications observed in Japanese children

compared to other countries. There have been a number of explanations proposed, but nothing has really been universally accepted.

The Japanese authors report continued high rates of influenza-related encephalitis and encephalopathy in recent flu seasons, but the mortality rates have decreased over the last four or five years. Some authors in Japan suggest that this decreased mortality is due to increased awareness and rapid diagnosis and treatment of influenza among children.

Interestingly, one author proposes that the use of pulse steroids is what has really made a difference in their mortality rates.

In contrast to the large series from Japan, there are only isolated case reports and small series of encephalitis and encephalopathy originating from the U.S. patient population. The largest of these series was published by Maricich and colleagues from Houston during the 2003-2004 flu season.

As you remember, this was the flu season that struck early, beginning in October, and was quite

severe in many places. Neither vaccine nor antivirals had really been distributed adequately at the time the influenza epidemic hit that year.

During that flu season, this group documented 478 laboratory confirmed cases of influenza A at Texas Children's Hospital. During the same time period, eight patients were hospitalized with neurologic symptoms.

In these cases, antivirals were used only after admission, and four patients received rimantidine, and one received Tamiflu. There was one of the eight patients who was left with significant neurologic sequelae, consistent with the syndrome of acute necrotizing encephalopathy.

The Division of Antiviral Products and the Office of Drug Safety requested additional information from both the Japanese regulatory authorities and from Roche regarding the neuropsychiatric adverse events, as you have heard from Ms. Truffa. The responses confirmed several points that we thought were important in our evaluation of these events.

First, the Japanese undertook active

surveillance of influenza associated encephalitis and encephalopathy beginning in the late 1990s. Also, the Japanese national health service actively facilitates rapid diagnostic testing for influenza in children and subsequent treatment. Currently, much of the treatment is with Tamiflu.

Information from both the Japanese authorities and from Roche confirmed that Roche, through its Japanese affiliate, Chugai Pharmaceuticals, actively solicited adverse event reporting from 70,000 physicians, clinics, and institutions during the 2003-2004 flu season as part of the Japanese reporting requirements. These solicited events are included in our AERS database, along with our usual spontaneous passive reports.

Now I would like to turn attention to the dermatologic adverse events. This slide shows the results of the integrated analysis of skin and hypersensitivity reactions from the pediatric clinical trials of Tamiflu, and is set up very similar to the previous table I showed you.

In this table, all patients who received

Tamiflu, whether it was prophylaxis dose or full treatment dose, are compiled in the first column, and all those patients who had adverse events who received placebo or were not treated are in the second column.

A variety of dermatologic adverse events were reported in the clinical trials. Unspecified dermatitis -- that is dermatitis not otherwise specified, for those of you who are not familiar with MEDRA terms -- were the most common and were seen in two percent of the patients who received placebo or no treatment.

Overall, dermatologic and hypersensitivity reactions were identified in 29 of 903, or three percent, of Tamiflu recipients, 22 of 660, or three percent, of no treatment or placebo patients. It is of some interest to us, however, that the only cases of erythema multiforme, facial and periorbital edema and localized exfoliation are in patients who received Tamiflu.

None of these dermatologic events in the clinical trials were reported as serious adverse events.

The pediatric literature is really less revealing when you search for influenza associated dermatologic events. There are only rare case reports of dermatologic manifestations of influenza in children.

The best of these that I found was a survey of respiratory viruses in Great Britain that was published in 1969. These authors note "rash" was present in approximately two percent of patients with influenza A and eight percent of patients with influenza B. The rashes, however, were not further described in this survey.

Pediatric and infectious disease textbooks do not include skin reactions or rash as a usual manifestation of influenza.

In conclusion, we have to acknowledge that a search of our AERS database identified deaths, an unusual pattern of neuropsychiatric adverse events, and serious skin reactions reported in children receiving Tamiflu.

Although the post-marketing safety reports identified these events, reanalysis of the comparative

pediatric clinical trials data used in the approval of Tamiflu failed to identify significant differences in these events between children receiving Tamiflu and those who received placebo or no treatment.

A further investigation into the possible explanation for this pattern of events reported in Japanese children identified several things that may have contributed to the number and pattern of reports.

First, the syndrome of influenza associated encephalitis and encephalopathy was described in the pediatric literature well before the approval of Tamiflu.

There was an increased awareness of these neurologic complications in influenza in children in Japan. We have evidence that, because of these events, there was an increased use of Tamiflu in children compared to other countries, and we also know that there was likely an increased level of adverse event reporting from Japan that coincided with the BPCA review period.

I guess after the break, you will hear presentations with additional information by

representatives from Roche Pharmaceutical that will clarify some of these issues a little further.

You will also hear a presentation from Dr. David Shay from the Influenza Branch of the CDC, who will present an update on the influenza surveillance in pediatric patients in the U.S., with particular attention to mortality and the neuropsychiatric adverse events, and it may be a case of, at least with the neuropsychiatric events, if you look harder for it, sometimes you find it. Clearly, the Japanese have been looking for it since the mid-1990s, but the U.S. population has, I think, been less aware of this entity.

Thank you.

CHAIRMAN NELSON: Thank you very much. We will take a break now for 15 minutes, and then reconvene with the sponsor presentation. My watch says 20 of 11:00. So we will try to make it five of 11:00 in terms of starting again. Thank you.

(Whereupon, the foregoing matter went off the record at 10:43 a.m. and went back on the record at 10:57 a.m.

CHAIRMAN NELSON: In case anybody is wondering, there will be no lunch break, unless we decide to go way past our allotted time to end. So we will push through until the completion of the meeting.

We will start with the sponsor presentation, and it is Dr. Hoffman, or I guess you can all introduce yourselves as you get up. Feel free.

MS. CONRAD: I am Robin Conrad. I am with Regulatory Affairs in Hoffman-La Roche. I would like to thank the agency and the Committee for the opportunity to present here today on the pediatric post-marketing safety data for Tamiflu.

As we heard earlier this morning, Tamiflu is indicated for both the treatment of influenza in adults and children greater than one year of age, and also for prophylaxis for adults and adolescents greater than 13.

We have currently pending a prophylaxis supplement that would take the age range down to greater than or equal to one year of age and, as mentioned earlier, we did receive pediatric

exclusivity in March of 2004, and we are back here, basically, for a one-year safety review following that exclusivity period.

This morning we have a number of individual experts available to answer questions from the panel, including those from clinical science, drug safety, preclinical and clinical pharmacology.

Dr. Joe Hoffman, our Vice President of Clinical Science at Hoffman La Roche will be doing the primary presentation, and I will turn it over to him now.

DR. HOFFMAN: Thanks, Robin. On behalf of the sponsor, I would like to thank you for the opportunity to address you at the meeting today. If it makes Ms. Truffa feel any better, it is my family's custom to always drop the second "n" from the name.

I am an internist. I am critical care physician, and I am currently the group leader for virology and transplantation, and my objectives today are to provide a brief overview of the pediatric safety experience with Tamiflu since FDA approval in December of 2000, to respond to the FDA request for

review of neuropsychiatric SAEs and deaths, and to compare the global experience with that of Japan.

Beginning with just the position of -- our position of the Tamiflu experience, Tamiflu was shown to be safe and effective in the registration program in patients down to the age of one.

The Roche Drug Safety Database called ADVENT of post-approval use supports the current product labeling, with the exception that a proposal has been submitted to FDA to update the U.S. package insert with information on skin events.

The increased reporting in Japan is secondary to a number of factors, including burden of disease, the number of courses dispensed, clinical use patterns, and safety reporting practice.

In terms of the overview, what you can see in this slide are the prescriptions for Tamiflu through about mid-year, and you can see Japan is the leading prescriber at 24.5 million, with the USA second with 6.5 million, and the rest of the world about a million, giving a total of 32 million.

When that is broken down into adult and

pediatric use, you get the following numbers for Japan and the USA: For adults, about 12.9 million prescriptions in Japan, about half that, 5.2 million, in the United States. For children, 11.6 million in Japan, and for the U.S. about 1.3 million.

The reason why the number here is a little bit higher than what Ms. Truffa presented is that was syrup only, and older children take to take capsules rather than syrup. So the numbers don't look higher.

So for the approximately 13 million prescriptions in the pediatric population, we have seen the following serious adverse events and have them on our ADVENT database: A total of 325, of which 275 come from Japan, 25 from the U.S., and 25 from the rest of the world.

So you can see that there are about 10 times more pediatric prescriptions which have been written in Japan versus the U.S., and there are also approximately 10 times the number of serious adverse events reported in Japan versus the U.S.

This slide just breaks down further the types of serious adverse events, and this is a

percentage of those 325: Nervous system disorders, 20 percent; gastrointestinal disorders, 25; skin and subcutaneous disorders, 14; and psychiatric disorders, thirteen.

The gastrointestinal disorders are largely already covered in the label, and the skin and subcutaneous disorders we have already submitted a proposal to FDA which will under discussion shortly. So we are going to focus on the nervous system and psychiatric disorders.

There have been a total of 59 patients meeting the criteria, which was shared with us by FDA, regarding neuropsychiatric events. The number is different from what you have seen, because that was for the year from the granting of the exclusivity. This goes back to the availability of Tamiflu.

Of those 59 patients, 57 of them are in Japan, one in the U.S., and one in Germany. In terms of the types of events, I have grouped them here. There were 19 with convulsion, encephalitis, encephalopathy; 15 with depressed consciousness; 13 with hallucination, delusion; 10 with delirium; and 10 with abnormal

behaviors or other neuropsychiatric events.

These have been assessed in our Drug Safety Department, and the findings are that: In 51 of the cases there is a possible alternative explanation; in six cases there is insufficient information for an accurate assessment, and in two cases there is no alternative explanation. These cases: An eight-year-old male with abnormal behavior, and another eight-year-old male with abnormal behavior and disturbed consciousness.

The complicating factors in those 51 cases with a possible alternative explanation are shown here. The primary one, responsible for about half of the cases, is influenza itself and the secondary complications of influenza, also high fever, dehydration, the use of concomitant medications, orthostatic hypotension, and a long latency. That would be the event occurring more than five days after the last dose of Tamiflu.

So for these neuropsychiatric events, for the total of 59, the majority of them have possible alternative explanations or contributory factors, and

there are only a few where we don't have that alternative explanation.

Now turning to mortality, there are 13 fatalities which have been reported to Roche between January of 2000 and June of 2005. I want to point out here the reason why there were 13. There is one case on our database which was an eight-month-old with a ventricular septal defect who suffered a respiratory arrest while on Tamiflu, and then died months later of another event, which was considered not related. So we have it on our database, and we have included it. That is not included in the FDA database, and that would be the case right there, the eight-month-old.

Otherwise to break down all cases from Japan: 10 in children ages one to five, and two greater than five years, one a nine-year-old and one a 14-year-old. I am not going into detail on these, because you have already heard the detail.

In eight of the cases, there are confounding factors, either major complications of influenza or preexisting diseases. In five of the cases, including the four that appeared in the

newspaper article, we just don't have enough information to be able to judge relationship.

Now as with any drug safety database with an approved drug, all the cases that are on the database come from patients who were on drug. So you don't have a control group.

So what I would like to show you now is additional data from three sources, the Pediatric Registration data -- you have heard a lot of that already -- data from a large claims database, United HealthCare claims database, as well as a recently completed prospective Japanese pediatric study which was referred to earlier this morning.

In the Pediatric Registration Program, excluding Japan, there were a total of 1,180 patients who were randomized to either placebo or Tamiflu in approximately equal numbers. The age range is here: 1-2, 173; 3-5, 226; 6-12, 633; and 13-17, 148.

The most frequent adverse events -- that is, adverse events occurring with a frequency greater than three percent -- were GI disorders, infections, and respiratory disorders.

When one compares the specific adverse events, neurologic, psychiatric and skin, between placebo and Tamiflu, you can see that the numbers are very close for the two different treatments, 0.8, 0.6 for psychiatric; 3.3, 2.7 for skin, and 2.3, 1.0 for neurologic. So very similar.

In addition, there were 15 serious adverse events, five on placebo, 10 on Tamiflu. None was considered to be related to study treatment by investigators, and you have already heard about the one neuropsychiatric event, viral encephalitis in a patient on placebo.

Sixteen patients withdrew from the trials, eight from each treatment arm. None of these were for neuropsychiatric events. The most common reason was vomiting, and there were no deaths reported in the registration program.

Now from Japan, the experience is limited to a single open label study which supported the filing. That was in 70 children up to age 12 with a median age of four years. Adverse event profile was similar in this study to what was found in the global

registration trials.

The most frequently reported adverse events were gastrointestinal, vomiting and diarrhea being the most common. Severity was mild in most cases, and the duration of the events was limited largely to a single day, and again there were no fatalities and no neuropsychiatric events reported in that experience.

Now there is a large database available from United HealthCare which represents more than 20 million subscribers. It is a claims database. It is not a respectively defined database.

On that database there are many patients with a diagnosis of influence represented here, about 176,000. What this database allows us to do is compare patients with the diagnosis of influenza who have been given Tamiflu and those who have not. So we can look to see if there is any excess in mortality or in certain adverse events.

So it has limitations, but we think it has value to look at it, because of its large size. So there were two studies that were done, two analyses of

this database. The first was a morbidity study which was limited to children, represented by 63,261 children; and then there was a mortality outcome study which was represented by patients of all ages, 176,000.

What was done was an examination of the diagnoses and deaths reported in patients with a diagnosis of influenza via claims analysis and, as I mentioned, this a comparison of those with a Tamiflu prescription and those without.

What was looked for were the number of outcomes, including nervous system and psychiatric events, and deaths.

The first of the studies is the morbidity study in children which was conducted between November of 1999 and March of 2004 in children age 1-12 with a diagnosis of influenza. The breakdown of ages seen here: About half the pages were 1-2 years old, and the other half about 6 to 12 years old.

The number of patients who had a prescription for Tamiflu was almost 9,000, those without Tamiflu more than 54,000. The most common

diagnoses were infections and respiratory, ear and general disorders.

Importantly on this database from the adverse events perspective, for psychiatric diagnoses the number of patients with claims was 0.6 no Tamiflu, 0.6 on Tamiflu. So no difference. And for nervous system diagnoses, about the same, No Tamiflu 0.3, Tamiflu 0.2. So from a neuropsychiatric standpoint, no apparent difference.

The second study was specifically a mortality outcome study performed during the same period of time, 1999 to 2004, in patients with diagnosis of influenza. So this includes all patients, all ages, with the diagnosis of influenza.

The number of deaths on the database: One out of 39,000 for Tamiflu, giving an incidence of 0.003 percent; and 58 out of 136,799, giving an incidence of 0.042 percent.

So the power of this database is its size, and what it indicates to us is there is not an excess mortality associated with Tamiflu. In fact, the absolute numbers are in the opposite direction.

Now specifically in children, there were 68,317 children who were on this database with influenza. Here I have broken it down by age group, 1-5, 6-10, and 11-15. What you can note here is that the prescriptions for Tamiflu, the group given Tamiflu, is a bit lower than it is for the group not given Tamiflu.

So it is difficult to draw conclusions, other than to say that in each of the Tamiflu groups there were no reported deaths, and in the two groups representing children 1-5 and 6-10 there were a total of four deaths. So again, I think what we can say here is that there is no evidence based on this database of excess mortality due to Tamiflu.

The third source of data that we have with a control is this recently completed study, prospective trial in Japanese children less than one year of age. What we have is preliminary data, as the study was just completed earlier this month in Japan.

This was actually a requested from the Japanese Health Authority to Chugai to prospectively monitor patients less than one-year of age given

Tamiflu and not given Tamiflu.

It was conducted by the Society of Ambulatory and General Pediatrics of Japan and the Japanese Society of Pediatric Infectious Disease earlier this year.

Adverse events were collected, as I said, in patients less than one year of age, with and without Tamiflu treatment. The total number of patients on this database, 1771. There were no deaths reported in this study, and the final report is planned for the end of the year.

What I can share with you are the neuropsychiatric events. Now these are neuropsychiatric events, not necessarily serious adverse events, and the bottom line is the total percentage, because the number on Tamiflu is about four times as high as -- three to four times as high as that not on Tamiflu, the opposite of the database of United HealthCare, but that the incidence is right around one percent for both Tamiflu and no Tamiflu.

Looking at the particular adverse events: Febrile convulsion, 3 in the No Tamiflu. There were

five in the Tamiflu. There were three convulsions in the Tamiflu group. If you put these categories together, then it's 0.79 percent for the No Tamiflu group and 0.61 percent for Tamiflu.

The only case of encephalitis was reported in a patient not given Tamiflu, and there was one case each of lethargy, tremor and excitability in the Tamiflu group. So, certainly, these data were very encouraging and very comforting in the youngest group of children.

Now what about differences between U.S. and Japan in the number of cases reported. We have already heard some possibilities along that line.

What I want to point out here: This is the burden of influenza by flu season in japan and the USA. What you can notice is that the numbers in Japan are either equal to or higher than those in the United States, and this is important, given that the Japanese population is a little less than half of the U.S. So the burden of disease in Japan seems to be higher.

I have already mentioned the high volume of usage of Tamiflu in Japan, with a tenfold higher

number of prescriptions having been dispensed since the approval of the drug.

Pediatric use patterns in japan are somewhat different. That may result in some differences in exposure in the Japanese children. These include dose, duration and administration. Dose is on a milligram per kilogram basis in young children in Japan, while it is a unit dose according to weight in the United States. So it is slightly different.

The duration per the package insert is for five days. It Japan it may be less than that, because the custom is to discontinue treatment when the fever resolves, which often could be Day Three/Day Four. And the administration is somewhat different in the youngest of children, because rather than giving the drug as a liquid, the powder is directly administered into the children's mouths. So they may not be getting a full dose.

So there might be exposure differences resulting in either a persistence or a recrudescence of the underlying influenza that is confusing the picture of the adverse events.

There are some differences in reporting practice. Most of them are the same for newly approved drugs in Japan. There are some mechanisms in place for active surveillance that might increase the number of reports that come in. And as already mentioned in the FDA presentations, there is an historical awareness that predates Tamiflu of influenza-related neuropsychiatric events in japan.

So in conclusion, the registration studies showed Tamiflu to be safe and effective in children. No new safety signals related to mortality or neuropsychiatric events post-approval have been identified, with the exception of a proposed label modification regarding skin reactions, which has already been submitted by Roche to FDA.

The increased safety reporting in Japan is mainly attributable to influenza incidence, the number of Tamiflu prescriptions, clinical use patterns, and safety reporting practices, and the bottom lien is that the risk-benefit ration for Tamiflu is unchanged and remains positive.

Moving forward, at a minimum Roche

proposes the following: Our Drug Safety Group will review on a weekly basis all new serious adverse events arriving for Tamiflu. There will be a monthly review of the literature.

There will be quarterly analyses of our ADVENT database for potential new signals, and annually we will analyze the United HealthCare database for mortality, neuropsychiatric events, and any other events of interest. Thank you very much.

CHAIRMAN NELSON: Thank you. Let's move to the final presentation before we open to questions and discussions from Dr. Shay of the CDC.

DR. SHAY: Well, thank you. One question: How do I make the slides go forward? Left one? Thank you.

Well, good morning, and thanks for asking us to come and give an overview of surveillance among U.S. children for influenza related mortality and encephalopathy.

Just a brief background: Of course, influenza causes annual epidemics. It is a major cause of morbidity and mortality, particularly among

young children, those aged over 65 and those with underlying pulmonary, cardiac and several other medical conditions.

Our nationally available data in the U.S. for surveillance of influenza and its complications does have limitations. Of course, relatively few respiratory illness cases are tested, and in the United States CDC does not attempt, for instance, to estimate incident influenza cases, and influenza traditionally has not been a reportable disease, unlike some other severe vaccine-preventable diseases.

For over 50 years CDC has made estimates of U.S. deaths and hospitalizations by using a variety of statistical models. Currently, we use retrospective death certificate data, hospital discharge data from the National Hospital Discharge Survey, and our viral surveillance data to make those estimates.

So these modeling studies estimate in an average year greater than 200,000 influenza associated hospitalizations, and approximately 36,000 influenza associated deaths. The highest rates of deaths,

particularly complications, are in persons with pulmonary and cardiac diseases, children less than five and older adults.

Mortality data for children are limited. We estimate, using the statistical methods, that approximately 92 influenza related deaths occur annually among children in the U.S., but we can't break it down to smaller age groups for children.

As has been mentioned by Dr. Lewis, there are several unusual features of the 2002-2004 influenza season. It began as early as October in some states. Influenza A (H3N2) was the predominant subtype, historically associated with more severe seasons.

There was a vaccine mismatch, and CDC began receiving reports of influenza related deaths in children in November of 2003, principally from large pediatric hospitals. As I said, we had no directly comparable historical data available. There was quite a bit of public concern and media attention and, of course, spot vaccine shortages.

So on December 12, 2003, CDC made a

request to state, territorial and local health departments for reports of pediatric influenza associated deaths. We called this enhanced surveillance, sort of enhanced passive surveillance, and the surveillance period was as defined there.

The case definition was in a U.S. resident less than 18 years of age who died during the surveillance period with evidence of influenza virus infection by at least one laboratory test, and those included rapid antigen detection test, IFA, culture, RT-PCR, or immunohistochemistry on autopsy specimens, if available.

So this has been reported. I think we have added one more death here. One hundred fifty-three deaths were reported from 40 states. The median age of these children was three, and it ranged from two weeks to 17 years.

Half of the children were male, and where we have race information, 67 percent were white, 22 percent black, and six percent Asian. Where ethnicity data were available, Hispanic ethnicity was present in 24 percent of cases.

Just looking briefly at the methods of diagnosis. At the bottom there, there were multiple methods made of diagnosis for 41 percent of these cases. Rapid antigen detection only in 38 percent; viral culture in 11 percent, RT-PCR in three, fluorescent antibody results in three percent, and again immunohistochemistry on autopsy specimens in three percent.

This shows the epidemic curve of the influenza associated deaths in children, along with a curve of the national Virologic Surveillance data, as I mentioned before. Again, CDC made the request in the middle of December, and there is a suggestion there that we probably missed some cases based on the local influenza circulation data.

Here is the age distribution of those cases. Note that most of these children were less than two years of age, but we did have children from every age category.

These are the age-specific mortality rates. For children age less than six months, there were 18 children, 12 percent of total cohort, and they

had the highest mortality rate of 0.88 per 100,000 children.

For aged 6 to 23 months, those for whom vaccine at that time was encouraged when feasible, and now recommended, there were 43 cases, 28 percent, rate 0.71. Children age two to four, 35 cases, 23 percent, 0.3, and older children 5-17, 57 cases or the largest proportion of cases, 37 percent, though, of course, because of the larger population, the lowest mortality rate. The overall mortality rate for children that year was approximately 0.2 per 100,000.

This is the underlying health status where we had information. Seventy percent -- or 45 percent of these kids were previously healthy based on record review that we had available; unknown, a small percentage; 15 percent had an underlying condition consistent with an ACIP recommendation for vaccination that year; 22 percent of the children had an ACIP condition plus another chronic medical condition or another medical condition noted in their charts; and 20 percent of those children had a medical condition at that time that would not prompt a recommendation

from ACIP for vaccination.

These are the location of death of the children. So 90 of these children or 59 percent were in an inpatient situation. Sixteen percent died while being evaluated -- Sixteen cases, 10 cases, died while being evaluated in the emergency room, and a sizeable fraction, 31 percent, either died at home or while in transit for medical evaluation.

Here are some lists of the clinical and autopsy diagnoses for these children. The top group, respiratory diseases most common was diagnosis was pneumonia in 71 children, made about equally on clinical information and on autopsy information.

Other common manifestations of influenza are up there, including pneumonitis, bronchiolitis, croup, and note that on autopsy there was a fairly sizeable portion of children diagnosed with Tracheitis or bronchitis. Sepsis or shock syndrome was also seen in a sizeable number of these children.

When we get to encephalopathy or encephalitis, eight children in this series had that noted in their clinical records. Two were diagnosed

only on autopsy, three in both, for a total of 13 of these 146 children for which there was information available.

Four had clinical diagnosis of stroke, one on autopsy, one on both, and 14 of these children had seizures before their death. Other noted conditions included myo/pericarditis in six, myocardial infarction in two, myositis or rhabdomyolysis in five, disseminated intravascular coagulation in 18, hemophagocytic syndrome in three.

This graphic presents antiviral medication use data that we had available. So of a total of 153 children, for 25 percent we were unable to definitively find out whether or not they had taken antivirals before their death. For seventy-five percent of children, this was known.

No antivirals were received by 89 children, or 77 percent. Antivirals were received by 26 or 22 percent of these children, a very short median treatment of one day, a mean of 2.6 days.

In terms of the specific medications, about evenly split. Twelve received oseltamivir.

Twelve received amantadine, two rimantadine, and none of the children received Zanamivir.

Limitations to these data: Of course, as I mentioned before, the request for case reports was made actually near the peak of the influenza season that year in December. This isn't a passive surveillance system, although much better than anything we had previously.

There are, of course, variations in testing practices and clinical and pathologic diagnoses made in many of these cases. Despite some rather heroic efforts, there was still incomplete medical records for many of these children, and limited information, of course, for those children who were not hospitalized before their death; and again, we had lack of directly comparable historical data in the United States. However, these data were persuasive enough to the Council of State and Territorial epidemiologists that laboratory confirmed pediatric influenza associated death became a nationally notifiable condition in the United States in June 2004, and reporting began in october of the

2004-05 influenza season.

The data now are reported weekly in the MMWR Table 1 and in our weekly influenza update. Last season, there were 43 cases reported from 18 states. Twenty-six of these children received oseltamivir, and none that we had documentation received any other antiviral.

Now to briefly look at the information we have available on influenza associated acute encephalopathy, again from the 2003-04 season: So influenza associated encephalopathy, as you know, is an uncommon complication of influenza. It can result in serious neurologic sequelae, most commonly reported in young children in Japan, including the 148 large case series that's been previously described, and also there were 25 U.S. cases that were identified and have been previously reported during the flue seasons from 1999 to 2003.

So again, this was sort of an enhanced passive surveillance for the same surveillance period. The case definition here was a U.S. resident age less than 18 years with a febrile illness, together with

laboratory confirmed influenza virus infection and some indication of altered mental status.

Here are the case classifications we worked with our Japanese colleagues to try to come up with where possible definitions that were fairly similar to theirs. So a probably case was defined as altered mental status for greater than 24 hours and onset of altered mental status within five days of fever onset, and no other cause identified for the mental status changes.

Suspect case was duration of altered mental status unknown, which was fairly common, or altered mental status for greater than 24 hours but unable to rule out another cause, or altered mental status less than 24 hours, or other cause for altered mental status identified and the child was status Epilepticus, or objective findings of cerebral inflammation, most commonly from MRI.

So here are the results from the 2003-04 season. There were 42 cases reported from 22 states. Twenty-two of these have been classified as probably and 20 suspect. Again, about half the cases, 48

percent, were males, probably cases 54 percent suspect, 40 percent.

Here are the information race, where available. Among the probable cases, 50 percent were white, 67 percent of the suspect cases. Thirty-three percent of both probable and suspect cases in children were black, and in Asian race was noted in 17 percent of the probable cases, and none was suspect.

Perhaps the only conclusion one would make here is that non-white children may be overrepresented in this case series.

Ethnicity information was available for some probable and suspect cases, and of those for whom information was available, 6 or 23 percent were identified as Hispanic. Broken down, probable cases, one Hispanic child among the suspect cases for which ethnicity data were available. Five were Hispanic

Here is the age distribution for these cases, a little bit different than what was seen for the pediatric deaths and a little bit different from what has been seen in Japan as well.

We had sort of a flatter curve without

that peak among children less than two seen in the death data, and substantial numbers of children 13 years of age or older. The median age was five years, and the age range here was six months to 17 years.

When we look for underlying high risk medical conditions in these children, 29 had no prior medical conditions, and 15 had at least one chronic condition. That includes seven probable, eight suspect cases. Five of these children had a condition for which ACIP recommended influenza vaccination for that season.

Here are some of those specific conditions: Chronic gastrointestinal disorder in one; arthritis in one; chronic lung disease in one; cerebral pals in two; prediagnosed seizure disorder in two; ENT abnormality in two; asthma in three; and developmental delay that was severe enough such that it was noted in the medical records of the children in six.

Here is the data on the time from fever to the onset of encephalopathy. Again, most of these children presented within three days, but again our

case definition permitted children to go up to five days.

Again, this is slightly different from some of the large case series seen in Japan where the onset of encephalopathy tends to be a little bit earlier by a day or so.

Thirty-three or 78 percent of these children presented with altered mental status. The duration was a median of three days with a range of one through 31 days among the 28 patients for whom this data were available. Twenty or 48 percent had seizures, nine of the probable and 11 of the suspect cases. Eight had status Epilepticus, and 16 of the children had multiple seizures.

Seventeen, or 40 percent, of the children were diagnosed with a movement disorder/Ataxia. Other neurologic signs and symptoms noted were decreased strength or flaccid weakness, hypotonicity and hypertonicity, slow movements, and unable to hold head or trunk properly while they were ataxic.

Here are the results of the neuroimaging studies. Twenty-six of these children had an MRI for

which results were available. Seventeen, or 65 percent, were abnormal; 17 of the probably cases. Eleven of those had an abnormal CT. Of the nine suspect cases, six had an abnormal CT.

Abnormalities included most commonly cerebral edema. There was also, again, evidence of infarct or stroke, tonsilar herniation, and focal cerebritis.

Eleven of these children only had a CT scan. Three of the probable children, one of which was abnormal, eight of the suspect children, three abnormal; and all four abnormal CTs showed cerebral edema and two with herniation.

When we come to diagnostic testing for these children, 71 percent had CSF studies done. Of 18 of the probable cases, seven had a white count greater than 5, with a range of 8-69 cells in the probable cases; and among 13 suspect cases, one had a white blood cell count greater than 5.

Influenza cultures from CSF were attempted in 17 of these patients, and one was positive in a suspect case from Texas.

Antiviral treatment was received by 18 of these children, nine of the probable cases. One received, obviously, oseltamivir and Rimantadine; nine suspect cases, 3 oseltamivir, three Amantadine and one not reported.

Outcomes of these children: Eighteen of these children have fully recovered, three probable and 8 suspect. Twelve had neurologic sequelae, 8 of the probable and 4 of the suspect; and nine died, 4 probable and 5 suspect.

Here are the outcomes by age, again the dark blue bars, children who fully recovered, the green with serious neurological sequelae, and the light blue children who died.

Again, there are limitations to this case series. It is passive surveillance again, and we certainly may have missed cases. There is probably more concern about selection or referral bias here, as many of these cases did come from large pediatric hospitals.

There was perhaps more marked differential reporting by states, again problems with timing of

surveillance, the fact that we had limited clinical data, and that again we had no real national baseline data on laboratory confirmed cases where attempted and made on a U.S. level to gather this type of information.

So at least 42 encephalopathy cases were identified, 22 probable and 20 suspects. Asian-Americans were not an especially prominent feature in this case series. Fifty percent of these children were less than five years of age, but older children were also affected, and 21 had severe outcomes, including death or severe neurologic sequelae.

So we all agree that further surveillance for this condition is needed. We don't have the resources right now to replicate this type of surveillance study at the present time, but we do need studies in the U.S. to assess prevention and treatment interventions for this condition, and to better educate physicians and the public about influenza associated encephalopathy.

Last season, again, while we didn't have this enhanced passive surveillance, we only had three

reports in the United States of influenza associated encephalopathy.

Here are some of the people who have participated in gathering these data.

CHAIRMAN NELSON: Thank you. Illustrating how much work goes into this kind of activity.

Let's move into our period of questions and discussion. What I would like to suggest is, if you have questions that are best directed to one of the presentations that have been stimulated by something one of the presenters have said, please just mention that and direct it. It is certainly appropriate for us to let them answer for themselves, and then we will see if others would have a perspective they would want to share on the same question.

At some point in our discussion, when it seems appropriate, I will ask Dr. Lewis to present the summary of the agency's comments and the proposed plan, but I thought it would be better to just have a general discussion of these four presentations, the facts and the interpretation, before we actually get

to concrete recommendations about action plans.

DR. WARD: Dr. Lewis, in your list of the dermatologic adverse events, as they are described I could not determine whether any would be classified as Stevens-Johnson or not. There is no -- You mentioned mucous membrane lesions.

DR. LEWIS: That is correct. There were no adverse events during the clinical trials that were described as Stevens-Johnson Syndrome. There was the one case of erythema multiforme, and again since these reports were all considered non-serious at the time of the clinical trials, there were no further descriptions of those events.

So, for instance, the case of localized exfoliation -- I have no description of how it extensive that was, whether it was a few centimeters of rash or affecting a large area of skin. There are really no further details available about those events.

CHAIRMAN NELSON: Dr. O'Fallon?

MEMBER O'FALLON: I am concerned with underreporting, and picking that up.

Dr. Hoffman first. I was wondering, how complete is the U.S. data in ADVENT? How do you -- If that is also passive surveillance, then how complete would you -- Do you have a feel for it?

DR. HOFFMAN: I have Dr. Paul Dolin here.

DR. DOLIN: Thank you. My name is Paul Dolin. I am head of Drug Safety at Roche. Yes, you make a good point there, that the lovely reporting -- this is the post-marketing reporting -- is based on a spontaneous reporting system in the U.S. It does have inherent limitations, that it requires someone to actually make that active report.

That is partly why I think you saw in our last slide that we had an action plan, and part of that action plan was not just to rely on the spontaneous reports, but actually go back to some of the automated databases so we can get into a better data source than entirely relying on these spontaneous.

So we are trying to take the appropriate steps over time.

MEMBER O'FALLON: Well, that is very

laudable, but right away I began to wonder -- hang on here. You know, there is a huge percentage of Americans that don't have any insurance, medical insurance, and how do you -- Do you have any feeling for how that fact will affect, say, your claims data that you were using?

DR. DOLIN: That is a good point. Again, what we are currently doing is we are looking at alternative sources of data as well, and one of the data sources we are particularly considering is a U.K. data source, the General Practice for Research Database which the FDA holds.

So that is a primary care database. It is a different country to the United States, but every person in the U.K. has a government doctor, and they are the gatekeeper to all services. So there is an anomalized database of those medical records, which again we will be looking at as another potential source.

We are similarly looking at the moment for other sources in the U.S. where we could get a handle on what could happen in the U.S., maybe Canadian data

sources.

In this area, again, we are very happy to work with the agency, the CDC. So let's work as a partnership here to find the appropriate way to get the best handle on this.

MEMBER O'FALLON: I think you sound like you are using every shred of evidence you can, and this is really great. But I'm still concerned that maybe in the United States we have a serious structural problem that leads us to have serious underreporting on things like this.

DR. DOLIN: Yes. I think the other thing is the United HealthCare database -- we did see, even with its limitations, that we had a mortality rate in the Tamiflu group was slightly lower -- certainly, no higher than in the non-Tamiflu group. So even with the caveats, the limitations, we feel some reassurance from that database.

CHAIRMAN NELSON: Do you have anything else, Dr. Hoffman? I saw you just sort of hovering behind.

DR. HOFFMAN: No, just two things.

Certainly, the awareness of the encephalopathy and encephalitis which the CDC is forwarding now will help us, I think, to recognize perhaps that syndrome more readily.

Also, we are happy to work with FDA in any way necessary to get accurate numbers of the safety of the drug.

CHAIRMAN NELSON: Dr. Fant?

MEMBER FANT: One question that I have is: In addition to sort of the more obvious questions but comes to my mind based on my own background is: Is there anything about the biochemistry of Tamiflu that may be relevant or that may have some relevance in understanding what is going on?

It is a viral neuraminidase inhibitor. A lot of enzymatic inhibitors, we find after the fact, both for research uses and clinically uses, aren't as specific as we may think they are.

What do we know about the specificity? What do we know about the polymorphisms of those gene products -- of those genes that lead to the products that may alter Tamiflu's specificity? And what impact

may cerebral inflammation have on altering access to potential targets or specificity for potential targets?

DR. HOFFMAN: The first part of the question, I don't have the answer to, and we don't have the person here who might be able to answer that question.

The second part of the question, though, is something I'm sure that we have thought about and, as you know, we had the data which was of concern to us with the juvenile rat and the fact that there was a lot of pro-growth getting into the brain at high concentration, which went away at Day 14.

We think now that maybe the rat wasn't the best model, number one, and we would like to go back now and do additional preclinical work, and what we would like to is exactly what you suggest, look at the case of inflammation. Is it different than in the standard models? So that's something we intend to do.

CHAIRMAN NELSON: Dr. NEWMAN?

MEMBER NEWMAN: I'm not sure if this would be Dr. Truffa or Dr. Lewis or other people from the

FDA, but I wonder, especially for these neuropsychiatric events, whether the medications that are sold over the counter in Japan for colds and the coughs might be different, and what the prevalence of use of those medications was, and how confident you are whether, if children had been using those, that that would have been recorded with the adverse event report.

DR. LEWIS: The recording in the adverse events is, as I said before, very sketchy. In some cases, we do have listings of over-the-counter or symptomatic medications. It is a little bit difficult for us to figure out sometimes exactly what those are, since many of them are not approved in the United States. But, clearly, we know that some of the over-the-counter products that are sold in the U.S. do have nervous system adverse events associated with them and are either stimulants or can have other neurological events.

Similarly, we know that both Rimantadine and Amantadine have neurologic consequences that have been pretty well described, but just going back to an

earlier question, in the adult testing of Tamiflu there was really not a signal that the CNS was affected by the drug use in the placebo controlled trials. That was something that was identified in the earlier studies with the M-2 blockers.

DR. JOHANN-LIANG: We did pose this question directly to the Ministry of Japan. We did ask this question regarding herbal therapies and being used concurrently in children. You know, the answer -- - Melissa, you can jump in as well, but the answer that we received was that, yes, there is over-the-counter -- lots of use of over-the-counter medications in Japan, because it is part of the medical practice question. However, we did not get specifics on what medications, for what age group, and there was no quantification.

We did receive an answer that there is this use, but we can't quantify it.

CHAIRMAN NELSON: All right. Go ahead, Bob.

DR. WARD: Can I just follow up on that? In Germany, the herbal products are very tightly

controlled as far as what is in them, more so than in the U.S. Is that the case in Japan? That is, are the herbal products there, their manufacture carefully regulated so we know what is actually in them, so that we can ascertain what the exposure is?

DR. LEWIS: I don't think we know the answer to that.

DR. MURPHY: I guess the only answer that you might make some hypothesis on, Bob -- They have a fraction of a number of the people we have, and you know how we don't regulate those products.

CHAIRMAN NELSON: If I could introduce a question of my own: It seems to me the majority of the data that we've seen, other than some of the registration data, looked at influenza with or without Tamiflu. Within the United HealthCare system, for example, would it be possible to look at prophylactic use, in the sense that you've got Tamiflu without influenza, and whether that would provide any information?

I mean, it is pretty clear that influenza is a bad disease. It is pretty clear that kids can

die from influenza. Any sense of the prophylactic use which might give you some idea of the drug alone?

DR. HOFFMAN: Yes, on those databases, because they are retrospective, you know, we know the -- Well, we know the patients had a diagnosis of influenza. I don't know, Paul. Do you know how many of the patients didn't have a diagnosis of influenza? Those presumably would be the prophylactic ones.

DR. DOLIN: Yes. In the data we presented here, we specifically said they need to have the influenza diagnosis, and we excluded the cases out which had Tamiflu and no influenza. So we could go back and actually reanalyze that data to look at that subset where we have potentially prophylactic use.

CHAIRMAN NELSON: Any idea how big that is in that dataset, out of curiosity?

DR. DOLIN: I don't have the numbers at hand. I think, just again because of the size of the database, I suspect we could find a reasonable size denominated to work on.

DR. LEWIS: Although I would remind you that Tamiflu is not approved for the indication of

prophylaxis in children under 13.

CHAIRMAN NELSON: I understand that, but--

DR. LEWIS: But we don't know how much off-label use there might be in that indication.

CHAIRMAN NELSON: You wouldn't, but since pediatricians often do that, as we all know, I would assume the United HealthCare database would include some off-label prophylactic use potentially. Maybe not. I mean, it's a United States database. It's hard to know.

DR. DOLIN: We believe around about five or six percent of that age group may be using off-label.

CHAIRMAN NELSON: Which someone could do the math quickly, but that's fine.

DR. DOLIN: That may be a reasonable denominator.

CHAIRMAN NELSON: Dr. Englund.

DR. ENGLUND: Yes, I would just like to say a few comments about the clinical use of oseltamivir, which I know about in part just from being part of the infection control in a large five-

state region, and I control all the oseltamivir in my children's hospital, which supplies it for five states.

I can talk about the shortages we have had and the fact that we haven't even been able to get it for the children that potentially needed it. But anecdotally, for our five-state region of Washington, Alaska, Montana, Idaho, we basically don't use it prophylactically. There hasn't been enough, and I would believe that the amount of prophylactic pediatric oseltamivir is going to be so small that you are not going to get data.

CHAIRMAN NELSON: But I assume those shortages are a more recent phenomenon as opposed --

DR. ENGLUND: Well, it wasn't used before, and then there's been shortages since it's been available. I mean, I'm saying practically speaking, I don't think it is used very much.

MEMBER O'FALLON: How about kids with asthma?

DR. ENGLUND: It is not used. It is not used in a clinical -- I mean, maybe --

CHAIRMAN NELSON: And I'm an ICU doc. So, obviously, when they get to me --

DR. ENGLUND: It is not used. It is not used. It is not used appropriately, and it is not used inappropriately.

DR. LEWIS; We did ask the Japanese regulatory authority if they thought there was use of prophylaxis in children off-label, and they said, because of the funding of their national health service, they did not believe that that accounted for a very significant percentage of their children who received Tamiflu.

We do have some isolated small case series, mostly from outside the U.S., of prophylactic use in, for instance, pediatric bone marrow transplant units or pediatric oncology units where patients are at high risk for complications of influenza and might not respond appropriately to vaccination, but again those have been very small case series with limited available data culled from the literature, but nothing particularly outstanding in those reports.

CHAIRMAN NELSON: That would be a very

murky population, I think, to try and draw any conclusions, but it sounds it would certainly be of interest to take a look at the United HealthCare's database and see what information might be gleaned.

DR. DOLIN: Yes. We've actually internally been discussing this very issue, and what we are thinking, particularly with the issue now of stockpiling, it may be very difficult going forward to answer. So we may actually have to look at the 2004 flu season before this potential stockpiling to get a clean dataset. So we are very happy to go back and look at that.

CHAIRMAN NELSON: Dr. Ward.

DR. WARD: Dr. Shay, is it possible for the CDC to ask that encephalitis and encephalopathy be a reportable disease for this next flu season?

DR. SHAY: The way those requests are made in the U.S. is they are proposed to the Council of State and Territorial Epidemiologists, which is the association of state epidemiologists, and they would discuss that and then vote on it, both in their Infectious Disease Subcommittee and then in their

Council as a whole.

While they had great interest after the '03-'04 season in making pediatric influenza deaths reportable for a three-year period at least, there was not as much interest at that time, nor has there been subsequently, in making encephalopathy or encephalitis associated with influenza reportable.

DR. WARD: Could I follow up? Do you have any suspicion why the encephalitis picture seems to be different in the Japanese population?

DR. SHAY: Well, I'm not going to be the only one put on the spot for that. I'll have some help over here and help across the table as well.

There does appear to be -- There are some differences in the presentations, I think it's fair to say, between how, when you look at the large Japanese series and, let's say, this large series or the large series reported from Texas Childrens Hospital.

One example we were talking about before is acute necrotizing encephalitis associated with influenza is definitely much more common in Japan, and it's not because of a lack of looking for it here.

You know, again, many of these children that we have information on were evaluated in tertiary care, pediatric stand-alone hospitals with full MRI facilities and physicians who knew what they wanted to look for. So that is just one example of an area where there does appear to be a difference.

I will ask for other comments.

DR. ENGLUND: You know, I think there is a difference. I think we don't know. I think the infectious disease community knows that there is a difference and has been looking for it for longer than five years. We have been looking for it.

Certainly, we don't miss, and I don't think my colleagues in the ICUs miss, bilateral thalamic necrosis. I mean, this is something that they are seeing. I mean, we don't miss it.

What we do miss in this country, absolutely, is the diagnosis of influenza. We are not good at diagnosing influenza. I personally know of many cases of mild neurologic cases which we in ID have -- not many -- several, and from other places and anecdotes from colleagues that give me a call.

We diagnose them last after they have already been seen by other physicians, by psychiatrists, neurologists, ICU, hospitalized; and a flu test is not done, because in the pediatric culture we don't do rapid tests for flu, the way the Japanese do.

I think the huge difference is the diagnosis of flu. I think we absolutely under-diagnose it, and because of that, we are missing some things. Having said that, I think there's a huge population and cultural difference.

DR. LEWIS: I'll just add one little thing, that in reading the articles that are written by the Japanese authors, as I said, there have been a number of different speculations about what this is; and even the Japanese authors believe that there may really be some significant pathophysiologic differences.

They have looked at levels of interleukins in spinal fluid and feel that those may be somewhat different in these patients with the acute neurologic syndromes. They have also pointed to other vasculitic

type processes like Kawasaki's disease, which was initially described in Japanese children and is clearly more common in children of Asian descent, and there's never been a good explanation for that either.

So there are certainly other disease processes where it seems clear that there are differences in the epidemiology based on demographics, and it just has not been identified what these events are.

CHAIRMAN NELSON: Let me ask -- I guess, put Dr. Shay on the spot for another speculation.

Looking back at your slides, I was struck by the nine out of 39 that you presented in terms of the mortality among those who probable or suspect encephalopathy.

Would one -- I mean, it's a fairly serious disease, and being experienced with that in the ICU, would one basically infer then from the reporting of deaths that it is a function of the incidence of the encephalopathy, not a difference in the mortality once that condition is recognized, so that it then goes back to a combination of our lack of vigilance, if you

will, in making the diagnosis, and then once that is made, I mean, then the mortality of the severe cases is roughly the same? Is that a reasonable guess, based on what we know?

DR. SHAY: I think that is a reasonable guess, yes. I have reviewed, and several other pediatricians have reviewed, many of the case reports, and in most of the neurologic cases have been two or three people who have looked at them, including a neurologist; and I think that that is probably a fair speculation.

CHAIRMAN NELSON: Dr. Newman?

MEMBER NEWMAN: I was just wondering whether, in the U.S., there is any seasonal difference in sort of encephalitis or encephalopathy that could be influenza, but it just isn't being diagnosed, and how that might compare to Japan. I don't know whether influenza would be a big enough proportion that you would ever be able to notice that or not, but whether there is a difference in the seasonality of encephalopathy in the two countries.

DR. SHAY: That's a good question, and we

could certainly look at it in this country using several different databases. We could look at hospitalizations. We have one of those diagnoses fairly easily.

DR. LEWIS: Although again, remember that arboviral encephalitides are also seasonal, although it is a different season. So you see West Nile virus. You see the St. Louis and other encephalitides usually during the summer. So off-season or non-flu season encephalitides might not be tested for flu, but might be tested for a range of other encephalitides that might or might not prove to be confirmatory.

CHAIRMAN NELSON: Seeing no further hands, maybe this is a good time to have Dr. Lewis present the summary of the agency action plan and charge to Committee, and then we will have further discussion and see where we go from there.

DR. LEWIS: Well, after the last discussion, the summary will be relatively brief. I would like to summarize the FDA's conclusions regarding the Best Pharmaceuticals for Children Act post-exclusivity safety review for Tamiflu in

pediatric patients and the FDA's plan for further action in this regard.

On the last slide, I will pose the questions for which we would like the Committee's input and that were stated in the background material that I think the Committee members received prior to coming to the meeting.

We really appreciate the Committee's consideration of this. This has been a somewhat unusual set of findings for us, and we evaluated these, I think, in more detail because again we are trying to be as transparent as possible and do as thorough a job as possible in evaluating anything that might be associated with drug related safety events.

After reviewing all of the information available to us from the adverse event reports, the reanalysis of the pediatric clinical trials data, and a review of the pediatric literature, we believe that there is insufficient evidence to establish that the pediatric deaths and neuropsychiatric adverse events represent a safety signal associated with Tamiflu.

The pattern of the neuropsychiatric events

is more suggestive of increased adverse event reporting from Japan during the review period, increased use of the drug in Japan, and an increased awareness of previously described manifestations of influenza in that population.

We cannot exclude, however, that similar events might be reported in the U.S., if Tamiflu use increases substantially or, especially, if the awareness of the neuropsychiatric complications of influenza increase in this country.

We believe that the severe skin reactions are less likely to be manifestations of influenza, and we have more concern that these may represent a true drug-related adverse event. Additional data regarding these events is currently under review.

Our planned course of action is as follows: As mentioned by Ms. Truffa in the earlier presentation, the Division of Antiviral Products and the Office of Drug Safety are reinstituting regular monthly monitoring of adverse events reported with the use of Tamiflu and other antivirals during the coming flu season.

We have a confidential information sharing agreement with the CDC and, therefore, are able to share adverse event information with them in regular conference calls, and we can discuss these events in the context of ongoing U.S. influenza surveillance data. By combining these efforts, we can find any trends that need to be investigated further pretty much in real time.

I will say that we began identifying these Japanese case reports during our real time monitoring of the adverse events during the last flu season when they started coming in to us.

This monthly review and discussion with the CDC of influenza and possible drug related adverse events is a system that we put in place last year, because we were concerned about the possible shortage of influenza vaccine and perhaps increased use of Tamiflu during that time frame.

We think it was a good system. It was quite effective for us last year, and we are going to continue that.

At this time, we have no plan to change

the Tamiflu labeling related to deaths or neuropsychiatric adverse events. An update of the general pediatric safety information and severe skin reactions are planned when the current supplement is completely reviewed.

We propose to update the Pediatric Advisory Committee on continued adverse event reporting at a future meeting.

Our specific questions to the Committee for discussion:

The FDA is proposing that it continue to monitor pediatric adverse events that are being reported for Tamiflu and return to the Committee with an additional report within the next two years.

Does the Committee agree with this proposal, and do you have any further comments about this proposal?

The FDA will propose additional information in the Tamiflu labeling regarding serious skin reactions. As you have heard from Roche, they have made a proposal for that in their current supplement.

Does the Committee agree with this approach, and any other comments that you might have about that?

CHAIRMAN NELSON: Great. Thank you. So let's sort of discuss going forward an action plan. Let me start off with a particular question.

From the standpoint of Roche and their pharmacovigilance, what is the process by which one would communicate your findings to the FDA in the course of this?

I would also be curious the interpretation of how much of that reporting is required under the adverse event reporting that is part of the regulatory oversight versus how much are you going to go beyond, if you will, the letter of the law to report your findings as you continue to look at this?

DR. DOLIN: First of all, of course, we adhere to the FDA regulations in our reporting. So all serious reports that we naturally report would be part of that. In fact, just on that point, we follow it on a global basis. We use the FDA rulings. We apply them globally to all our cases, no matter where

they come from.

The second thing that we would be quite happy to do then is at the end of each flu season, to provide a report of our epidemiological findings: What have we found from these databases that we are looking at? We are very happy to share that with the agency.

Again, we would be quite happy with the agency to work on the design of these studies and make sure that the agency is happy with the way we are looking at these datasets.

CHAIRMAN NELSON: And to just follow up on my previous question, if you go back and look at the United HealthCare on the drug absent influenza, once you complete that, you will be willing to share that in some way with the FDA?

DR. DOLIN: Quite certainly.

CHAIRMAN NELSON: Maybe even with the public?

DR. DOLIN: We are very happy to work with the agency and have transparency on all these issues.

DR. WARD: Skip, could I follow up?

CHAIRMAN NELSON: Yes, go ahead, Bob.

DR. WARD: Would you be sure and provide the denominator for frequency of use with those data, especially the international data, so that we can look at real incidence?

DR. DOLIN: Yes. I think this is partly where the trouble is. We have been looking at reporting rates rather than true incidence rate. We will always try and provide incidence rates as person years or a true denominator, wherever possible. So we will take an epidemiological approach to these analyses.

CHAIRMAN NELSON: Deborah?

MEMBER DOKKEN: I just have a simple question of clarification for Dr. Lewis. Your recommendation is within the next two years. Does that mean at the end of or sooner than, because my reaction would be different?

DR. LEWIS: Well, I guess one of the things that we have to keep in mind is that, because this is influenza, we are talking about the flu season is limited to the specific time period, usually

November or December through March or April.

So if we came back to you within a year, we would basically have only one additional flu season. We can do that, although I am not certain that that would provide us with as much data as will be very useful, again based on these are relatively small numbers, but again this is something that we would appreciate the Committee's input on.

CHAIRMAN NELSON: Well, let me follow up. It's one thing to have only one season, and generalizability of that information may be limited. What is the suppleness within which one gets the data and analyzes the data to where -- I mean, whether it is at the CDC level, etcetera, and the flu season ends in March. When is the data even available for analysis, even if it is only one season?

DR. LEWIS: There is a lag, and it takes several months to collect that data and make sure that you actually have it all. In the BPCA review, it went from March to April of the next year.

They actually added that extra thirteenth month in order to be sure that things had sort of come

in from that flu season. But it does take at least a few months to be sure that we have all of the reports because of the lag in reporting.

Sometimes these reports, particularly the international ones, go initially to the pharmaceutical company. If they are in a foreign language, they have to be translated. Then they have to get to us, and we have to review them.

So particularly for the non-domestic reports, the time lag is more substantial.

DR. MURPHY: Debbie, I think what we can tell you is routine on these 50 drugs that we have just done, it takes us a minimum -- We do the one year, and then as they said, we add the thirteenth month to make sure we have all the data, and then it takes us another couple of months to just get it all analyzed, written up and ready.

So we are working on a minimum of 15 months in our one year -- Our one-year is 15 months is what I'm trying to say. So you've got at least three more months on there.

DR. LEWIS; But again, you know, we are

doing sort of routine surveillance during flu season and, if we identified anything that was concerning, I think that we would let the Committee know that we needed to present it sooner rather than later.

CHAIRMAN NELSON: Let me then just ask, following up on that: You have already -- There's a lot of the work that's already been done. In some sense, sort of templates for all the data analysis are already in place.

Is it unreasonable to then say after the next flu season, which would basically be a year from now -- When you are looking at it, is there anything of concern, and at least have that sort of, if you will, preliminary report that, no, there is nothing different that we've seen that is of concern, and then have a more complete report after two flu seasons. Is that a reasonable approach?

DR. LEWIS: That certainly seems like a reasonable plan.

CHAIRMAN NELSON: I don't see any other hands up. There's Mike.

MEMBER FANT: The only additional point

that I would make, in addition to the surveillance -- and I think we all agree is necessary to really try to determine how significant these potential signals are, how real they are, and to whom they apply -- assuming we get to the point in one or two years where we realize that they are very significant and they may apply to the population in general or to specific segments of the global population, would that be the position of trying to understand what the mechanism is that underlies that?

I think that's pretty important now, because I think we are dealing -- We are all concerned about having to deal with more than just the usual seasonal flu seasons, you know, particularly as it relates to Tamiflu exposure.

I think I would hope that, as we go through the routine surveillance that we are discussing here now, that Roche in conjunction with whatever laboratories you think may be necessary either in-house or in academia, to really explore the pharmacologic and the pharmacogenetics aspects of the basic biochemistry and pharmacology of Tamiflu action

and how it may interact with the patient, with individual patients, I think, is going to be very, very important.

It may turn out to be an unnecessary activity, but I would much rather have started that now if we find ourselves a year or two down the road wishing we had that information, because it may have implications for significant segments of the global community who might be exposed to the drug.

CHAIRMAN NELSON: So I guess, to simplify the question or maybe -- What, going forward, are the potential linkages between pharmacovigilance and pharmacogenomics looking at when you have a wider distribution among the population. Say, if we get better in the United States in either prophylaxing or diagnosing as you get a larger population exposure, looking at variability in the adverse effects within the population based on differences in the pharmacogenomics of the drug, I guess, what might be on the table?

DR. HOFFMAN: I think the first thing we can say is that we do have collaborations right now

with NIH and with WHO regarding H5N1 and its appearance and characterizing that, and we do have surveillance programs that are being developed for that.

Specifically regarding the pharmacogenetics and genomics, our company is very interested in this area, as our main company is right now, and we have a specific group who does this, and this would be something we would be happy to discuss. We don't have the people here now who can do that.

CHAIRMAN NELSON: I don't think there is a concrete recommendation coming out of it, other than pointing out that over time, if population exposure goes up, it will be important to understand this information in a more targeted way.

DR. MURPHY: So let me be concrete. What I hear you saying, and maybe you were going to summarize this, Skip, is that as of what the Committee asks FDA to come back and re-present this information, one of the components is that you are going to expect to see some additional information, if nothing else, on process, where we might be looking and what's going

on, to try to address this question of what might be specific predictors or populations or interactions that might be occurring that would help us understand this phenomena. Is that --

CHAIRMAN NELSON: I guess I heard Michael asking a more fundamental question. It would be nice if, from the epidemiologic data alone, one could begin to identify subpopulations at risk of higher adverse event rates or severity. But I think Michael was asking a more fundamental question of linking that to the actual biochemistry and mechanisms of action of the drug itself, which would be beyond the epidemiologic data.

DR. MURPHY: That is what I was trying to sort out. You're really asking two things then, the epi question, but I'm trying to focus on what Dr. Fant as asking.

CHAIRMAN NELSON: Yes. I think he was asking a more fundamental pharmacogenetics question. If the epidemiologic data can be broken down at that level of detail, that would be great. But knowing the limits of the surveillance systems that we've talked

about, whether you can or can't do that, I guess, will be seen. Bob?

DR. WARD: One of the things I'm struck with is it appears that Dr. Morishima in Japan has a collaborative study group ongoing about influenza related encephalopathy. I know that the FDA has ongoing contact with their corresponding groups in japan.

It might be helpful if we could get a preliminary report about what their findings are, because it's the difference between the two populations, it seems to me, to be the biggest signal right now, and whether this is a signal headed our way that is likely in our population or not, they may have some ideas by that time that are not published.

CHAIRMAN NELSON: Okay.

MEMBER DIAZ: I also would like to understand a little more the reporting practices of adverse effects by countries other than Japan and the U.S., because if you look at the number of prescriptions of Tamiflu in the U.S. in children, it is 1.3. For the other countries, the total

prescriptions is 1 million versus 1.3 million. But the reporting side effects or adverse effects, it's the same in those other countries as the U.S.

So they are also reporting more adverse effects compared to the number of prescription use in children. That means the U.S.. I will be curious to understand that a little more.

CHAIRMAN NELSON: So that might be one way of trying to get at this population variability issue as well.

MEMBER DIAZ: And also -- right -- to all the other countries, which include Germany, France, U.K. and others. Are they more similar to Japan in the way they report and their surveillance versus the U.S., and why in the U.S. do we have so much lower adverse effects reporting?

CHAIRMAN NELSON: Which actually reminds me of a question I was thinking of asking. I think in the presentation you mentioned the U.K. general practitioner database and then made a comment about that being available to the FDA.

I guess there's two questions. Is it

available to the FDA, because I have not heard us get data from that? If it is, I guess then that would be something that would be on the table for the next time we see it. I don't recall ever seeing any data -- and maybe it flew by on some of the other drugs -- out of that particular database.

DR. MURPHY: The Office of Drug Safety contracts for the General Practice Research Database. We now have about a year's experience learning to use it. It is a very complex database, and certainly one of the candidate studies that we might consider is whether or not some study of influenza morbidity and mortality conjunction was -- these products' use could be done in it.

CHAIRMAN NELSON: So it would be reasonable to anticipate, if not expect, that a year from now or two years from now that that database would have been woven into this analysis, or is the learning curve longer than that?

DR. MURPHY: This just relates to other safety studies and the number of safety studies that we might be able to conduct at any one time in that

system. So I wouldn't commit to our ability to do it within that year, but certainly we can work with Roche in their use of this data system. Certainly, we would be very interested to see more closely the details of their United HealthCare system, and certainly, our epidemiologists can make suggestions and conduct independent reviews.

So I think we will work with the sponsor to pursue that.

CHAIRMAN NELSON: So with partnering, that could be done?

DR. DOLIN: I think that we are very, very happy. I think the first step is where you actually need to go and look at these datasets to do a feasibility assessment: You know, is Tamiflu actually on there? Are there sufficient numbers? If not, then we find out what are the appropriate databases that we could go with. But I think you know, we are very, very happy to work with the epidemiologists at the agency.

CHAIRMAN NELSON: So at least, in thinking about a sort of update, not the report but an update

after one flu season, it would be reasonable as part of that to just have at least a comment about where that stands if not done, at least being done, some preliminary assessment of feasibility of that in answer to that question? Is that reasonable? Working together?

DR. DOLIN: I think the issue there is the time frame, because the data have to be clean. I mean, I know the agency has huge trouble with duplication reports. For example, these reports may come from Japan straight to you. We may report them from Chugai direct to you, and just removing the duplicates actually takes a lot of time, because we don't have named patients and --

CHAIRMAN NELSON: No, I understand. It may be as simple as we are not done yet. That's fine. I'm not placing expectations of having the finished data, but an update. As part of the update of where things stand, it would be helpful, I think.

DR. DOLIN: For us, it's no problem.

DR. MURPHY: I think we would be happy to give you a status update. Bear in mind, epidemiology

databases have some additional timelines in terms of reporting and cleaning of data. I can't speak to whether or not we would have anything near preliminary results, but perhaps feasibility could have been assessed by that time.

I think what you are hearing, Skip, is that we are going for nearer of the two. You know, we think that whatever we need, it's going to take us a while to at least get that one year, then look at what other -- wherever we are at that time with other data and other information. But it's one of the reasons we came up with that number, is that we understand it is going to take a while.

CHAIRMAN NELSON: I understand. One reason I asked is, even though it may not be a requirement, but often businesses might be able to accomplish what the Federal government might not be able to accomplish.

DR. MURPHY: We are well aware of that.

CHAIRMAN NELSON: I won't get into the politics of Katrina on those points.

DR. MURPHY: And we do ask them.

CHAIRMAN NELSON: Wal-Mart and Home Depot, etcetera.

Well, why don't I -- Dr. Englund?

DR. ENGLUND: I just have one more comment, and that is to ask is Tamiflu used -- Is it licensed yet and used in the U.K.?

DR. DUTKOWSKI: I am Regina Dutkowski. Yes, Tamiflu is licensed in the EU, and it is used in the U.K.

DR. ENGLUND: In children?

DR. DUTKOWSKI: It's licensed in children at one year and older.

DR. ENGLUND: I would just like to say, anecdotally, in my experience with the European Pediatric Infectious Disease Society, it is not used a whole lot, and I"m just saying, for us to expect to get a lot of useful data in children in one year, you might be thinking --

CHAIRMAN NELSON: Then the update report would be: We looked at the number of hits on Tamiflu in the database, and it is 12.

DR. ENGLUND: I'm just saying, I don't

think we should be relying on that kind of database to be giving us pediatric information. I think we need to be mining the information we have in our country to the best of available, because it is going to be potentially more complete and more of it.

CHAIRMAN NELSON: Okay now. So why don't I at least summarize this discussion, as a way of just sort of identifying additional points.

First of all, let me just start by commending what I think the plans are. I think the pharmacovigilance plans on the part of Roche, I think, are commendable. What the FDA has done to date and what they plan to do, I think, is commendable.

So the only question sort of in addition to that is to take a look at the database, looking at -- trying to sort out the prophylactic use and whether there is any insight that that generates, and then sharing that; a discussion as to whether there would be any useful information, with questions about whether there will or will not be, which may well be true, that it is not useful to try and get information out of the U.K. database that is available; and as

part of this, understanding there may not be the capability of having any sort of usable or complete information that can be generalized until we go through two flu seasons, that at least after one flu season, there would be at least a reporting back, which could be as abbreviated or as complete as the agency feels necessary of just where we are in this process, which could be as simple as to say we've not seen anything new of concern relative to what we have already presented, now that we've got this experience in analyzing these various databases and sort of watching and doing that surveillance; understanding that the earliest with which one could hope that that might be done would be a year from now because of the flu season and then the month's lag in the data. That's not to say it has to be a year from now, but that would certainly be the earliest, I would imagine, that it could be expected.

That's what I have heard around the, if you will, fine tuning of the plans that have already been presented. Did I miss anything?

Any further discussion or can we take

action on the plan with the, if you will, minor modifications that we have discussed?

So I guess I would like to go back to the questions, the questions that were put forth. The FDA is proposing to continue to monitor pediatric adverse events that are being reported to Tamiflu -- we've talked about that monitoring -- and return to PAC with an additional report -- let's call it a fuller report -- within the next two years. We have commented on that proposal, and suggested a minor modification on that in terms of an update at least, hopefully, a year from now -- may be a little longer.

So why don't we take that action alone, and then talk about the skin reaction and labeling separately. So we are asked if we agree with this proposal. I am going to frame it as do we agree with the proposal, as we have talked about those minor modifications? So I will ask for just a show of hands.

You would agree with that proposal, with the minor modifications that we have made? Is there anyone in disagreement? So the record should show

that it is unanimous among the Committee.

Then the second question we were asked is about the additional information on the Tamiflu labeling regarding serious skin reactions. I might point out, we've not seen the labeling. So we are not being asked to frame it, but whether we agree with the sponsor and the FDA working toward mutually acceptable language around that labeling, which I gather is in the Supplemental NDA that has already been submitted.

Any discussion of that point? So I will ask for a show of hands of all of the Committee members that are in agreement with that approach to the recommended labeling. Anyone in disagreement?

So we are unanimous on that second question as well.

Let me ask if there's issues that are unaddressed that we need to address? Deborah?

MEMBER DOKKEN: Yesterday in some of our discussions we made reference to the fact that consumers now had access to information from a variety of sources, including the Internet and the media. I guess, although I am very comfortable with the

recommendations and the way the Committee responded, I can't help but think about what I heard on the radio this morning coming here, and how consumers receive some of this information.

I know there is now a Q&A on the website, and I especially like the last question and answer about what do I do if I think my child -- On the other hand, I'm not sure how many people routinely go to the FDA website.

So I think I've asked it at other meetings. You know, this feeling that I wish there were a more proactive way for information like this, because I feel there is a need right now for consumers to know, based on the media reports, that the safety of their children is being very carefully watched and taken care of, and I'm not 100 percent sure how this information is going to get back out again.

CHAIRMAN NELSON: Well, then I think that we invite comments on both the part of the FDA and perhaps on the part of the sponsor. I think there is interest for us to use the drug appropriately. It is not approved, I guess, for prophylactic use in the

United States at this point, less than 12 years of age, but anyone want to comment on efforts to educate the public appropriately about the use of Tamiflu?

DR. MURPHY: Well, we always depend on the company to do their part. I guess what I'm asking, Deborah, is are you -- You all have made recommendations before. Are you making a specific recommendation or you just want to make sure that -- like we had the Q&As. Are you suggesting that we now provide -- As you know, we have talked about ways we can do this.

We can have a press release from the FDA. Is that what you are suggesting?

MEMBER DOKKEN: I think, Skip just slightly misinterpreted. I'm not as much talking about public information about use of Tamiflu. I am talking about a very specific response to headlines that people heard today, 12 pediatric deaths, and a need to know in a time where people are bombarded by information about avian flu and maybe some concerns about how they are being protected and government response.

I'm talking about a very specific response, that this was carefully discussed and that children are safe in the short term, and there is going to be continued monitoring, and how that gets out other than on the Internet and in the news media.

CHAIRMAN NELSON: I suspect that it is out. You've just said it. There's half a dozen cameras in the back of the room that you didn't see in the previous two days of our discussion, and I think it is fair to say that this Committee does not think, based on the data that we have been presented, that there is any concern at all that Tamiflu had a role in the deaths of the children that were reported out of Japan.

So that news will, hopefully, circulate out through the reporting of responsible journalists. I'm not sure how much more can be said on that particular point, but there will be continued vigilance to make sure that, in fact, that assessment remains the case, that as far as the data can be said at this point in time.

Any comments or further questions or

discussion? From our FDA colleagues, any issues that we have not addressed that you feel we need to, before we adjourn?

DR. MURPHY: I count on you guys never leaving anything unturned. So, no, as always, a wonderful reasoned review, and we really, particularly in situations like this where, to be quite blunt, we think a focus, an inappropriate focus, was placed in the media, and I think your deliberations today should help the public understand that not only the agency but we've brought these reports to a panel of experts, and that they very carefully looked at the data, and I know you guys did a lot of reading. I can tell by the questions, and brought your expertise and your thoughts today to this meeting, and you have found no reason for us to do anything different than what we are proposing, which is continue monitoring.

There is, at this time, no evidence that we need to be anymore concerned about Tamiflu causing the type of events that were being reported, and that we will see you guys back in two years -- no, before then.

CHAIRMAN NELSON: Well, on this topic maybe two years.

DR. MURPHY: With a report.

CHAIRMAN NELSON: Well, I would like to thank everyone for their patience and participation, and this meeting is adjourned.