over people stocking up at home, etcetera. But really not much of a difference in either the clinical manifestations of flu season last year nor the use of oseltamivir in this country.

This graph -- actually, you know, we want to thank the sponsor, Roche, for this graph, but it's their depiction of what goes on globally in the use of Tamiflu. And as you can see, it is very striking the amount of use of this drug in Japan as compared to what's used in the U.S. in the pink bar and then the white bars is what's used in the rest of the world. Orders of magnitude sort of differences here.

And just to note that this looks like it is by calendar year, so it's a little bit different than what I showed you before. And the last set of bars is probably not complete yet, you know, since we are still in 2006. And the point, you know, that I just want to reiterate from what the discussions

that went on last year is that there is so much use in Japan.

And we are seeing, you know, the numerators coming in about the adverse events, you know, in relationship to the denominator, the tremendous denominator use. And is it an overlay of something specific in disease manifestation of flu in Japan with the neuropsychiatric event or is it just simply a matter of the use?

So if we were to have a pandemic or such in this country and there was a tremendous increase in use, we would be seeing these rare events as well. So those are kind of the discussions that went on last year. And again, the pattern of use through the last year's flu season remains similar to what you were all shown last year.

This is the safety update on the serious skin and hypersensitivity reaction. Very quick, because it got labeled last December, in December of '05 post-marketing

safety review identified 43 cases of serious skin reactions in the AERS database, including three fatalities, which were all in adults. 16 of the 43 were pediatric patients. 24, you know, cases were serious skin SJS, 14 erythema multiforme, 4 cases of TEN and 1 case of pemphigus.

Now, it's important to, you know, just have a little caveat on the side. We have been discussing about this drug causal issue. And I have said over and over again throughout the day today that AERS is not something we can use as a database to say anything about causality of the drug, except in, I guess, very few cases.

And I would say skin and severe skin and anaphylactic reactions are one of those adverse events that I think, you know, in general we agree that if we have these serious skin events coming in post-marketing, that is probably an area that we think has more to do with the drug.

I guess another one would be like, you know, neuromuscular blocking agent and you give it to a patient, one patient and they go into a blockade. That would be something else. But this is a case. This is an adverse event that we would consider we can make some more inferences from the AERS database.

So that's what happened. And then it was labeled last year with the supplement for prophylaxis in kids. A statement went into the Precaution section under a subcategory of serious skin and hypersensitivity reaction. And there is also that, you know, the laundry list down in the Adverse Events section regarding post-marketing observations of adverse events.

Okay. Now, going over to the pediatric death reports. You know, this Committee has told us over and over again that you are interested in serious adverse events and you are particularly interested in hearing about the fatal events. So we do want to give

you a brief update on what happened since last year.

Last year in November, Melissa Truffa spoke to you about the 12 pediatric deaths that were in the AERS database with this drug, less than 17 years of age. She also gave you a little appendix with the 13th report of a boy, 17 year-old boy. So that's what you heard last year. She said that all those reports were from Japan, all those death reports. And these cases, you know, had a lot of co-morbid and confounding factors, lots of limited and missing data and it was really difficult to assess the causal -- what caused the death.

There were issues which translated reports and limited access to follow-up making information hard to interpret or challenging. So based upon that available data, it was agreed in last year's Committee deliberation that it was hard to establish a direct relationship between the use of oseltamivir

and the reported deaths.

Okay. So since then, we went back into AERS and pulled out, you know, and queried the database to see if there were any extra fatal events since last year's time. And this time we were asking for less nor equal to 17 years of age. And they retrieved five additional unduplicated deaths reported since November of last year. And this time we do have two cases which were domestic.

A 3 year-old health girl with flu reported altered mental status, had a diagnosis of severe strep pneumonia and died due to sudden respiratory and cardiac arrest. That's basically all we really have.

An 80 year-old girl -- 8 year-old girl with a history of SJS and TEN and anxiety after use of Tamiflu and ibuprofen also known to cause these adverse events needed prolonged and extensive rehab and actually died many months later after the use of these drugs.

So out of these five additional

deaths, the rest were again all from Japan. Three Japanese cases. A 7 year-old boy with Down's and flu had difficulty breathing and then had sudden death with GI hemorrhage.

A 3 year-old boy with flu A and cardiopulmonary arrest. Death possibly due to encephalopathy or cardiomyopathy as per report.

A 12 year-old boy with fever to 40 degrees took one capsule of his brother's Tamiflu and several hours later died in a fall from a high rise apartment building. That last report came in pretty recently. That's probably the most recent report of fatal event.

So, you know, when we looked at this out of the total of 18 reported death in patients less or equal to 17, you know, we were concerned at this pattern that three out of 18 had death due to traumatic injuries from basically, you know, falling off or, you know, leaping in front of a truck.

A 14 year-old boy after one dose fell off the 9th floor. A 17 year-old boy, you know, jumped over a wall and leapt in front of a truck. A 12 year-old boy that I just talked about.

So from the available data still, I mean, again we come back to this. It's difficult to establish a direct relationship between the use of Tamiflu and the reported death. However, we are concerned about the pattern of these events.

So I'm going to turn over now to Dr. Mosholder to walk through with you our most updated review on the neuropsychiatric adverse events.

DR. MOSHOLDER: Thank you, Rosemary. Just for background as Rosemary just mentioned, in December of last year following the AC meeting in November and also coinciding with the prophylaxis indication, our division undertook an AERS review and identified 126 cases of neuropsychiatric

events of all different types, including three with fatal outcomes. 17 were classified as abnormal behavior, including two deaths as just described. And the conclusions at that time was not to label, but to continue monitoring for these types of events through the 2005/2006 influenza season and then reassess.

So what I'm going to present is the updated post-marketing surveillance analysis following the most recent flu season for neuropsychiatric events. And this describes methods for the AERS Search. We looked at reports to see if during the time frame, August 29th, which was where the December review last year ended, through the July of this year, the MedDRA terms selected were for the high level terms, "suicidal and self-injurious behavior" and also 30 additional preferred terms representing various neuropsychiatric events.

The reports were required to have

indicated oseltamivir is the suspect drug. We looked at all ages and after we reviewed the reports, we grouped them into categories of cases based on the clinical characteristics.

So this most recent Search returned the total of 129 reports, 26 we excluded for various reasons, they were not felt to be relevant to the issue, leaving 103 cases for the analysis. 95 of which the vast majority were from Japan, as we have heard before. Five were domestic and three from other countries.

These were predominantly pediatric shown by the median age being 12, but there were adults. The vast majority involved treatment of confirmed influenza and only three involved prophylactic use. And there is about a 2:1 male:female gender ratio.

So this slide shows the categories that we classified the reports into after doing the manual review and you will see by far the largest category turned out to be what

we call delirium with prominent behavioral disturbances. It was a total of 60 reports, one from the U.S. There are also smaller numbers of reports for the suicidal events, panic attacks, delusions, convulsions, depressed level of consciousness, loss of consciousness or syncope and finally some miscellaneous reports.

We looked at those, out of these 103 reports, that had fatal outcomes and the first was actually an updated report on a case that had been reported previously, the 14 year-old boy who died in a fall. Then there were two reports of suicide in adult males, both again from falls. In one case, the patient actually left a suicide note. And in the other case, the coroner ruled it an "open verdict," presumably some uncertainty.

So next we wanted to look at the age breakdown for these neuropsychiatric reports. And this slide displays that. And you will see for the majority of these

categories, there is a small number of events for both adults and children. And, of course, the one that really stands out is the delirium with behavioral symptoms in the pediatric age groups specifically.

So we wanted to focus more on that specific category. And this describes some more about the cases of delirium with behavioral disturbances. There were a total of 60 reports, only one from the U.S. Three-quarters were male and only eight were in patients 17 or older. The other 52 were in the pediatric age group with the age distribution shown there.

We were somewhat impressed with the time to onset and that the median number of doses was 1 and 52 of the 60 cases had either one or two doses before the onset of the symptoms. 35 were considered to have positive dechallenge from review of the narratives and six negative dechallenge.

In 25 cases, actually, this is a

slight error here. It's 25 cases had absence of neurological findings. They weren't all necessarily imaging, some were EEG. In 25 cases there was documented abnormal behaviors despite the absence of overt findings on neurological studies. The median degree of fever was 39 and, in fact, 11 of the 60 had actually a very slight fever up to no more than 38 degrees.

And there was only one report with prophylaxis. Of course, in trying to distinguish the drugs contribution to these events versus the underlying illness, reports with prophylaxis would be more persuasive, but there were not very many.

Just to give you an example of the sort of character of these events, these are selected cases from that category of delirium with behavioral disturbance. There was an 11 year-old boy who took two doses and then had a fall from a landing fracturing his skull and the femur.

There was a 7 year-old boy who shortly after the initial dose ran from his house screaming and was later found at a neighbor's house.

A 13 year-old child after a single dose apparently began hallucinating and screaming about being chased, ran towards a 9th floor window and fortunately was restrained.

There was one case report from the literature. An 8 year-old boy who about an hour and a half after an initial dose became agitated, was growling, tried to run outdoors and was said to have severe memory impairment.

And to illustrate sort of the developmentally appropriate quality of the phenomenon, this was a 6 year-old boy who after a first dose began responding to command hallucinations from a huge Pokemon. The reporter was impressed that the child had very minimal fever at the time of this.

So the obvious question is why do we have so many reports from Japan? There are

several possibilities. The pediatric use there, as we have said, is much, much higher than it is in the United States. Speculatively, there could be unknown genetic risk factors for these types of events that are more prevalent in the Japanese population. And also, a case can be made that there is a more sensitive post-marketing surveillance system in Japan, so that would result in increased detection. And, of course, it could be combination of any of these factors.

Some additional points to consider, of course, influenza itself can be associated with delirium and in some cases frank encephalitis. And we don't have good data to show the relative contribution of the drug versus the underlying viral illness without systematic data.

I want to comment on this last point actually. Just in the past few days and too recent to incorporate into the slides, we received from Roche a summary of an

observational study from Japan that was a survey methodology of about 2,800 children, most of whom, but not all received Tamiflu for influenza.

And at first glance, the data would tend to implicate the influenza more than the drug in terms of development of what they termed abnormal behavior. And also, incidentally, they found a lower incidence of pneumonia as a complication among treated patients compared to untreated. But as I said, we just got these data a few days ago and there appear to be some methodologic issues that we don't have a handle on yet. So that's one thing we have talked about trying to explore to see if there is more than can be learned from this survey.

Another point is the degree to which the drug crosses the blood-brain barrier during an acute illness is unclear. Obviously, you would think that would be a prerequisite for CNS adverse events. That

would be due to the drug.

I mean, so also, of course, influenza is associated with serious morbidity and mortality and when we are weighing the drug risk, it's always in the balance of benefit versus risk. And, in fact, last year the sponsor cited observational data suggesting that treatment with oseltamivir can reduce complications in mortality from influenza.

The ideal situation would be to have data that could tell what the increased risk of these types of neuropsychiatric events from treatment with Tamiflu over those events that might occur with just the influenza by itself and to be able to weigh that quantitatively against reduction in complications and mortality, but unfortunately we don't have those kinds of data to inform us.

So with all those caveats, the emphasis currently is to make sure people

monitor for these types of events. And, in fact, the labeling change was just enacted earlier this week, which I'll get to in a minute.

There were some characteristics of the reports that, despite all these caveats, it made it difficult to dismiss the contribution of the drug to the events. As I mentioned, the temporality, most of it occurred with a single dose or perhaps two doses. In many of the reports, the reporting physician gave the opinion that the events were related to the drug.

There was an absence of reports of negative sequelae after the drug was discontinued in those cases, in which was discontinued. There was an absence of evidence of frank encephalitis among these patients. And there was a sort of peculiar compelling pattern to the behaviors, as I tried to describe earlier, which seemed to be a bit different from what has previously been

reported or the more common variety of CNS symptoms from flu.

So with those considerations in mind, it was felt to be prudent to update the labeling to be similar to what already was in the Japanese labeling and, of course, this could become even more important if the use in the United States begins to increase as it has in Japan.

So the labeling, this actually says labeling recommendations, but as I'm sure people probably saw, earlier this week the labeling was enacted and was announced. It is under precautions. It describes the post-marketing reports mostly from Japan of self-injury and delirium following use of the drug, primarily among pediatric patients.

It says the relative contribution of the drug to these events is not known and advises monitoring for signs of abnormal behavior immediately after starting Tamiflu and throughout treatment. And then in

actually in the patient package insert now it says that health care providers should be contacted if there are such abnormal behaviors and the idea is to determine whether Tamiflu should be discontinued or not, recognizing the possibility there may be a clinical need for it even in the face of abnormal behavior, depending on the specific circumstances.

So anyway, that concludes the update on neuropsychiatric events. And just to summarize what Rosemary and I have presented, the labeling for serious skin and hypersensitivity reactions has been updated. Drug utilization for the past flu season appears to be similar to previous years.

We have reviewed the more recent AERS pediatric reports with fatal outcomes and neuropsychiatric adverse events. And the plan, the final bullet there, is to return next year for a full report as recommended in November of 2005. And ideally, Roche will have some additional study data to address

these issues.

And just to conclude, I want to thank the other FDA colleagues and, of course, the sponsor for their assistance and we can have questions.

ACTING CHAIR WARD: Dianne, let's be very clear, I think, for the Committee. This report this year is really to just bring us up to date on the nature and extent of adverse events that have been reported during the last year. Is that correct?

DR. MURPHY: Correct. I mean, if the Committee -- the Committee made a number of recommendations last year what they wanted to see and certainly if the Committee has any other recommendations on what they want to see next year, we're not saying that you can't say anything.

ACTING CHAIR WARD: Right.

DR. MURPHY: But we just wanted to make sure you are aware that to those who are new, this Committee has already said next

year, that's what the last bullet was about.

ACTING CHAIR WARD: Full year.

DR. MURPHY: That we know we're coming back, Roche knows we're coming back. There have been certain things that have already been asked for. The Committee is open to make any other recommendations. We, you know, would have presented the proposed label to you if Roche hadn't already agreed and the division hadn't already gotten it done and, you know, had to comment, but they were able to get it done.

MS. DOKKEN: Given that the labeling, you know, that the action has already been taken, I wanted to use this as an example of something that we talked about earlier, which was what goes in the patient information. And to me, essentially, how do we create opportunities for parents to collaborate with their providers and parents to, you know, be informants in the health care of their own children?

And I applaud the approach on this that it, you know, really sets that up and makes -- you know, I think sometimes on this Committee, because pediatrics is such a vulnerable population, we're in a box, not a black box, but we're in a box of, you know, what we're really supposed to be addressing and doing. And so we struggle with how do you educate physicians? How do you educate families, the AERS database?

But this is a good example still within the purview of the Agency and this Committee that, you know, it makes an approach toward education. So I would like to just say I think this is a model and we could go back and look at some other patient information and labels, because I think this sets, you know, a good working relationship between families and their providers.

ACTING CHAIR WARD: Robert?

DR. MURPHY: Could you tell us something you really like. We would like to

hear. No, no, is there some component that was particularly -- so that when you do things that are done well, you want to know what it was that you did really well and keep on doing that and we'll hear what we shouldn't keep doing, so we'll try and look at that. But can you just, for the division, they are here, you know, tell --

MS. DOKKEN: Well, I think the main thing that I'm focusing on is that guidance. I'm assuming the language will be the same in the parent information. I'm only reading from this September 20th memo, page 20. And the sentence is if patients develop abnormal behaviors, their health care provider should be contacted immediately, etcetera, etcetera.

I'm hoping in the patient information piece it would be a little more explicit. If your child develops the following kinds of behaviors, you, as a parent, would contact your doctor or whatever

we're doing to make it more. But it's that. It's empowering parents to look for something and then to know what to do when they see something that's out of the ordinary.

DR. MURPHY: That was helpful, because you pointed out the two elements that you thought were helpful in there. So thank you.

ACTING CHAIR WARD: Okay. Robert and then Larry.

DR. DAUM: So I'm sure everyone in the room would join in with me on this, but I'm struggling to understand what people are using this drug for and what makes the culture of its prescription at clearly a high rate in Japan go forward versus even -- and we're not so great, that's a judgment. We're using it a lot, too, in the U.S. I mean, we're the second, based on the data I saw, most frequent prescribers in the world or we prescribe the second most.

And so I wonder if there is any

information from either the FDA side or possibly even the manufacturer's side as to what is this drug being used for? I mean, I get the sense from the slides it's not a prophylactic use, which is a relief to see. And I also thought I saw flash by on one of the slides that most of the cases were confirmed in some way to be influenza.

And so what are docs doing in Japan or for that matter this country? Are they doing some kind of rapid influenza tests and then prescribing oseltamivir? Is it routine? Is it only for people who are very sick? Is it for, you know, someone who has a little sniffle and a positive test? What's going on with use?

DR. MURPHY: Well, we actually had a fairly extensive review of that last year and I'll ask OSE or anybody else who wants to summarize it. All those things you listed are what's happening. And there was also in Japan a high level of concern because of a lot of

cases of encephalopathy and encephalitis that were reported previously and so, you know, there is that going on and the rapid diagnosis.

It's just -- oh, Linda is here. Linda, do you want to come and make some comments about that? There is a whole different approach to how you get this drug, you know, how they use rapid diagnostics, etcetera.

DR. DAUM: And maybe if Linda is going to come up, what happens in this country? What is -- there is a lot of use here, too. Why is that?

DR. LEWIS: Hi. For the people taking dictation, I'm Linda Lewis. I'm the Primary Reviewer for Tamiflu in the Division of Anti-Viral Products and I presented to this Committee a year ago when we first discussed Tamiflu and these events.

What we found our during our investigation last year and follow-up has sort

of proven this out that for whatever reason, and there are many reasons, the Japanese use an inordinate amount of Tamiflu, particularly in children. Some of the reasons that we identified is that all through the 1990s and into the early 2000s, the Japanese pediatric providers were very focused on what appeared to be a high rate of influenza associated encephalitis that had very bad outcomes.

And so they encouraged their population both to get influenza vaccine and they made as part of their national health insurance program reimbursement or provision without cost for rapid influenza testing in physician offices and clinics and provision of antiviral drugs. And so both Tamiflu and I believe relenza also.

And so the entire population was encouraged and physicians were encouraged to both test for influenza and then to provide specific treatment for it, because of concern for very bad outcomes if younger children

developed encephalitis. So that was part of it.

The other part was sort of a more cultural less well-defined perception that the Japanese population likes to have pills to treat things. And, you know, that's true in this culture also, but it seemed to be more true in that culture.

DR. MURPHY: And Linda --

DR. DAUM: Can I follow?

ACTING CHAIR WARD: Let me let Robert respond and then we'll move on.

DR. DAUM: I would like to follow-up. I mean, maybe -- and I wasn't here for the oseltamivir discussion last year. I guess it shows that I wasn't here. But if -- I guess the question is has anything been done to confirm the veracity of the claim that there is a higher rate of encephalopathy or encephalitis in Japan with flu? Because that may go to what is being seen here and it may be a confounder rather than a true thing.

And I guess I'll reiterate one other question is why are we the second most frequent country prescribing it? We don't have that encephalopathy physician marketing by the media or whatever issued here or do we?

DR. LEWIS: As far as I know, the identification of actual rates of encephalitis and encephalopathy associated with influenza is very difficult to determine. Last year we had a presenter from the CDC who came and actually presented data from a review of U.S. reportable cases of influenza during that very bad 2003/2004 flu season.

And there were actually a large number of deaths, if you remember back a few years in the pediatric age group and there were a relatively large number when these events were solicited of cases that sounded like they might be encephalitis or encephalopathy. Although, again, this was a retrospective case review of cases that were reported to the CDC.

So whether we actually have a lot less of it in the U.S. is, I think, still not entirely certain, but clearly it has been more highly publicized in Japan over a longer period of time.

Now, getting back to the question of why do we use so much of it in the U.S., I'm not sure that we really do. I mean, how many children do we have in the United States now? Something like 100 million, 50 million. And we use maybe, you know, 550,000 doses last year. So, I mean, I think if you think about it in a per capita setting, I'm not sure we use that much of it. It's just that we're a really, really big market.

So, you know, I think that you have to look at -- we're looking at total numbers of prescriptions not per population. You know, the U.S. population is greatly more than the Japanese population, yet they use 10, 15 times as much of the drug as we do.

DR. DAUM: I'm comparing us with

the rest of the world and surely you don't mean to say that we have more people than the rest of the world? We're the second most frequent users, at least what I saw.

DR. LEWIS: Yes, but I think that's true of probably every pharmaceutical product in the world that is produced in the U.S. I mean, we use a lot of drugs period, not just a lot of Tamiflu.

ACTING CHAIR WARD: Okay. Larry?

DR. SASICH: A couple of comments and then a couple of questions for the FDA on the issue of getting information to patients. And I think it's absolutely required if one of the recommendations or one of the precautions for a drug is monitoring the patient for, or a child in this case, a specific adverse event, the parent has to have that information. It doesn't mean anything to put it into the professional product label.

There is no specific -- there is a patient labeling section in the professional

product label for this drug and other drugs, that's only a recommendation to health care providers that they tell patients. There is no requirement to do that. The only way that you could ever begin to get this type of information in the hands of patients is with the medication guide. And then we're not even sure if the medication guides are being passed out and I wouldn't be opposed to medication guides. As a matter of fact, I would support medication guides for almost everything.

The next comment is that we saw in a lot of pharmacies around the country during the last year with all of the stories about bird flu. Tamiflu was flying off the shelves and being hoarded for bird flu. I don't know how much of an impact that that had on sales, but I was curious is there anything different in the manufacturing or the formulation between the product that is sold in the United States versus Japan or do they come from the same factory?

DR. MURPHY: That question was asked last year. I cannot give you the specifics of the response except to say it was looked at and there was no difference that was seen. Linda, do you have anything on that?

DR. LEWIS: It's the same product.

DR. SASICH: Okay.

DR. LEWIS: We got that directly from Roche and, I mean, it's made in several manufacturing facilities around the world, but it's the same manufacturing process and the same product --

DR. SASICH: Are you --

DR. LEWIS: -- that is distributed.

DR. SASICH: -- able to comment on any differences in the Japanese reporting system? Is it voluntary? Is it -- are there any major differences where there might be heightened reporting in Japan versus the U.S.?

DR. JOHANN-LIANG: Yes, there is differences. So the way -- you know, we

talked about the United States AERS system and, as you know, we have a set of regulations and it's basically a passive surveillance. The Japanese seem to have a six month sort of, I'm going to call it, active surveillance every time there is a regulatory action.

DR. SASICH: All right.

DR. JOHANN-LIANG: So it's not just with the first, you know, Tamiflu coming to the market it appears, but every time there is, you know, approved for children, there is another six month kick in that the health professionals are supposed to report adverse events.

DR. SASICH: Like the British Black Triangle for new drugs in the first two years.

DR. LEWIS: Yes.

DR. SASICH: Okay. The last thing, on page 4 of the memo, one of the things that drives me crazy is redacted documents. And so the Agency's original

proposal for language for a warning is redacted. Is it stronger than what we have now or was the original weaker or can you answer that?

DR. MURPHY: It is actually in their later on and it's a long --

DR. LEWIS: I think Debbie was --

DR. MURPHY: -- miscommunication process that went on here. That looked like a label that they thought they had to redact because it was in the midst of negotiations, when actually it was just a recommendation and that's why it got redacted in the first part where it looked like a label.

DR. SASICH: Okay.

DR. MURPHY: But it's actually on somebody --

DR. SASICH: Well, no, the full language of the recommendation --

DR. JOHANN-LIANG: Are you talking about the DDRE/OSE memo that we sent, that we did? Which memo?

DR. SASICH: This is from Dr. Edwards.

DR. JOHANN-LIANG: Yes.

DR. SASICH: September 20th.

DR. JOHANN-LIANG: Yes, okay.

DR. MURPHY: Yes.

DR. JOHANN-LIANG: So let me just say what happens is that we add the post-marketing side from Office of Surveillance and Epidemiology. We do a review of AERS cases and then we like to sort of say what we think about the situation and we recommend to the Review Division what kind of safety sort of initiatives should be started, including, you know, recommendations to labeling, to health communication, etcetera.

That's not to say that that's what's going to end up in the label or what's going to be done. That really resides with the Office of New Drugs and the Review Division to have purview of the life cycle of that drug. So when this happened, I think

what was happening was that there was an active negotiation going on between the Review Division and Roche and it was decided at that time that certain warnings that we had recommended should really not be sort of, you know, presented at this time, because there was a negotiation going on.

DR. SASICH: Personally, I would really like to see the FDA's recommendations and compare them with what ultimately winds up in labels. I think it would be very interesting.

ACTING CHAIR WARD: I don't think the lawyers would let you do that.

DR. BIRNKRANT: The label is already posted on the FDA website, Drugs at FDA, the final label that was approved on the 3rd.

DR. MURPHY: Yes.

DR. SASICH: She means this. I know. What I wanted to see was the original recommendation.

DR. BIRNKRANT: Well, it's on page 23 of that.

DR. SASICH: No, no, the redactions that are on page 23.

DR. BIRNKRANT: The same exact wording appears on page 23.

DR. SASICH: That was my question.

DR. MURPHY: We're telling you that what's on page 23 was the same thing that was on the redacted part.

DR. SASICH: So there were no changes. Okay.

DR. MURPHY: And yes, there are some differences, but what we're trying to point out is that it is in there. The recommendations from OSE are in there.

DR. SASICH: Okay.

DR. MURPHY: And that the first part got redacted for stylistic reasons, if you will.

DR. SASICH: Okay.

DR. MURPHY: Thinking it was in

the midst of a negotiation versus a recommendation. So you do have the original recommendation OSE made in that handout.

DR. SASICH: Thank you.

ACTING CHAIR WARD: Don?

DR. MURPHY: Page 23.

DR. BIRNKRANT: With regard to --

DR. MURPHY: I'm sorry, 20.

DR. BIRNKRANT: -- informing patients and their caretakers, there is a patient package insert with this label. It's in the form of a question/answer piece.

DR. SASICH: Oh, I didn't see one on --

DR. BIRNKRANT: You may not have it.

DR. SASICH: The Agency passed out a label, but I didn't see a patient leaflet for the drug.

DR. BIRNKRANT: Yes, it's clearly written though. Some of the questions are what are the possible side effects of Tamiflu?

How and where should I sort it, etcetera.

DR. SASICH: Yes, but that's information that nobody knows who has responsibility for distributing it. The only piece of information that the FDA has any control over and where there is regulations that say that it's supposed to be distributed are medication guides. It's not the things at the end of professional product labels.

DR. MURPHY: So let me make sure we understand. You like what's at the end. You just don't think it is going to be distributed?

DR. SASICH: No, I haven't seen what's in the end. The label that I have doesn't have information for patients.

DR. MURPHY: Well, it's the same thing, isn't it?

ACTING CHAIR WARD: I think it does, Larry. It's at the end of the label. It begins on the first page with the symbol of Roche above it and then Tamiflu.

DR. SASICH: Oh, I see.

ACTING CHAIR WARD: Okay?

DR. SASICH: Okay.

ACTING CHAIR WARD: And the issue has to do with allowing patients, allowing pharmacies to have you sign and say no, I don't need counseling. Okay. If that were not there, they actually have a legal obligation that the patient has to be counseled.

DR. SASICH: Only to offer.

ACTING CHAIR WARD: Pardon?

DR. SASICH: Not to counsel, only to offer. They sign that away.

ACTING CHAIR WARD: No, and that's what -- right.

DR. SASICH: And when they think that they are signing an insurance form. The only way that patients can be guaranteed, at least to begin to be guaranteed, information from the Agency is through a medication guide and then the Agency is going to have to do

oversights on pharmacies to make sure that information is being distributed. And the little bit of information that we have right now is that that information is not being distributed by pharmacies.

So it's easy to say well, write some patient information and wash our hands, but it doesn't work.

DR. JOHANN-LIANG: Okay. Perhaps this is not the time, but the discussion over medication guides and possibly some other way that patients can be given a very user-friendly information with every drug label change or whatnot, I think that is a discussion that would be good to have, especially in light of pediatrics.

The issue with medication guides per say, that is the only way really right now the FDA has to make sure, although we don't know whether this is really reaching the patient, that the information that is in the labeling is translated in the hands of the

consumer or the patient. That is a pretty involved process to get a drug to a medication guide right now.

And so there is a Committee that presides over what should be a medication guide. There are criteria. So it's a whole big topic in itself. There is other medication inserts. There is an effort that is outside of FDA purview, that's an initiative that's ongoing as well, which is -- but, you know, that's something we should probably --

DR. SASICH: From the private sector the two large surveys that have been done nationally, the information that is distributed by pharmacies, that information has failed to meet minimum quality guidelines. So the issue is particularly for pediatric patients where the precaution is to monitor for a specific set of events or behaviors, how do you ensure that patients actually know about it?

ACTING CHAIR WARD: I would observe that this is a recurring theme and that we probably should have some feedback in the future from the Agency about how we as a country can disseminate information more effectively to patients.

DR. MURPHY: Okay. I'm taking the Committee -- we have presented information on what goes in the medication guides and done all that. But what you are saying is that what you would like to do is to have a session on focusing on how to get information out on pediatrics, because it's your impression that it's not getting out there, particularly, because we have all these changes.

And I could tell you last night I was looking up some stuff that was in our new labeling. If you go up on our website, you go into pediatrics, you can see all the new labeling changes and we have got them up there and they are still not, two years later, in the PDR. So, you know, it's clear that we do

have issues and this is a big issue, because there are so many changes to pediatrics right now and that's a topic that you would like us to develop.

ACTING CHAIR WARD: Yes.

DR. MURPHY: Is that what I hear?

ACTING CHAIR WARD: Well, it would seem to me that you would start with asking the consumers about and really determining whether our impressions are representative of the population. Do they have the information they need? Do they not? If they do not, what sources do they use? How would they like to obtain that information that would be convenient and reasonable, since not everybody is sitting on the Internet? And, you know, I think that would serve a public health good.

DR. MURPHY: Dr. Kweder, who is the Deputy in the Office of New Drugs, has raised her hand, is willing to come to the fray. So we would love to have you here, Sandy. As Bob has tried to say, this is a,

for the new Members, long ongoing issue, medication guides.

DR. KWEDER: No, you know, I think the issue -- good morning, everybody. I know we're keeping you from your lunch. I just wanted to say that this is an issue that is actually much bigger than this Committee or even the collection of people in this room. And it is the whole area of communicating information to patients, particular, about drug safety, is something that the Institute of Medicine Report that was just published a few months ago focused heavily on.

And the Agency is looking very, very closely at better ways to do that. We have done some things in recent years trying to put out guidances about risk management, but they really only scratch the surface as far as we're concerned.

And the points about medication guides, you know, it even goes beyond requiring a medication guide, because we also

know that medication guides don't necessarily reach patients and even when they reach patients, they aren't necessarily read. You can walk into many clinics and find them on the floor. Many pharmacies out in the parking lot you find them on the ground.

So we are looking at this very broadly and I think that the challenge with pediatrics, of course, is that there is an extra party in there. You are not only dealing with -- you have another intermediary. There is the physician, the pharmacist, then the parent, who is responsible for the child. So it offers an additional set of challenges and we'll be focusing on that as well.

ACTING CHAIR WARD: Thanks, Sandy. Okay.

MS. DOKKEN: Can I just make a comment? I do want to in pediatrics, however, to say there is an added piece or an added person, that's, indeed, true. But there is also a 30 plus year movement called family

center care where, you know, there would be a lot to be learned about where we don't talk about parents as being, you know, another party. But there is an up-front recognition that a child is part of a family system and that's how you have to go.

ACTING CHAIR WARD: Tom?

DR. NEWMAN: Yes, I support the deliberations on the med guides. This is sort of on a new topic. If I could, I just have one concern about the new label, which is the way I read it, it seems like if your child develops one of these severe behavior disturbances, you're supposed to call the doctor and decide whether you should discontinue the medicine.

And I guess my concern is well, if you call the doctor and they say okay, he'll call you back and so on and so forth and you don't get through, I would rather have it say, you know, rather have the default be to discontinue the medicine unless the doctor

says you should continue it, rather than continue it unless the doctor says you should stop it.

Because this sounds like it could be potentially life threatening thing, that if they can't get through to their doctor, they should -- I mean, it's like, to me, a severe reaction. You should when in doubt stop and then talk to the doctor. If you don't reach the doctor, you should stop rather than continue.

ACTING CHAIR WARD: Okay.

DR. MURPHY: It's BID dosing. I sure as heck hope they get to the doctor before they give another dose.

DR. NEWMAN: Well, you would hope that.

DR. MURPHY: I know our health care system is in pretty bad shape, but --

DR. NEWMAN: It could be, but they may, you know --

DR. MURPHY: 12 hours.

DR. NEWMAN: But the effect may not happen until 8 or 10 hours after one dose. You see what I mean? The time to take the next dose may be not that long after the time they call the doctor and try to find out what to do.

DR. MURPHY: Yes, yes.

DR. SASICH: And the FDA has labeling precedence for telling, for asking health care providers, physicians to instruct patients to stop a drug immediately, an antibiotic, in this case, fluoroquinolone antibiotics. The labeled recommendation is tell your patients to stop the drug immediately and rest and then contact the physician.

Okay. So here we have the flu or are trying to treat or prevent the flu, not necessarily a life threatening condition. Here we have potentially a life threatening condition. I couldn't agree more with the wording of language. I think it would be

appropriate to say discontinue the drug, call the physician for further advice.

DR. MURPHY: Debbie?

ACTING CHAIR WARD: Okay.

DR. MURPHY: Recommendation is made, at this point.

ACTING CHAIR WARD: Okay. Robert and then John.

DR. DAUM: Forgive me for harping, but I'm trying to squeeze any semblance of causality I can from what we have been presented with today and try and understand at least what I believe about it. So the first question to come back to is the issue of there being concern about encephalitis in Japan. And that's how this excess use, that's how this heavy use started.

And I guess the question is has anyone attempted epidemiologically to look at that? Because if there is a lot of encephalitis, that may be, rather than the drug, responsible for some of these behaviors

and it may even be synergism between it.

And the second question while I have the little red light on is what has the media in Japan done with these events? Because media can also, of course, fan the fire. So I wonder if there is information about those two things specifically?

ACTING CHAIR WARD: Last year there were some reviews of some literature published in the Japanese medical arena about frequencies of encephalitis, but I do not recall the details, but I can probably find those.

DR. MURPHY: And the Pediatric Society in Japan also got very involved in this whole issue, too, so there was a high level of awareness of this issue.

ACTING CHAIR WARD: And some of these events that have been presented were first brought to attention from the newspaper, not from a care giver necessarily, so exactly. Andrew? Okay. Excuse me.

DR. MOSHOLDER: Oh, thanks. As far as the issue of encephalitis, I guess one thing having looked at some of the Japanese literature on encephalitis, those kids are very, very sick.

I mean, you know, they are usually in critical condition. They have high mortality and that was different, you know, qualitatively different from the types of behavioral disturbances with hallucinations and agitation that we were trying to capture in the reviews.

So you start to get the impression there are sort of two different types of clinical pictures. Maybe both are due to influenza, we don't know, but the --

ACTING CHAIR WARD: That was my recollection as well, is that there was a high mortality. There was a significant more long-term morbidity being observed in Japan from these infections, and it seemed like a different manifestation of influenza than that

which we see in the United States.

DR. MURPHY: And what Danny is also trying to say, and different from these behavioral things, these kids are not, you know, suffering from obvious fulminate encephalitis, not that there couldn't be some CNS, but that these cases that they reported to you didn't seem to fit that criteria.

DR. JOHANN-LIANG: It's also important though, I mean, to realize, yes, we had a lot of discussion about this. Yes, there is no -- these cases in AERS is not of cases, you know, of very bad encephalopathy. That is really what the concern is in the literature, but there is also in the literature the flu itself could cause delirium and abnormal behavior without, you know, being prostrate or in bed at all.

So the disease itself could do this. What we're concerned about is this strange abnormal behavior that seems to be not reported with the disease itself, whether in

Japan or anywhere else in the world, but that we're starting to see more reports of this. So, definitely, there does appear to be some sort of a disease, you know, population, you know, effect and then the overlay of the drug on top, what is that doing.

And that is why it's unclear to us at this time how much of the blood-brain barrier is being disturbed on the onset of influenza and is that why, you know, these manifestations are being seen. You know, we have had a lot of discussions about this, but the exact causality of what happens is unclear, but these patterns of abnormal behavior is something that is over and above what we have discussed regarding flu, the disease itself, whether in Japan or in the U.S.

DR. MOORE: Yes. This is way out of my field, but it strikes me that there has been in our country a huge amount of media-driven hysteria about the bird flu, which has

waned quite a bit now, but during this time, you know, even the Cardiology Office felt the pressure of writing prescriptions for Tamiflu from a number of people.

And, you know, just hearing these anecdotal cases of these kind of compulsive events after one or two doses and people who, you know, may be at risk or may have, you know, early flu are very -- this is very disturbing to me given that, you know, there can be a lot of media-generated pressure to go out and get this drug and keep it in your medicine cabinet and use it, which I suspect is what was happening in Japan. It's hard to imagine anything else would be going on but that.

So, I mean, is it worth talking about putting a black box warning on this, you know, because that is one way. We have been talking about how to get people's attention and, you know, the labeling has been changed and we have discussed that and I think it is

appropriate to discontinue the drug. I totally agree with that, but taking it to the next level, maybe that is something we should discuss.

ACTING CHAIR WARD: My impression so far has been that there is still uncertainty about the interaction between drug and disease and I think to place a black box warning on it seems inappropriate without, for example, a controlled trial, a treated and non-treated group that really demonstrates the frequency of these events.

And keep in mind that there were, what, nine million prescriptions in Japan. I mean, it's an enormous exposure occurring and an enormous amount of flu, I suspect.

DR. MOORE: Well, it is an enormous amount, but nevertheless suicide after one dose.

ACTING CHAIR WARD: Yes.

DR. MOORE: Jumping out of -- is a fairly severe consequence.

ACTING CHAIR WARD: Yes.

DR. MOORE: And, you know, I don't think that every black box that has been placed on a label has been the result of controlled trials. I think sometimes it's the result of just an accumulation of circumstances and data and animal data and what have you.

And I'm not saying that we should do this, but I think maybe we should suggest this, but maybe we should discuss it. At least it occurred to me as we were talking about, well, you know, what precaution should be on the label and will anybody really pay any attention to this? Will they make note of it to the point where they know to stop the drug if their kid does something crazy afterwards?

And in the context of all the hysteria that has been created about flu in our country and obviously not worldwide, because they are not doing it in the rest of

the world, except for Japan, and there is plenty of world that can afford to buy Tamiflu besides us, you know, I just wonder if, you know, these events together don't call for some way to highlight this, this particular problem more than just putting it under the precautions and kind of being careful how the wording is written.

ACTING CHAIR WARD: Dr. Cnaan?

DR. CNAAN: Given how popular this is in Japan and elsewhere, maybe the right way to address this problem is to design a large trial, because for this drug and for the flu you can design a true large trial, controlled, blinded and see if you can see something, basically, not wait for the suicidality, you know, to occur, but to just have a very good observational outcome within the trial.

DR. MOSHOLDER: Yes. Well, that was sort of my pitch for trying to get good, quantitative data and going through this, the frustration was that we had a phenomenon

documented from spontaneous reports which was associated with severe injury or even deaths in some cases, but what was missing was whether or not those events were more frequent or more severe compared to untreated influenza on the one.

And then to the extent that there is sort of emerging evidence that treatment with Tamiflu might prevent serious complications or mortality from influenza, which is certainly the way the Japanese have approached it, we don't have good quantitative data to weigh that benefit against the risks, so that is -- so anything that could get us better data I think we would support.

DR. JOHANN-LIANG: One thing I just want to point out is that this whole discussion with Japan, remember in all of our AERS reports that we have, we don't have one single case of a domestic, these sort of strange abnormal behaviors.

So this is a conundrum, too, how

much of this -- we take the Japanese experience where there is a disproportionate amount of use per population and then we say let's now translate this to -- we want to be prudent. We want to say that this information is out there, but we also don't want to build another hysteria on top of the hysteria that is out there already regarding, you know, the pandemic issue.

So, I mean, we're asking for your advice, what will be the best thing to do. We did have a lot of internal discussions regarding the discontinuation part. The Japanese label currently does say discontinue and then consult your health care provider, but they have cases to this.

Domestically in the U.S., we don't actually have any case of this in the U.S. and then, I guess, you know, some of the differing opinions that came up internally is if we say right now go ahead and discontinue the drug, what sort of measure of quantitative risk and

benefit do we have to do that?

And then the last point I wanted to make is regarding these cases that actually have some descriptors who were able to discern some information, all of them seem to have -- that we have information on do not seem to have some kind of negative sequelae.

In other words, the kid takes one dose or two doses and starts doing these abnormal things and a kid will be running into a street. But if mom or dad is able to restrain the kid, the kid stays on drug, the next day the kid seems to be okay.

So there are a variety of aspects to this that we really did try to consider from all angles, to not cause, you know, public hysteria. But on the other hand, how do we inform, you know, the parent as well as the health care provider regarding this emerging issue that we are yet unclear exactly what the place of it is.

DR. MURPHY: I think that to try

to sum it up like Dr. Moore is that the Agency did not think that it reached -- that the evidence yet would compel them to think about a black box. They wanted to be prudent. These are all Japanese cases. You know, we don't know what else is going on, as you all sat through.

We wanted to be prudent and make sure that we're transparent and that because it's a monitorable thing, people will know, you know, to watch your kids after you take this medication and that there seems to be no residual.

Until we have a better definition, which we will continue to try to seek, the Agency did not think it reached the level of that, the evidence was of that level that we could with confidence say that this was what was happening as far as the drug causing that.

ACTING CHAIR WARD: I want to make two observations. One had to do with the timing of the behavioral changes really to

ingestion of the dose. I talked to Dianne about this earlier. This is a PRO drug and it takes time to absorb it. It takes time to then activate it.

Yet, some of these events were reported to occur within a very short time after ingestion, which makes me suspicious that it has nothing to do with the ingestion, that this was a child who was going to have bizarre behavior.

The other issue has to do with the label as written with respect to the child under a year of age and what appears to me to be accepting of rodent data about the brain concentrations, and extrapolating those to the human condition.

This is an animal that happens to metabolize the drug quite differently than humans do. The half-life is five times as long as a human in the rodent. Yet, we have used that at this point to really say don't give this to children under a year of age, the

age at which the highest mortality of influenza occurs in pediatric patients.

And we don't have dosing data. We don't have kinetic data yet in that age range, but this implies a degree of certainty to me that I think overextends the data you have.

DR. MURPHY: So we have another issue on the table. I don't know that -- if you want to go ahead and comment?

DR. BIRNKRANT: Okay. We can talk about that a little bit and that is, you know, we have heard that concern expressed by others as well. We heard that there is a need for this type of drug in younger children and based on the animal data, there we did proceed cautiously up front, but now it is being studied.

ACTING CHAIR WARD: I know.

DR. BIRNKRANT: Okay. So we have come full circle.

ACTING CHAIR WARD: Okay.

DR. BIRNKRANT: We exercise, you

know, a cautionary approach.

ACTING CHAIR WARD: Yes.

DR. BIRNKRANT: And how it is being studied.

ACTING CHAIR WARD: Outcome data can be obtained in rodents. There is a whole battery of behavioral tests, so these animals, a set of animals that had kind of exposure, could have been sacrificed, the brain concentrations measured and their developmental behavior could have been tested later, as odd as it may sound, and you can detect ADHD in rats. All right. We're at --

DR. MURPHY: We're in a quandary.

ACTING CHAIR WARD: Terribly late.

DR. MURPHY: Yes.

ACTING CHAIR WARD: Yes.

DR. MURPHY: Because we have to train you guys during lunch and you are going to go upstairs, not take any delay in doing so, eat your lunch and we're going to talk to you at the same time.

ACTING CHAIR WARD: The public --

DR. MURPHY: And then you have to be back here in time for the 1:30 public.

ACTING CHAIR WARD: Right.

DR. MURPHY: Which we are not going to be able to do at 1:30 even though I told you by law we have to. Yes, what we could do --

ACTING CHAIR WARD: Okay.

DR. MURPHY: -- because we're going to have to move the public hearing.

ACTING CHAIR WARD: Right.

DR. MURPHY: Which I know we're not supposed to, because it's in the Federal Register, but I don't know anything else to do at this point, is to move it for at least a half hour to 2:00 and we can ask if anybody who is here now who had wanted to speak at 1:30, if you would, please, raise your hand and we would have you speak at the moment.

I hear only growling stomachs, so okay. The public session will be at 2:00. We

ask the Committee, please, what room are they to go to?

DR. JOHANNESSEN: I'll have to lead them.

DR. MURPHY: Please, follow Jan Johannessen on the crumbs on the sidewalk and he will get you there, and we will all be back here at 2:00.

(Whereupon, the meeting was recessed at 1:07 p.m. to reconvene at 2:03 p.m. this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2:03 p.m.

ACTING CHAIR WARD: On target. Is there anyone in the room who wants to speak at the Public Hearing? If so, could you raise your hand or let us know? All right. I'm not seeing anyone indicating you want to speak, so we will move ahead. Let's see. Masucci?

DR. MASUCCI: Masucci.

ACTING CHAIR WARD: Masucci? Okay. Iris Masucci is going to talk about updates on current FDA labeling initiatives.

DR. PENA: And Dr. Masucci received her PharmD degree from the University of Maryland and is a board-certified pharmacotherapy specialist.

DR. MASUCCI: Okay. Please, let me know if you have trouble hearing me. I don't have the strongest voice in the room. I am happy to be here speaking to you today, give you a little break from all your drug-specific talk and talk to you a little bit

about labeling issues that are going on specifically within CDER.

This Advisory Committee probably deals more with labeling than a lot of other committees, so it's really a great opportunity to inform you of what is going on. So I'm actually going to cover two topics today, the first being an overview of our new labeling requirements from the new regulations, and then a discussion on some initiatives on how best to incorporate pediatric information into our labels.

So, initially, we had our old labeling regulations that dated back to 1979, but these have recently been updated. Oops, sorry about that. This is very, very sensitive. Okay.

So, as I said, our old labeling regulations go back to 1979, but as we all know since then medical knowledge has evolved, our knowledge of drugs has really evolved, but our approach to labeling didn't evolve and we

recognize that, that our labels are not the best tool for clinicians, for anybody out there, and we really thought this was going to be a great opportunity to make our labels better, more informative and more helpful to clinicians.

I keep going the wrong way. So what has come to be known as the Physician Labeling Rule was published in January of this year with an implementation date of June 30th.

This is the package insert as we have all come to know it over the years in this order starting with the description and, you know, right off the bat when you open a label, you get the chemical structure, which is probably not terribly helpful to most of you or anyone making a prescribing decision. So that is just an example of how we thought it was really time and labels were ripe for a change.

So under the new regulations, our labels are completely overhauled format-wise

and there is a lot of content changes as well. Our labels are now divided into three parts. We have our Highlights, our Contents and our Full Prescribing Information or FPI.

Probably the biggest change is the creation of a Highlights section, which is essentially a very high level short and sweet summary of the essential information that prescribers need when deciding whether or not to prescribe a drug.

The Highlights is in a very easily accessible format, bullets, tables, very succinct. It's not meant to be lengthy pros and it's really based on feedback from focus groups and prescribers on what they wanted to see and what they found would be most useful in labeling.

Our Contents is really just that. It's a table of contents, nothing we have ever had in labeling before. People who are unfamiliar or didn't go to labeling very often with the older format really had to struggle

to find the information they needed, so a table of contents is certainly going to be helpful with the new format and when labels are available electronically, you can see how hyperlinks could become even more useful.

Some new additions to labels that has never appeared before is a section in the Highlights called "Recent Major Changes," and this will enable the reader of the label to look up a label and say there is something new in here which we have never been able to do before. We always had a date at the end of the label, but you never knew what was new, what was old.

And now there is a specific place in the label where that information can be identified, and it captures specifically new information in five sections of the label, the Boxed Warning, the Indications section, Dosage and Administration, Contraindications and Warnings and Precautions.

So if anything has changed within

the past year in the label, this will be listed under "Recent Major Changes," and the corresponding text in the Full Prescribing Information will have a vertical margin mark on the left margin, something we're all kind of familiar with from using word processing.

Warnings and Precautions are no longer two separate sections. Nobody ever really knew where the line was between a warning and a precaution. It was just kind of a gray area, so we solved that problem cleverly by calling the new section Warnings and Precautions.

The Precautions section used to be kind of a catchall for any kind of safety information we could always kind of lump under the Precautions section, but now part of that has been divided up into their own required subsections. Drug Interactions is now its own section, Use in Specific Populations and there is a new emphasis on Patient Counseling Information. That was never a required

section before, but now it is.

A lot of us didn't know that, but under the old labeling regulations, clinical studies was an optional section. Most labels have that, but certainly if you look at older labels you will see there are some labels out there that don't even have clinical studies information in it, and that is now a required section, as is Nonclinical Toxicology where any preclinical data would go.

There is also a new Dosage Forms and Strengths section that appears in the Highlights and in the FPI, and that is intended to be a really easy quick reference for someone writing a prescription. They want to know what size tablets the drug comes in, very short and sweet.

Some other new additions. Now, the initial U.S. approval date is going to be in the label. You will know when the drug first hit the market, something that has never been in a label before. Pharmacologic class

will be including into the Indications section and Highlights. There is more prominence given to adverse reaction reporting. The FDA MedWatch contact information is going to be in labels in Highlights, as is the company's contact information for that.

And, as I said, there is an additional emphasis on patient counseling, so any approved patient labeling, a patient package insert, a med guide, any instructions for use, that is going to be now appended at the end of the label.

So starting with the Highlights section, this is the breakdown of what type of information goes into Highlights, but it's actually going to be more helpful to you if I show you an example. This probably doesn't translate that well on the screen but, hopefully, you might have it in front of you.

This is what the Highlights section under the new labeling rule looks like. It's a half page. You will see

everything is very succinct, bulleted. This drug has a boxed warning. You will see right above boxed warning, that is where you will find your initial approval date.

Every entry in Highlights is followed by a number in parentheses and that is your cross-reference to the full information in the FPI. And at your leisure you can take a look through this and see how it's going to help you.

Next after Highlights are the Contents, the Table of Contents section, and these are the standardized numbering for the sections of the label. These are going to be consistent in every label. Description will always be 11. Adverse reactions will always be 6.

So it's establishing for the first time some consistent format and structure to our labels, and here is an example of a Contents section for a fictitious drug. You would see the Highlights as a half page and

then the Contents would be a half page, and then the full prescribing information would start on the next page. And you will see here each subheading had its own numerical identifier and, as I said, these are standardized.

The Physician Labeling Rule, the implementation date, as I said earlier, is June 30th of this year. So any new NDA or new biologic or efficacy supplement submitted after June 30th, the label is going to have to be in the new format. So everything we're currently receiving at the Agency is in the new format.

There is kind of a tiered hierarchy time line for getting everything else into the new format. If something was already in-house at FDA on the date of implementation or had been approved in the one year prior to that, the company is going to have three years to update their label to the new format.

And going all the way down to the bottom, anything approved prior to 2001 is not technically required to change to the new format, but we are encouraging it and we're already seeing some people, some companies, saying, you know, this is something we want to do. We want to do it maybe even earlier than we have to.

So, as you can see, you're going to see labels in both the old format and new format probably for the remainder of our lifetimes at least. You probably won't see a lot of these hitting the market and hitting the pharmacy shelves until sometime next spring, given that the implementation date was June 30th this year and then you have 6 or 10 months to get these drugs approved. It's going to be awhile before you see a lot of them out there.

If you just can't get enough of this, you can go to our FDA web page on Physician Labeling Rule. There is a lot of

information there. The actual rule itself is there. You know, if you print it out, it's about this thick. I am one of the few people that has actually read it, but we encourage you to thumb through it. There are guidances that go along with labeling sections, which are very helpful, these fictitious examples that I presented as well as templates and some FAQs.

So that is a very brief overview of the Physician Labeling Rule. And now, the other topic that I'm going to talk about today is how best we can incorporate pediatric information in labeling, something that this Committee is confronted with every time you convene.

Given that we have a new focus in CDER on labeling and kind of a rededication to labeling efforts, this is really a great time to make our labels better and try to get more consistency across review divisions and kind of evaluate and reevaluate our current

labeling practices on a variety of issues, one of which is incorporating pediatric information.

And we completely recognize that we have been rather inconsistent in this and this is our chance to review this. You can pick up a label now, read the pertinent pediatric sections and still come away and not know if it's approved in kids or you can pick up a label that has no efficacy data in kids, no studies, but there is a dose given in dosage and administration.

So it's very inconsistent and kind of perplexing for the reader and, admittedly, perplexing often for FDA reviewers on how to do this. So what I'm going to propose here today is, again, a new standardized approach to how we want to do this.

And really what people want to know when they pick up a label is are there any studies in kids and has safety and efficacy been established, two very basic

questions that are not always attainable from reading a label.

So when we're looking at adding pediatric information, really the bottom line question. Are the new data sufficient to warrant a pediatric indication? Basically, you know, is the risk-benefit ratio positive? So based on your answer to this question, this is going to help guide where in the label this information should reside.

If the answer is yes, if this is good, strong data, the information would go in the label just as any other indication or any other adult indication. You would have something in Indications and Usage. You would have the pediatric dose in Dosage and Administration. You would have adverse reaction tables from any pediatric studies. You would have some statements under the Pediatric Use section. You would have kinetics findings and the actual studies would be in the Clinical Studies section.

However, if the answer is no and we are not granting a pediatric indication, but we're incorporating information into the label because we feel it's important, instead of spreading the information throughout the label, we're proposing that all of this information for a non-approved indication be relegated to the Pediatric Use section.

And I mean all information, kinetics information in kids, safety information, dose finding studies. Whatever clinical studies you may have would all appear in the Pediatric Use section. And the aim of this is really to avoid the implication of approval again with the example I gave before.

If a dose appears under Dosage and Administration, one would probably conclude that that is an approved dose. But if everything is kept to the Pediatric Use section, it can be more tightly controlled and when it's in one place, what we can do, what I say here is adding some contextual language to

explain this, to explain what the data are that we have and what we have and what we don't have.

And, actually, this is kind of interesting and what I have found from talking to FDA reviewers is when we add this so-called unapproved information to a label, what we're essentially doing is adding off-label information to a label, which is something that kind of goes against the grain of what we're all taught to do at FDA.

So a lot of people have understandably struggled with the best way how to do this and the labeling regulations, both the old and the new, are not very prescriptive in telling us how to do it. So there has been a lot of leeway and a lot of different interpretations on the best way to do that.

So we have this yes/no answer, is it going to be approved or not approved, but we can further break that down to kind of the next level again to help us, to help guide us

in these decisions.

And I want to acknowledge Debbie Avant from FDA. She kind of helped us work on whittling these types of data down to these four categories and helped us come up with some of these examples. And I'm going to go through an example of each of these types primarily using the drugs that you have reviewed today that you can be familiar with.

So our first category of pediatric data is when there is substantial evidence in both adults and kids for the same use, essentially, the first part being based on adequate and well-controlled trials in both adults and kids. The indication is the same. The example here are the statins that you talked about today for the familiar hypercholesterolemia.

Another subcategory of this is when there are adequate and well-controlled studies in adults and other supportive information in kids like the ritonavir review

that you talked about today. So this is an example of, yes, this is approved. Everything would go in the usual place in the label.

A second category is not terribly different, but this is when the evidence is in children only because either the condition is unique to children, there is no corresponding adult indication, or maybe the drug was studied only in children. The example today is meloxicam for juvenile arthritis that has the adult osteo and rheumatoid arthritis indications or oncologic agents for childhood leukemias or for conditions specific to newborns like surfactants and things like that.

Again, this will be an approved indication, so clinical studies would go in Clinical Studies. Doses would go in Dosage and Administration. But what needs to be thought about here is the wording of the indication needs to be very explicit as to what indications are approved for what age

groups.

Now, Category 3 is for drugs that are studied in children, but the evidence is not substantial. So this falls into the no category, that we have data, we have some studies, but for whatever reason we're not going to be granting the approval for this. And these really fall into three subcategories themselves.

Either efficacy is not established, so don't use it, and examples from today are linezolid for the CNS infections or gemcitabine that didn't show any clinical benefit from either of those. The second category is safety is not established, so don't use, and this again would be benzyl alcohol-containing products as a good example there.

And the last subcategory here is we do have data, but the data is inconclusive to warrant an approval and the examples here are citalopram for depression and

rosiglitazone. So what we're saying with those is we have some data, but there is limitations and there's problems with the data with the strength of the studies, so this information is going in the label, but we can't strongly say don't use it or use it.

So what we're doing here, this is the no category. All of these types of information, this would all go in pediatric use. The studies for citalopram and rosiglitazone, some people's first instinct may have been to put those in Clinical Studies, but they don't represent substantial evidence, adequate well-controlled trials and a corresponding indication, so they should go in Pediatric Use.

Now, with this I'm not saying everything has to be in Pediatric Use. For example, benzyl alcohol issues and similar safety things would often warrant a Contraindication or Warnings and Precautions saying do not use in neonates because the

benzyl alcohol component. See, Pediatric Use. And then the more detailed information would be in the Pediatric Use section.

Our last category here sounds kind of strange, but it does exist, substantial evidence not available in any population. You're thinking, well, why would we put that in the label? This is really a combination of Category 2 and Category 3 together, Category 2 being a condition unique to children, but Category 3, the evidence is not sufficient to warrant an approval.

These don't come up very often, but an example here is tamoxifen for McCune-Albright. Tamoxifen has the breast cancer indication in adults, but is used for girls with McCune-Albright and if we were doing this label today, we would say that all of this information should go in the Pediatric Use with careful wording and not be scattered through Clinical Studies and Dosage and Administration.

So my last three slides, I know I talked pretty fast, are some issues we would welcome feedback from the Committee, from the audience, some of which I have brought up today, the first being does the Committee think it will be helpful to have pediatric information for approved indications placed in the usual places in the label, and information related to an unapproved use in the Pediatric Use section?

This is kind of the new paradigm that we're proposing here and we would certainly welcome your feedback on that. I'm just going to throw all three out there and then we can have some discussion time.

Secondly, does the Committee think that the language explaining the lack of evidence to support approval in the Pediatric Use section will be useful? So for drugs that aren't approved when everything is put in Pediatric Use, there almost is going to have to be some contextual language, some not

really disclaimer language, but some language added there about limitations of the data.

You know, we have these safety findings, but efficacy has not been established or all we have is pharmacokinetics findings. Safety and efficacy has not been established. So the reader really gets the full picture and is not misled by the inclusion of the pediatric data.

And, lastly, this is one that I actually didn't talk about, but we certainly want your feedback on this. Does the Committee think the Indications and Uses section should explicitly state the approved patient population?

And what I mean here is if a drug is approved for asthma in adults and kids, should it say this drug is approved for patients with asthma aged 5 and older or should it say approved for adults and children with asthma or should it just say approved for asthma, and then you can infer that it's

adults and kids.

And there has been a lot of inconsistencies with the way review divisions approach this. Some always put a minimum age. Some don't. And then kind of on the flip side, when a drug is initially approved, most commonly only in adults, if a new drug is approved for asthma with adult clinical studies, should that initial first indication say this drug is approved for adults with asthma?

I will tell you most drugs just say this is approved for asthma. No one ever thinks about it until a pediatric use gets added about really being as specific as we can about that. So those are the issues and the questions. I will certainly welcome questions on the new labeling issues. We can do that first if anyone needs more clarification on that. We can discuss these feedback questions.

ACTING CHAIR WARD: Iris, I think

those are great questions and thank you for the presentation. Larry?

DR. SASICH: One thing that I always thought that has been confusing to clinicians is substantial evidence, and substantial evidence from well-controlled trials, I think is the exact language from the statute. And you have go on and read the exact language of the statute where it says that this information or this evidence is deemed by experts, which is you guys, which is FDA-approval.

So why don't you just say FDA-approved or not approved? Substantial evidence has a regulatory and a legal meaning. It has a meaning that we use in everyday English, just as safe and effective does. Safe and effective has a regulatory meaning, but we use it in a totally different way when we're talking amongst each other. So I don't know what to do with it.

I know what you're saying when

you're saying substantial evidence, because of the statute, but I think substantial evidence is an unclear phrase. I think it's FDA-approved or it's not FDA-approved.

DR. MASUCCI: Right, and I think probably people in this room who are educated about this understand those nuances and would be interested in whether something is approved or not approved or has substantial evidence or doesn't. This nuance about where the information goes in the label is probably of less interest to most clinicians out there, certainly, and, you know, they don't know the term substantial evidence.

If we used safety and efficacy not established in labels, that is something that people can kind of wrap their hands around more, but the goal of trying to figure out the best way to present and the best places for this information wouldn't be as useful if we didn't add more explanatory language. And I certainly understand where you're coming from

with that, but I think it's just something that we have all come to live with and we, you know, it rolls off our tongues.

DR. SASICH: Yes, I know, and it rolls off of mine, too, and I understand that.

COURT REPORTER: Microphone, please.

DR. SASICH: Oh, it rolls off of my tongue often, too, and I understand that people don't understand, you know, may not know what I'm actually meaning. It's not clear in the way that we normally use these words like safety and efficacy and substantial evidence.

ACTING CHAIR WARD: Bob?

DR. DAUM: I would like to comment on your last question, and I think pediatricians feel like they are an under-served population with respect to these kinds of drug information sheets, and so that I would weigh in, I guess, to say that I would

always say it's approved for asthma in adults and children.

I would say it and I would always say what the lower limit of age is. And so I think that those two pieces of information will be welcomed as very refreshing by the pediatric community.

ACTING CHAIR WARD: Could I just add to that? I think that as we talk about it's indicated for a particular disorder in a particular age range, the dosages in the dosing section need to report for that age range as well.

And I will change hats real quickly to that of the neonatologist and we're currently reviewing labeling status for drugs used in the newborn ICU and it is very difficult for many of the older drugs to determine whether they were actually labeled. It says less than 5 years. Well, is that a 26 week preemie or not?

So when you get to the neonatal

section, they do represent a unique population within pediatrics and I would really like to see as much explicit data that helps us with the developmental changes in both responsiveness to the drug and kinetics. Tom?

DR. NEWMAN: Yes. I just -- really great presentation. Would it be helpful -- and I have sort of comments on all. Should we like go through the questions one at a time or should --

ACTING CHAIR WARD: Yes.

DR. NEWMAN: Because maybe you want to --

DR. MASUCCI: You want to stick to this one?

DR. NEWMAN: Well, maybe you want to back up and we'll do the first question first and then -- and I'm just --

ACTING CHAIR WARD: All right.

DR. MASUCCI: You can answer all three for us.

ACTING CHAIR WARD: Yes.

DR. NEWMAN: No, I don't know if you want to do it that way. Do you want to ask?

ACTING CHAIR WARD: No, I think that is excellent unless there are any other general comments. So Question No. 1, does the Committee think it will be helpful to have pediatric information for approved indications placed in the label in the usual places and information related to unapproved uses in the Pediatric Use section?

This is a remarkable change in philosophy, I think, you know?

DR. MASUCCI: And this is something that --

ACTING CHAIR WARD: With USP just down the street.

DR. MASUCCI: This is something that Lisa and I have talked about for years and we have never really had an opportunity to kind of push it forward, but with everybody looking at labels now, we really want to see

if this is something worthwhile.

ACTING CHAIR WARD: Rich? General pediatrician.

DR. GORMAN: I think knowing both the positives and the negatives in detail is going to be very helpful and if there are some uses where it's clearly unapproved, then those should be listed as well. If there are issues where the data is inconclusive, then you have to wrestle with all those other issues.

But I think approval information is very valuable and if the drug has been studied and found warranting, as opposed to found ineffective or inconclusive, I think that is information that will prevent pediatricians from continuing to perform uncontrolled clinical trials with an n of 1 in their office.

ACTING CHAIR WARD: Amen. To be able to say that it was tested and found not to work, you know, provides better health care.