DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE
CDER PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE
AND THE
FDA PEDIATRIC ADVISORY COMMITTEE

Tuesday, September 14, 2004

7:56 a.m.

Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

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Wayne Goodman, M.D., Chair
Anuja M. Patel, M.P.H., Executive Secretary

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GUEST SPEAKERS (NON-VOTING)
Kelly Posner, Ph.D.

PARTICIPANTS (Continued)

GUESTS (NON-VOTING)
Samuel Maldonado, M.D., M.P.H.

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Robert Temple, M.D.
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PARTICIPANTS (Continued)

Thomas Laughren, M.D.
M. Dianne Murphy, M.D.
Anne Trontell, M.D., M.P.H.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. GOODMAN: Welcome to day two of this joint two-day session of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee being held on September 14, 2004, here at the Holiday Inn in Bethesda, Maryland.

We are convened to address recent concerns about reports of suicidal ideas and behavior developing in some children and adolescents during treatment of depression with selective serotonin reuptake inhibitors and other antidepressants.

Our goal is to gather information from a variety of sources and perspectives to help us understand this complex situation and ultimately, to offer the best possible recommendations to the FDA.

Now, I would like to turn the microphone to Anuja Patel of the FDA Center for Drug Evaluation and Research and Executive Secretary of this committee to read the conflict the interest statement into the record.

Conflict of Interest Statement

MS. PATEL: Good morning. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

The topics to be discussed today are issues of broad applicability. Unlike issues before a committee in which a particular company's product is discussed, issues of broader applicability involve many industrial sponsors and products.

All Special Government Employees and invited guests have been screened for their financial interest as they may apply to the general topics at hand.

The Food and Drug Administration has granted particular matter of general applicability waivers under 18 U.S.C. 208(b)(3) to the following Special Government Employees which permits them to participate fully in today's discussion and vote: Jean Bronstein, Dr. Joan Chesney, Dr. Wayne

Goodman, Dr. Lauren Marangell, Dr. James McGough, Dr. James Perrin, Dr. Bruce Pollock. In addition, Dr. Philip Wang has been granted a limited waiver that permits him to participate in the committee's discussions. He is, however, excluded from voting.

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

In addition, Dr. Judith O'Fallon and Dr. Victor Santana have de minimis financial interests under 5 CFR Part 2640.202 that are covered by regulatory waiver under 18 U.S.C. 208(b)(2).

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant, and guest speaker.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committees, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Dilip Mehta and Dr. Samuel Maldonado are participating in this meeting as industry representatives acting on behalf of regulated industry. Dr. Mehta is retired from Pfizer and Dr. Maldonado is employed by Johnson & Johnson.

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

Thank you.

DR. GOODMAN: Thank you, Anuja.

We will be starting off this morning with a presentation from Tom Laughren who will give us an overview and also pose the questions, the five questions to this committee.

Following his presentation, I would invite questions. I also think it would be a good time before we get into the meat of our discussions to ask representatives from the FDA questions, to

further interrogate some of the data that was presented yesterday.

Before we get into the actual discussion of the questions, I would like us to think of the questions that were carried over from yesterday, pose those, and then we will take a short break, reconvene and start the process of discussing the questions.

Is that clear? Okay.

Tom, are you ready?

Opening Comments

Thomas Laughren, M.D.

DR. LAUGHREN: Good morning. I would also like to welcome everyone back to the meeting today. I would like to do a couple of things in my few minutes here.

First of all, what I want to do is to briefly review what I think are some of the key findings from Dr. Hammad's presentation yesterday, so that you have these in mind as you are considering the questions before you.

Then, I want to talk a little bit about

what I think the data mean and talk about what some of the regulatory options are as you are considering our questions, and then I want to go over the questions and the topics again.

These are the 24 trials that we are considering. Again, 16 of them were in major depression, and the other 8 trials were in several various psychiatric disorders - OCD, GAD, 1 in SAD, and 1 in ADHD.

Again, just for summary, I think these are the three contributions that the Division made to this effort. Again, we went to a lot of effort to make sure that we had complete case finding. With the help of Columbia, we accomplished what I think is a rational classification of these events, and we both obtained and included patient level data in our analysis of the suicidality data again to try and understand some of the differences both between trials, within programs and across programs.

These are the outcomes that we looked at again. The focus of the analysis was on two areas, the suicidality event data and also on the suicide

item data.

For the event data, could we have the other slide up that we had running yesterday? Our primary endpoint, as you recall, was the combination of suicidal behavior and ideation, Codes 1, 2, and 6, where 1 was suicide attempt, 2 was preparatory actions, and then 6, suicidal ideation.

So, that was our primary endpoint, but we also looked at secondary endpoints, at suicidal behavior, in other words, Codes 1 and 2, and then suicidal ideation, Code 6, and then for our sensitivity analysis, we looked at this larger outcome including 1, 2, and 6, but also adding in 3 and 10, where again, 3 is self-injurious behavior where the intent is not known, and 10 is not enough information. Again, these are the cases where there is injury, but it is not possible to tell whether it's self-injury or other injury.

With regard to the suicide item data, we looked at two measures about worsening suicidality on that item or emergence, and these again are the

cases where the patients are normal at baseline and have some increase during the trial.

In terms of our analytical plan, the major focus was on doing risk ratio analyses, both for the suicidality event data and for the item data. In both cases, we looked at individual trials, as well as for the event data, we looked at various pools.

We looked at both by drug, we combined all the SSRIs, MDD trials as a group, we looked at all of the other indications combined as a group and also did one pooling which included all 24 trials. For the item data, we looked again at individual trials and then a pooled analysis over all trials.

Dr. Hammad put a lot of effort into again trying to explain the differences that we were seeing between trials within programs and across programs, and I just want to spend a couple of minutes talking about exactly what he did.

He looked for confounding within trials using both the univariate approach and a multivariate approach. There were a total of 17

covariates that he looked at. He was not able to find any evidence for important confounding in that search.

He also did stratified analysis to explore for effect modification. The three variables that he looked at were age, gender, and history of suicide attempt or ideation, so basically, what he did in each of these is to stratify on these variables within trials to look to see if there was basically an interaction.

Again, he did not find any evidence for that, so basically, what that means is that on these variables, you find the signal both in children and adolescents, you find it both in males and females, and you find it both in those with and without history of suicide attempt or ideation.

Finally, he looked at 12 trial level covariates, again, as an attempt to try and explain the differences across trials using a meta-regression approach. Again, that approach was not able to explain the variability.

Now, I would say that one of the problems

in doing these kinds of explorations is that there is very limited power, you have a very small number of events. When you use an eyeball approach to the data, you can't help but thinking that trial differences might have made a difference.

I just use the TADS, the fluoxetine situation as an example. The company had three trials. There was no signal coming from those three trials. If you look at the careful screening that was done to obtain the patients for those samples, and the exclusions of patients with prior histories of treatment resistance, and so forth, and then you look at the TADS sample, which is many ways was probably more representative of the community of patients who actually get treated, there is quite a difference. Again, as you recall, in the TADS trial, you see quite a striking signal for suicidality.

So, even though quantitatively, we weren't able to tease that out and to explain the differences using various quantitative approaches, it is hard to think that that may not have made a

difference.

In my next three slides, I am going to present very briefly some of the data.

What this slide is, is presenting the risk ratios for various poolings. So, in this column, you have the risk ratios on our primary endpoint, which was suicidality ideation or behavior, 1, 2, and 6.

In the second column, you have this expanded sensitivity analysis, 1, 2, 6, plus adding 3 and 10. The first row is all trials, so this is a pooling across all 24 trials. In the second row, you have the pooling of the 11 trials with SSRIs and major depression.

Now, there are two things I want you to notice about this slide. First of all, in every case, the risk ratios are around 2. They range from 1.7 to 2.2, but they are sort of in the vicinity of 2.

Secondly, if you look at the confidence intervals on these risk ratios, in every case, it does not include 1, so in that sense, it is a

statistically significant finding. So, this is the pooled data.

What I have given you in this slide are a different set of poolings. Here, what I am doing is pooling the individual depression trials in the 7 programs that looked at depression, and these are the 7 programs listed here. Every row is a separate depression program.

What I have given you here, first of all, is the outcome on our primary endpoint a combination of 1, 2, and 6. I have also given you, in the second column, the outcome on suicidal behavior, and in the third column, the outcome on suicidal ideation.

There are a couple of things I want you to notice about this slide. First of all, in every instance where we have events, and we had no events for Serzone, but in the other 6 instances where you have events, the risk ratio is always greater than 1.

Now, I want to turn to trying to tease apart where that overall effect is coming from if

you break it apart by behavior and ideation. Dr. Hammad made this point yesterday, in three cases it appears as if the overall effect is coming from behavior, in three cases it looks like it is coming from ideation.

So, if you look at Celexa, here is the risk ratio for behavior, 2.23. There is nothing happening for ideation.

If you look at Paxil, again, it looks like it is coming mostly from behavior.

If you look at Prozac, it looks like it is probably coming more from behavior than from ideation.

For Effexor, there is a signal coming from both, but it is clearly coming more from ideation. Here, the confidence interval is almost significant.

For Remeron, it is all coming from ideation, and from Zoloft, there is nothing happening for behavior, it is all coming from ideation.

I am not sure what this means. As Dr.

Hammad pointed out, this may simply be a small numbers problem, but we are not seeing a consistent finding in terms of where the overall effect is coming from.

Finally, what I have given you in this slide is the data from the individual other 8 trials in non-MDD indications. As you get into these trials, the number of events you are dealing with is very small, and just to illustrate that, I have put the actual number of events in this slide.

So, in each of these parentheses, the first one is the number of events for drug, and the second one is for placebo. So, you can see the small number of events that we are dealing with.

If you recall from the previous slide, for Effexor, we were seeing quite a strong signal for major depression. These are two GAD studies. There is nothing at all happening here.

For Luvox, again, Luvox was only studied in OCD, there was no depression trial. Just one study in depression, only two events. They were both happening in the drug group.

For the two non-MDD Paxil studies, one in social anxiety, one in OCD, again, small numbers of events, but in both cases, they were happening in the drug group.

The same for the Prozac OCD, just one event, but it happened in the drug group.

No events for Wellbutrin.

For Zoloft, this is the only case where the one event is happening in placebo, and not in drug.

It is hard to know what to make of all of this, although the one thing that you can't help noticing is that even though there are a small number of events, where events occurred, they most happen on the drug side.

Just to summarize these data, again, if you look at various pooled analyses, the risk ratios hover around 2. They range from 1.7 to 2.2. In all cases for those poolings, it appears to be a significant finding.

The signal appears to be coming mostly from major depression, although perhaps not

exclusively. Despite those findings, there still are these inconsistencies in this risk, both across trials, within programs and across programs.

On the other hand, my view is--and there isn't necessarily one consistent view coming out of FDA on this--but my view is that this is a reasonably consistent signal for risk. You are seeing it in seven of nine programs. We don't see any events in Wellbutrin. On the other hand, Wellbutrin was only studied in ADHD, just one trial.

There is no signal coming from Serzone, which was studied in major depression. I am not sure if that means that Serzone is free of risk or it simply may mean that the events, the ascertainment in those programs was not good enough to pick them up. I don't know the answer.

One other point that Dr. Hammad made yesterday, that I want to return to, is a way of thinking about this risk is in terms of risk difference, and if you look over all these trials and estimate what the risk difference is, that is

the difference in the risk between drug and placebo, so you are subtracting the placebo risk from the drug risk, it is in the range of 2 to 3 percent.

What that means is that again, out of 100 patients treated--this is short term now, short-term treatment--you can expect 2 or 3 out of that 100 will have some excess of suicidality above and beyond what would be in the background that is due to drug.

As a clinician, what you have to do is to balance that risk against the perceived benefit. The problem here, of course, is that we only have, at least from FDA's standpoint, a demonstration of benefit for Prozac, but if you take the TADS trial as an example of benefit, there, you can look at the benefit difference, and the benefit difference in the TADS trial, difference between drug and placebo in percent of responders, using that as the measure of benefit, it is about 25 percent.

Again, you can interpret that in the same way, so that if you look at 100 patients who are

treated with fluoxetine, you can expect that about 25 out of 100 will have that benefit if you are looking at response as the benefit.

So, you balance that against the risk, which again in that trial, the risk actually was greater than the 2 percent, it was probably more on the order of 7 percent, but you balance that risk against the benefit. That is the kind of calculus that a clinician has to do.

Finally, as was pointed out, there were no completed suicides in any of these trials.

Again, we did not see the same signal in looking at the item data. One exploration we tried to do to see if that could be explained by patients dropping out, and unfortunately, that was not an explanation. The analysis of completers did not show really any difference from the analysis of the patients who dropped out.

So, how should these findings be interpreted? I think that this is an indication that there may be some increased risk for suicidality during short-term treatment, and I

think this is probably a class effect. Again, you are not seeing it in every drug that we looked at, Serzone and Wellbutrin being the two exceptions, but I think there is enough here to suggest that this is probably a class effect.

The signal appears to be most compelling in major depression. It may not be limited to that population, but again we are left with this very unusual variation in the signal across trials, within programs and across programs that we have not been able really to explain.

What I want to do next is to talk about what some of the regulatory options are, and I first want to talk about possible labeling changes.

As you recall, we already made a fairly major change to labeling back in March, and all of those changes have now been implemented. There is a fairly prominent warning statement that directs the attention of prescribers to this possible event.

Now, that language as it currently is written suggests that causality has not been

established. One thing that might be done to modify that, if there is agreement on this, we could say that causality has now been established for this risk in pediatric patients.

In addition to that, we could go beyond that and provide specific suicidality findings in the labels for different products. We could also provide more specific information about the efficacy findings for specific products in that language.

There are other things to talk about in terms of that warning statement including things like bolding language or putting black boxes. These are all options that are on the table.

The other option that you need to think about, and you heard many yesterday in the open session ask us to do this, you can think about contraindications. The one thing I want to point out is that in this country, for our label, a contraindication means never. It means that that drug will never be used in treating these patients, it is not an option.

The other thing I want to point out is that the term "contraindication" has different meanings in different regulatory settings. In some settings, it does not mean never. If you read the fine print in the UK, for example, there is a suggestion that specialists may still use that drug. So, you need to keep that in mind that in this country, a contraindication means that that drug is never an option.

In addition to labeling changes, there are some other obvious actions that we can and almost certainly will take. Our plan at present is to write a medication guide. This is basically labeling which ideally would be attached to the medication when it is prescribed in unit of use packaging.

In addition to that, we will undoubtedly have another public health advisory when we decide on what needs to be done, and we will try and communicate these findings to our partners.

Now, what I would like to do again is to quickly go through the questions and the topics.

The first topic is again we would like to have your comments on our approach to classifying these cases and to our analysis of the data.

One of the questions for which we really need to have you vote on is do you feel that the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients.

If the answer to that question is yes, to which of these nine drugs does this increased risk apply, in other words, is this a class effect for all antidepressants, does it apply to certain subclasses within this broader class, or to specific drugs?

If this is a class risk or if it applies to certain drugs, how should this information be reflected in the labeling for each of these products, and what, if any, additional regulatory actions should the agency take?

Finally, there is this question about what additional research is needed to further delineate the risks and the benefits of these drugs in

pediatric patients with psychiatric illness.

At our last meeting, I suggested one type of study that you might think about, and I am going to make that suggestion again, because we think that this is one study that might get at one of the deficiencies here, and that is, not only do we not have enough information about short-term benefit, we also have little information about longer term benefit or risk.

One way of getting at longer term benefit is the randomized withdrawal study. Basically, the way the study works is that patients who are responders or appear to be responding to treating, at some point in the course of treatment, are randomized to either continue on drug or randomized to placebo, and one looks at time to relapse as the outcome.

Now, I know there are concerns about that design. You know, one concern is the ethical issue of taking patients off a medication when they appear to be responding. I agree that is a concern, but I think there is a way of dealing with that.

The usual randomized withdrawal trial is done after too short a period of time on treatment. I mean typically, they are done now after 12 weeks or so of treatment. That is too soon. No clinician would take a patient off of one of these medications at that point in time.

On the other hand, at some point in the course of treatment, whether it is six months or nine months or a year, it seems to me that it is a reasonable question. At some point, you reach equipoise where the clinician has to ask the question, well, is this long enough, you know, is there any benefit in continuing the treatment beyond this point in time.

Now, that is a much harder study to do, to keep patients on treatment for nine months or a year before you randomize them, but that would be a way of answering that important question of whether or not there is continuing benefit beyond that point in time.

The other concern that has been raised about these trials is the issue of distinguishing

between withdrawal symptoms and relapse. Again, I agree that this is a reasonable concern, but I think there is also a way of addressing that.

In clinical practice these days, these drugs are tapered. One doesn't stop them cold turkey. I think that could also be part of that design, and that could address that issue. So, that is one thing to think about.

Before I end, I want to leave you with two thoughts. We clearly have an obligation at FDA to inform clinicians and patients about the risks that are associated with these drugs, and we take this obligation very seriously.

Along those lines, I just want to point out that our current regulations do not require the same level of certainty with regard to safety in terms of causality as is required for efficacy. In other words, we can issue warning statements with somewhat lesser certainty about causality than is required to support a claim.

Secondly, as I have pointed out several times, the lack of efficacy data in this setting

for most of these drugs needs to be part of this discussion. On the other hand, and I am not making your job easy, please bear in mind that depression, whether in adults or children, is a very serious illness that is associated with morbidity and mortality quite apart from whatever role antidepressants might have.

As was pointed out yesterday, this is the major cause of death in this population, the depression itself, so please bear that in mind.

I have very profound respect and gratitude for the clinicians who are out there on the front lines still willing to take care of these patients despite what has become a very controversial and difficult environment.

I hope that as we discuss these issues and make a decision, that we not make it impossible for them to practice medicine.

Thank you.

DR. GOODMAN: Thank you, Tom, for a cogent and clear presentation.

I would like to ask committee members if

they have any questions of Tom.

Committee Questions and Discussion

DR. FOST: This is for Tom or anyone else who has a handle on the numbers. I know there is no precise answer to it, but it would be helpful to me to just hear you or someone else, maybe Dr. Shaffer, if he is still here and is allowed to talk, this question.

Suppose there were no SSRIs, suppose they were contraindicated, that is, prohibited, approximately, let me just ask the question about suicides, about completed suicides, and I understand there is no suicides in the FDA data, but based on everything that we know, approximately, would there be more suicides, fewer suicides, or the same amount if there were no SSRIs in children?

DR. TEMPLE: There is not going to be any way to answer that, in part because you can't do rigorous studies of the kind that would answer that. No one is going to let you not treat, not institutionalize, et cetera, someone who is getting

worse and worse, and it would require long-term studies presumably against no treatment, and it is not easy to figure out how anybody is going to do those.

So, you are left with the kind of data that people have pointed out is always uncertain, the data on suicide rates and whether they are going up or down, so it is very hard to answer that question.

There were no completed suicides in the pediatric data, so that doesn't give you a clue. You can form your own judgment about whether increased suicidal behavior or thinking is going to lead to suicides in a certain fraction of cases. It is hard to imagine that it couldn't, but you don't know what that ratio is.

The success rate of suicidal attempts is relatively low. I gather it is higher in males than females, but I don't think there is going to be ways to put numbers on that.

You have to form your judgment about whether you think the overall decline in suicides

has got something to do with therapy or has something to do with other aspects of life in the United States, and nobody can give you a firm answer to that, as Dr. Wysowski said and as others have said. So, it is very hard to answer that question.

Certainly, some of the people who spoke yesterday, some of the treating physicians were quite sure that they were helping people with the drugs, and you heard families who said that their relatives were made much worse by the drugs. Putting numbers on that, though, isn't feasible based on the data we have.

DR. FOST: A related question. To those, Dr. Shaffer and others who note a decline in suicides in the United States, in parallel with the increased use of SSRIs, and let's just say which should be an increase in suicidality, suicidal ideation due to SSRI, what is the hypothesis there, that there is fewer suicides, but more suicidal ideation? That is what the data seemed to suggest, and I am confused by that.

DR. TEMPLE: Can I make another comment? The studies you are looking at are all the short-term studies. As Tom was pointing out, we have none of the long term sort of relapse prevention data. It seems entirely possible that a drug could be causing early suicidality, but once you are over that period, it prevents relapse, which could have an impact.

You know, there is just literally no way to sort that out with present data. I mean it has never been my thought that any benefit these drugs have consists entirely of their treatment of the acute episode, because in adults anyway, we have lots of data showing that the likelihood and timing of relapse is affected by continued therapy.

As Tom said, most of those studies go earlier than you would like to do in a pediatric population, because they consistently show that quite reliably. Maybe that is where their importance is, it is very hard to know.

DR. GOODMAN: Dr. Pine is next.

DR. PINE: I have a question about some of

the regulatory options. In thinking both about a number of the comments that were made yesterday, as well as your comments at the end about how difficult the decision that we will have today, related at least in part to the dearth of data that we really need.

Are there any options from a pharmacovigilance standpoint as far as regulatory actions that might increase the degree to which we are focusing over the next time period on the emergence of these events or bring, you know, new data over the next months to years based on a regulatory action?

DR. KATZ: There is the mechanism of Phase IV requirements that say we can impose requirements on sponsors to do various studies in Phase IV and postmarketing environment. The question would be what those studies would look like. I think that is the question.

There are other obviously entities, the NIMH and others who were set up obviously to do large trials, and again the question is what would

those trials look like. You could do I suppose large long-term, and again, you have heard, I think, a lot of people say that there is a need for long-term data.

I suppose you could do long-term comparative trials, you can't do long-term placebo-controlled trials, so other than the sort of randomized withdrawal design I think that Tom talked about.

So, there is a mechanism to require studies.

DR. PINE: I guess I am not so much asking about studies, and this maybe is a bit of an unfair analogy, but in New York, for example, as well as other states, whenever you write a prescription for a psychostimulant, there are a whole host of procedures that kind of go with that, that are designed to allow monitoring of the use of psychostimulants and the associated effects.

Is there any--again, I realize I am thinking a little bit out of the box--is there any form of, I don't know, computer based or monitoring

system that might give us a better handle on how many of these events are actually happening in regular treatment?

DR. TEMPLE: ODS should comment on that, but it is worth just looking at, say, the study Dr. Jick tried to do. There isn't any no-treatment group in that. He is just comparing the risk with one group of drugs with another, and you can definitely do studies like that, but if you tried to compare treated people with untreated people, there will always be the concern of whether the groups are fundamentally different, a very difficult problem because people are treated.

There might be environments in which treatment is not so common, where there is less likelihood to treat. Maybe in those environments, you could do something like that, but Anne wanted to talk.

DR. TRONTELL: Just to expand briefly, you are talking about using observational data as Dr. Temple pointed out, where you don't have a control group, and although you might register patients, we

have seen even in clinical trials that we have been discussing this past day, that the issue of ascertainment of these events is very complicated when you actually have a clinical trial mechanism in place to capture those events.

The other challenge that you face with observational data, because people don't receive the drugs randomly, there is a phenomenon called "confounding by indication," in fact, some of your sicker patients you might presume are the ones who are getting the medication.

We try and control for that, but it is very complex. I think the better option is to think of some systematic way, and then you are in the realm of studies, as Dr. Katz was saying.

DR. MURPHY: I just wanted to follow up on one last thing. Because we already know that using the system we have now for follow-up post-exclusivity because it is already mandated that we do one-year reporting once these products, whether they are approved or not, so we are looking at all-use.

We do look at that and we report that, and we know that that is not going to inform us, you know, to answer the questions we need to answer, because of all the things that will impact that reporting.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I just wanted to mention one related, but not quite on-point matter. We talked yesterday about concern that the studies that had been done to gain exclusivity might have been not as good as we would like.

We weren't particularly talking about the design of the studies, which we think is okay, but let's say the approach to them. Maybe there was too much of a rush, and so on. If we were to put out a written request now, it would be one that required a third arm to the study, namely, a Prozac arm, because we know that Prozac can be shown to be effective.

So, the study wouldn't count unless it had been able to show that it had what we call "assay sensitivity," the ability to tell effective drugs

from ineffective drugs. We couldn't do that before because there wasn't anything at the time we wrote those requests that was known to be showable in children, but now there is. There is three studies that all seem to show something.

So, we should have much better information about what the pediatric population does in future requests. That doesn't help the present discussion.

DR. MURPHY: I wanted to address that issue again, too, because I think I want the committee to be very clear on the fact that the Agency tells the company very clearly the type of studies that need to be done.

We do give them, you know, a broader picture of the number of patients. We tell them what we know will be the minimum, and, in general, I think Tom would agree that most of these studies have come in with the numbers in each arm that we have seen in other studies where they have shown effectiveness.

So, the point here being that we do have

control over the types of trials that are done, the number of patients, and the monitoring. However, because there is a template up on your web that basically tells you what we ask for in depression trials.

When you look at what the safety is, as has been pointed out many times, these trials were not set up to answer that question. So, I think it is those kinds of issues that we would like to hear more about today. As Dr. Temple said, it is how better to do these trials in the future.

Thank you.

DR. GOODMAN: Thanks for that statements, Dianne. I just want to make sure I understand it completely.

I think what you are saying, that if the conditions had been different at the time, that is, that the drug company was required to show, not only have a study, but a study that was positive. Then, the design would not have been any different, the sample size would not have been any different under those circumstances than the ones that

existed at the time.

DR. MURPHY: I think what we are saying, that for the trials that we designed, they were the same for the one that did show some effect, which is Prozac, as those that did not, and that what we don't know is if a company is putting a trial together, and let's say we said that they had to have 300 patients to get their exclusivity, but for other reasons they really wanted this product approved, and they felt the enrollment was not going the way that they needed, would there be some other push within that company to then go out and get more patients, so that their enrollment would be better versus an exclusivity where all they had to do was meet that criteria.

I am making that number up. I think the issues that people were trying to get at is that is there a difference that affects behavior when you just know you have to do certain things versus you have another goal, which may be approval.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: The requirement for a third

arm in evidence of assay sensitivity leaves it up to the company to decide how they are going to do a successful study. They can look at the available data on Prozac and say, oh, here is the number I need, here is the kind of patients I need. That succeeded in those three trials.

They would then know that the trial would have to be one that can show the difference between Prozac and placebo. That doesn't mean their drug has to show a difference between drug and placebo.

That would be determined by the results, and there is no obligation that the drug be successful, but we would at least know we had a study that was capable of detecting effective drugs and distinguishing effective drugs from ineffective drugs.

That would then become a requirement for meeting the terms of the written request because they would have to show that they had an adequate study. Before there was an effective drug, there was no way to do that. You couldn't tell whether the study was a good study or not.

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: If I could go back and address the question of what would the hypothesis be for long term, certainly, in the absence of data, there is some degree of speculation. I do have a question directly to the FDA. Is it okay if I respond?

I think the number one hypothesis would be in the short run when you have depressed patients who are not yet stabilized, you may see an increased risk, and you do see certainly in this population an increased risk of suicidality.

I imagine that what we would see with longer term data is a substantial decrease in suicidality over time, and that is what we are inferring from the cohort and the epidemiologic data. I think that clinically makes sense, as well as mechanistically makes sense.

The question for the FDA, can you give us a sense, I mean do we feel confident that we actually have all the available studies now in both children, adolescents, as well as in adults, and

what is the FDA policy on requiring review of those studies including negative studies, when do they come to you and when do they become publicly available?

DR. TEMPLE: Well, let me start, others can comment. When you submit to us an application to change the labeling, to add a claim, say, for pediatric use, you are clearly obliged under the law to provide every study, successful ones, unsuccessful ones, things that were interrupted, and so on.

As far as we know, we are getting all those studies. Of course, if there were something that were done that we didn't know about, well, then, we wouldn't know about it, but as far as we know, we are getting them all.

So, most of the pediatric submissions to us were associated with labeling requests or something like that, so as far as we know, we have all those data.

Dianne can tell you what is required under the best BPCA, and I think there, too, they have to

provide them. We have no rule that affects whether people have to publish results. Congress is considering that, so are the journals and everybody is talking about that.

Under BPCA, however, when we grant exclusivity, we provide summarized results, and we have done that for the drugs where the written requests were written after the BPCA, and we have gone back and asked the companies for permission to summarize our analyses for all of the others where it wasn't totally clear whether we could do it or not.

So, the summarized result, that is not the same as a complete study report, the summarized results are now available publicly on all of those. I am sure between PhRMA's commitment to provide a registry between the journals insistence that they will get a registry, between congressional interest, I am quite confident that there will be a change in the way things get published.

DR. MURPHY: The only thing that I could add to that is that for the committee, for the

routine practice within FDA, if a company submits an application, we review it, the studies are negative, there is no public acknowledgment of that unless the company for some reason wants to make that knowledge public. We are not allowed to comment on that.

Now, under BPCA, it said, it has a disclosure section that says you, FDA, will publish, as Dr. Temple is referring to, the summaries, the medical and pharmacology summaries up on the web--make them public, and actually, we have chosen to do that on the web--and we have done that.

One of the issues that has happened is that between the enactment of the new legislation and the old legislation, legally, things were considered issues under the old legislation, so even though the studies came in, we had to reissue all those written requests to be able to say they now were subject to this new mandate.

So, what again Dr. Temple was telling you is that unfortunately, many of the antidepressants

came in, in that period when we had not yet issued that letter, but despite that, we have asked the sponsors to allow us to put those summaries up, and they have given permission to do so.

That is why yesterday we said up on the web now are the summaries. Again, this is not the data. There is variations in, you know, some medical officers will put in more information than others in how much data is in these summaries, but they are up now, publicly available.

DR. MARANGELL: Is that true for adults, as well?

DR. MURPHY: No, adults are still under the same standard. In other words, if the study is negative, we don't talk about it.

DR. MARANGELL: So, as an example, if an antidepressant manufacturer did a study in a new indication for a drug that is currently available, found increased risks of suicidality, no one would be under any obligation to make that public?

DR. MURPHY: That is a different issue.

DR. MARANGELL: But that is the question.

DR. MURPHY: The issue is safety, and the Agency always has the ability to make public safety issues that arise.

Bob, do you want to say anything else about that?

DR. TEMPLE: We consider, for example, if someone with an antidepressant comes in for, I don't know, obsessive compulsive disease, and we don't buy it, we do not make those data available, they are considered confidential commercial information. Obviously, a lot of the people, a lot of the public doesn't like that approach. We think that is what we are required to do. I can't comment on that, I am not the lawyer here.

However, companies have a separate obligation for drugs that are marketed to report serious and unexpected, and any serious adverse reactions to us, and to do so promptly. A finding of increased suicidality where that was not known, clearly meets that test, and they would be obliged to report it to us. If we then thought that was true, we would add it to the label or do whatever

we are supposed to do.

So, safety data meets a different standard. A new carcinogenicity study or something, those do have to be reported to us.

Other studies have to be reported in the annual report, but they are not necessarily reported in detail, and not that much is necessarily made of them, and they do not necessarily become public.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: Yes, the serious safety issue would have to be reported while the trial is ongoing to you, right?

DR. TEMPLE: Well, if it arises from a trial, it has to be. Actually, the requirements for reporting serious unexpected events in a trial are more or less identical to the requirements before a drug is marketed. They have to be reported to us within 7 or 15 days.

A finding from an epidemiologic study, there is some judgment involved in whether that represents the kind of thing that has to be

reported promptly, but they basically do.

DR. KATZ: There is also some judgment involved in whether or not an event is considered to be unexpected. So, for example, suicide in a study of patients who are at risk anyway might not be reported to us in real-time, because it might be considered to be expected, the blind is still intact, you don't know if it's drug or placebo if it is in the context of a controlled trial.

Afterwards, though, when the trial is done and analyzed, and it turns out that there is an increased incidence on drug compared to placebo, that is something we would find out about.

DR. GOODMAN: Go ahead, Dr. Pollock.

DR. POLLOCK: I actually wanted to explore your thinking a little bit about the recommendation for a maintenance trial. I guess there are a couple of things. One is if there is this acute toxicity that we are concerned about, clearly, it doesn't address that because you are dealing with the children or the adolescents who have actually responded, and then are withdrawn.

But I wondered if there was implicit in your request for that, a concern that still that the shorter half-life SSRIs seem to be, maybe not statistically, but certainly qualitatively more at risk in causing this phenomenon.

I was taking that as implicit perhaps in your suggestion, maybe I am over-interpreting it, but is there a belief that somehow--I mean it just seems more than coincidence that signals seem a little bit higher.

I know it has now emerged with Prozac, but certainly, Effexor, venlafaxine stands out at one end, then followed by paroxetine, and if there was kind of an implicit question that you were asking, assuming that people are still using after we are finished, you know, those medications, that you can require that those manufacturers actually conduct a serious maintenance trial as part of you were saying your Phase IV regulatory requirement.

DR. LAUGHREN: We certainly, you know, until we saw the TADS data, were entertaining the notion that discontinuation might be one

explanation for the bigger signal, the apparent signal that we are seeing with Paxil and Effexor.

The TADS finding certainly challenges that notion as a unitary explanation, since that is the single trial among the 24 that, by itself, has a statistically significant finding for that signal. That doesn't mean that the other explanation isn't possible. I mean this could be a much more complex situation than one might seem at first glance.

But a maintenance trial is not going to answer all those questions. I mean a maintenance trial is only going to answer the question of longer term benefit, but the reality is that many clinicians, despite these concerns, are probably going to continue to use these drugs, and we have a dearth of information about what the longer term benefits are. The maintenance trial is one way, I think, of getting at that.

Now, there is this issue of how to interpret emerging symptoms in that setting, you know, when you take patients off the drug. Of course, the drugs like Paxil and Effexor, that are

known to have a stronger signal for discontinuation, obviously are a challenge in doing that kind of trial, but I think that one could, as one does in clinical practice, taper those patients to try and address that, and then look for what would be considered for relapse.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: There is another reason to do randomized withdrawal studies. As everybody knows, in adults, the failure rate for conventional clinical trials of the acute episode is about 50 percent. That is, half the trials can't tell drug from placebo, and that is true even when you include a third arm of a drug that is known to work. That appears to be the nature of the beast.

Nobody really has a good explanation because if they did, they would fix it, but we at least think it has something to do with the environment and the discussions that go on even informally, even if it is not planned as part of the treatment.

In the randomized withdrawal setting, the

success rate for drugs that are known to work is nearly 100 percent. Very few of those trials ever fail.

There are at least two reasons. One, only people who seem to be doing well are in the trial, so they are enriched with a responder population. You can make of that what you will.

The other possibility, though, is that the environmental things that help people get better aren't really there, they are just out living in the community, there is nothing nurturing about it. They are just back in their usual environment.

So, one of the attractiveness of these is to find out whether the drugs actually provide some benefit, even in people who seem to be doing well on them, which seems an important question here. I mean, as Tom has pointed out repeatedly, the failure of most of the drugs to show effectiveness doesn't mean they don't work. On the other hand, we don't have evidence that they do work, and that is not irrelevant either.

A good way to show that, if they do, is

the randomized withdrawal study. At least that has been the history in adults, so there is a lot of attractiveness to it.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: Thank you. I have two questions. The first one is for Dr. Murphy and Dr. Temple, and the second for Dr. Laughren. The first question addresses the exclusivity issue. I feel like in this case, we bypass the Phase I/Phase II stages that we would normally go through with new drugs, so we never did do the pharmacokinetic/pharmacodynamic dose finding in children that we would have done had these been new drugs.

I wondered, I probably should know this, but could either of you explain, when we offer exclusivity with a new drug, if it is a new drug to children, do we require those studies, or do we not? I am sure it is not that straightforward.

DR. MURPHY: We did required pharmacokinetic studies. Actually, on the template, we outline three types of studies. They

have to do two randomized, double-blind, placebo-controlled, acute treatment trials with recommendation at six to eight weeks for safety and efficacy. They also are to do a pharmacokinetic study to provide information pertinent to dosing of study drug, and they are to do a safety study.

So, all of those were asked for. Now, if you are asking do we go back and demand redoing dose finding again in these, no, they were not worded that way. It was said that the PK study could be a traditional PK or, alternatively, a pop PK, and actually, I don't think that the study had any other information that would have, in essence, told the company that they needed to redo the dose finding, if that answers your question.

DR. CHESNEY: So, do we have dose information on all of these drugs? Do we know what the usual ranges are, and what excessive ranges are, all those things?

DR. GOODMAN: Go ahead, Dr. Katz.

DR. KATZ: I think Tom mentioned this in one of his slides yesterday. The written requests

that we issue now are very different from the written requests we issued that probably generated most of the trials that we are talking about here yesterday and today.

As Dianne pointed out, for example, in pharmacokinetics, we gave sponsors the opportunity to generate the kinetics in kids based on so-called population pharmacokinetic analyses, which is to say from data generated in the controlled trials.

So, it was sort of after the fact. It was just what is the kinetics of the doses you happen to give in the trials.

In the earlier written requests, it was sort of the pediatric drug development was sort of tacked onto the adults, in other words, when the trials were designed even, the treatment effect size, for example, was used to calculate sample size was taken from the treatment effect size seen in adults. We had no information, even preliminary information in kids.

So, we didn't have a lot of preliminary information in those days that could inform

adequate trial design in this population, in this setting.

Nowadays, we ask for different things. We ask for formal PK, so we can learn before the definitive trial design, what the kinetics are, what doses give rise to what plasma levels. We ask for dose finding studies, so we can determine before we design the definitive trials what the tolerated dose range is.

So, the written requests are much different now than they were at the time that the requests are generated, these data were written.

DR. MURPHY: Just to reinforce that is that these were some of the earliest written requests that went out, so they really, as has been stated, and I think we tried to say this earlier on, we are learning.

I mean because of the lack of prior research and some fundamental scientific questions haven't been answered, we are learning from the trials that we have now about how to do a better job on designing some of these trials, but these

were some of the very earliest ones that were issued.

DR. CHESNEY: Dr. Temple, did you want to comment on that?

DR. TEMPLE: Well, I just wanted to say there isn't any pharmacodynamic measure to allow you to do what is called PK/PD other than effectiveness itself. In a lot of cardiovascular settings, there is at least something you think relates to the desired effects, so you can do relatively short-term studies and get a PK/PD relationship.

Here, your only way to do it is to insist that every drug, every study be a dose response study, which is of considerable difficulty. We have trouble getting really good data even in adults actually given the sample sizes involved, but there isn't any measure yet. Maybe one of these days there will be an MRI measurement or something, but not yet.

DR. CHESNEY: Well, I don't want to overstay my welcome, and I do have a question for

Dr. Laughren, but one does wonder about some of these children who didn't even express ideation and just suddenly, very early on, if they didn't have excessive levels. I guess that is one issue I was getting to.

Dr. Laughren, I wanted to come back to the point Dr. Pine was making. I thought Dr. Reisinger's point in the open session yesterday was a very interesting one, which is that you would have to undergo some kind of computer-based learning program or some kind of program that authorized you to prescribe psychoactive drugs.

Certainly, we have to do computer-based CBLs for all kinds of things in our hospitals and in other areas nowadays. That had a real attraction to me, and I guess the question is what kind of authority does the FDA have in an area like that, can you say that anybody that prescribes SSRIs must do a computer-based learning program on line, or is that something that the professional societies take on?

You offered several options, black boxes,

revised label warning, but is this a potential option?

DR. TEMPLE: We can certainly recommend things like that. Every labeling for a cancer drug says that this should only be used by people who are trained in oncology. That comes with no enforcement on our part except that people may be anxious about the consequences if they don't have that training.

A labeling recommendation is certainly a possibility. A step further to limit the drugs to people who have been given that way, those are very iffy questions, and it is not clear whether we can, in fact, do that. There would have to be a debate about it.

There are some examples of fairly interventionist activities. As you all know, you can't get clozapine unless you have a white blood count, so no blood, no drug.

There are not a whole lot of other examples like that, but there are other cases where patients must be given a form that lists what some

of the adverse effects might be, and things like that. You have to weigh the risk you are concerned about with the burdensomeness to the community and to the medical profession of those kinds of interventions.

Putting something in labeling about what you should know doesn't carry those kinds of concerns, so if something sensible, suggesting that people ought to be trained in a certain way seemed like a reasonable thing, we could certainly consider that.

DR. TRONTELL: I would just like to add on to Dr. Temple's comments, because the FDA regulates drugs, but doesn't regulate the practice of medicine, and we walk a fine line in terms of dealing with some drug products where we may feel, as with clozapine, that only very tight controls on prescribing and dispensing and use of the product are allowed.

There are a very small handful of drugs, they tend to be the exception rather than the rule, where training has been required as a condition of

approval. One product in particular is the drug product dofetilide, where, in fact, training is required for pharmacists or clinicians. There is a highly structured way in which that product can be used.

Again, those have tended to be reserved for situations where we feel the drug cannot be safely used without that very high level of precaution. It is extremely difficult to put those in place for products that have already been marketed and used by professionals.

DR. CHESNEY: The public sees your role I think in a much broader perspective, as we heard yesterday, and I think that is something that is useful to clarify as to where your limits are. You mentioned there is a fine line, and I think that is what we are all looking for, is where does your authority end and that of prescribing physicians begin, I guess in a sense.

DR. TRONTELL: I don't think we yet have an answer. I think we always have the authority of our agency and hopefully, our ability to persuade

individuals, but I think that the actual legal authority to do some of these is a matter of debate within and outside of the agency.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: I would like to return to the topic of the incentives on the part of industry to perform well-conducted trials.

There has been a lot of discussion about the evolution of the written request and about the improvement with three-arm studies and changes in the ability to request that, but my understanding, I am interested to know if this is accurate, is that there is still two potential linkages that don't exist that might decrease the incentive to do a well-conducted study, and that is, absent safety concerns, there is no tie to putting any efficacy information in labeling, so that they receive exclusivity if a labeling change occurs.

Second, is that there is no link of exclusivity to a well-conducted study unless that has changed with written request, since I read them on the current web site, there is one asthma study

where there was members of the drug group that had no drug level, members of the placebo group that had measurable drug levels, and the FDA concluded that the data was uninterpretable, but nevertheless, exclusivity was granted.

I am wondering, is that a problem with the written request that is now fixed, or is there other solutions that would need to be put into place, such as legislation, to address those two, what I perceive as gaps.

DR. MURPHY: I think there was significant discussion about how exclusivity should work, should it be only if the product is approved. I was not privy to those discussions, but I know they occurred.

The reason for why it was put in place the way it is, I can't give you, Dr. Nelson, but I can tell you that one of the explanations I have heard is that there was such little data, and FDA was given the authority to define the trials, so again, as you have heard, we would like to improve, and we know we have to learn from what trials we have,

that by providing FDA the authority to define the trials, that they hope that the trials would be, you know, of the best that they could be, and that, therefore, we would learn from the trials even they were failed, because that is important information, failing is important.

So, I guess what you would say, you are asking if, and that is in a number of our labels, and that is a whole other discussion, but in situations, you know, we know that is the only study we are going to get and this is it, failing is put, that they failed to show effectiveness has been put in the label in a number of situations, and certain dosing or safety information.

As I said, about a fourth of the time, we are describing, even irrespective of whether the study is positive or negative, we are finding safety signals, you know, important dosing information, and we are able to put that information in a label.

The intent is that the information that is obtained, whether the product is proven to be

effective or not is important, and that safety information, et cetera, would be obtained.

So, that is the best explanation I can give you as to why it is set up the way it is right now.

DR. NELSON: I understand, but let me focus my question, I guess. Right now the efficacy or lack of efficacy data is not in the existing labeling that we are discussing, so, for example, just to pick one, paroxetine, there is five studies, and the pediatric use just says it has not been established.

Although that is a true statement, it is a bit misleading because many people interpret that to mean the studies hadn't been done.

The other question is you could ask them to do a three-arm active control study, but if they do it badly, do they still get the money? Even if they have done it, if they do it badly, do they still get the money?

DR. GOODMAN: Dr. Temple wants to respond.

DR. TEMPLE: If the written request says

you need to do a three-arm study and need to show that the trial has assay sensitivity, that is, the ability to distinguish active drugs from inactive drugs, and the Prozac arm doesn't beat placebo, then, they would have failed to meet the requirement of the written request.

We couldn't do that before, as I said, because we didn't have a known active control, so we wouldn't have known what to say. So, in that case, the incentive to do a proper study becomes quite clear. If they don't do a proper study, and succeed in showing that, they would not get exclusivity.

In other cases, we have insisted that the variance be such that for, say, a blood pressure drug, an effect size of 3 or 4 millimeters of mercury could be detected, so if the whole thing is done sloppily and they could not have detected such a thing, then, they would not get exclusivity.

Some of the other things, however, that you mentioned, don't have an obvious remedy. I mean I guess following the example you said, we

could say, oh, by the way, people should have blood levels showing that they took the drug. Well, we hadn't been smart enough to think of that, and maybe that is something we should be adding, that is, some kind of compliance check.

That, I don't think has been part of written requests to date. That doesn't mean it couldn't be. The test that Congress imposed is that if you comply with the terms of the written request, you get exclusivity. That means if we weren't smart enough to ask a question, that is not considered their fault, and they are supposed to get it.

DR. MURPHY: And we have denied exclusivity where we thought the trials were done sloppily, and actually, sometimes when the sponsor said, well, we know you asked for this, but we didn't think it was correct to keep going, so we didn't do this for some reason, and we said, no, you should have come in and talked to us about why you weren't going to do it, you didn't do it, we told you, you need to do it, sorry, you don't get

it.

So, what I guess we are trying to say is if it's really sloppy, and they don't do what we tell them, we deny them exclusivity. The problem I think we are dealing with here is that we all are learning how to better do the trials, and your other question about whether that should go in the label, the negative information should go in the label, is a whole other discussion.

DR. GOODMAN: I have a list of seven other committee members who wish to speak. After we give them that opportunity, I am going to ask Dr. Wysowski to come up to the podium. We had asked her to follow up on something from yesterday. Is there somebody else that has a burning--we have one more and that is it--two more, that's it.

Dr. Irwin. His question has been answered. Thank you.

Dr. Rudorfer.

DR. RUDORFER: Yes, thank you.

I would just like to revisit a couple of issues that concern me at the front end of these

studies, and I recognize everyone from the FDA is pointing out that this is a learning process, on the other hand, we are faced with the dilemma of having these particular trials to deal with.

The dosing question that was just discussed brings to mind a concern I have related to how the suicidal events we have been looking at were ascertained.

As I understand it, for the most part, these were from adverse events questionnaires and surveys. Is that correct? I mean there was no particular suicidal scale?

DR. LAUGHREN: Well, all of these trials included standard depression rating instruments like HAM-D or CDRS, and so forth, and there is a suicide item in each of those instruments, and that is part of what we analyzed.

But the problem is we don't really know how those were applied. My guess is that most of the event data we are dealing with were spontaneous report or general questioning rather than specific ascertainment.

That is really one of the areas that we are trying to explore with Columbia to try and work on a more specific instrument for improving ascertainment for suicidality, but no, in these trials, I don't think ascertainment was very specific.

DR. RUDORFER: My question, as we deal with these data, would be this. I appreciate the very dedicated and elegant work that both the FDA and Columbia have applied to these findings. The question I have relates to the issue of the active drug versus placebo groups.

Since it sounds as if much of the data were spontaneous reports or I assume perhaps discussion between the raters and subjects, or the investigators and the subjects, I am wondering if part of this is not dependent on the assumption that the blind was kept intact throughout the studies, and I wonder if we have any measure of that or any sort of quality control on that issue.

DR. LAUGHREN: No, we have no idea of that. That is typically not something that is

really ascertained. It is the assumption, but how would you check on that?

DR. RUDORFER: In some studies, patients and raters are asked at some point. I mean here, I am just wondering if, in fact, if a patient volunteered that, for instance, they were experiencing some side effects, they come in, the rater asks how are you doing this week, and their first comment relates to GI distress or something that sounds like a side effect, if they simply don't get more attention, in other words, maybe there is more discussion, maybe there are more questions asked as opposed to a patient that comes in and say, gee, I am feeling pretty good, I don't seem to have any side effects.

Again, that would not obviate the fact that if we find signals, then, the signals are present. I guess I am just concerned about the active drug versus placebo difference.

DR. GOODMAN: Let me interject. I don't think I am as concerned about the unblinding, but your question raises at least in my mind the

possibility that in the data, is it possible that we would see other somatic symptoms, more side effects reported in those patients, who also reported suicidality than in the opposing group, was there any attempt in the data to look at whether there were any other--was any other increase of adverse experience outside the target symptoms of suicidality in those patients who reported suicidality, the reason being that if there was, that would suggest it was part of a larger behavioral syndrome that was being induced by the medication.

DR. LAUGHREN: Our analyses had to be limited by what we had in our database, and we had to design this database late last summer. We didn't anticipate all of these questions. As it was, the database we had was a very time-consuming process to put together. It took a number of months to get it.

They are all good questions, but we don't have all those answers, but I agree that ascertainment for suicidality was not optimal here.

DR. GOODMAN: But the question is at this point, could you go back to that same data and look to see if there is a higher rate of other adverse experiences reported in those patients who were also identified as experiencing or exhibiting suicidality.

DR. LAUGHREN: Not without designing another database and going back to the companies and waiting for a number of months, and I am not confident enough in the quality of the data we have here that that would justify that additional effort.

I mean again, these are all good questions, but we are faced with making a decision at this point in time with what we have, and we are asking the committee's advice on what you think we can do now based on what we have done.

DR. GOODMAN: No, I agree with that, I understand that, but we were also asked what other advice we would give in terms of future research or studies or data that we would like to see.

DR. TEMPLE: Tom, we did look at the

association with certain kinds of things, the activation syndrome, things like that, right?

DR. LAUGHREN: We included in our database two other symptoms, hostility and agitation based on the preferred terms that the companies used, and again, we haven't looked, I suspect that there is variability across different companies in what actually got subsumed under those two things.

There are the only two other events, and we don't even have the timing for that. All we have is an indication of whether or not, at some point during treatment, a patient experienced agitation or hostility. We don't have all the other somatic kinds of things that you are alluding to. That would mean going back and trying to create another database.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: Let me just mention one other thing that has come up briefly and that Dianne touched on, and that is inclusion of negative results in labeling.

As Tom has explained at the previous

meeting and now, as a general policy, we don't usually put in labeling the fact that a study hasn't worked, because we don't think that proves that it doesn't work. It just means that that study failed.

But we are actively thinking about that policy for the pediatric part, because the whole point of doing the studies was the possibility that adults and children are different, otherwise, you wouldn't even think about doing that whole program. All I can say is we are actively thinking about it.

It is not an easy to thing to do, however, because what you would want to say could depend on how good you thought the study was, and then there is the conundrum of what do you do if there is one study that says yes and one study that says no. That is virtually somebody a claim, which we really wouldn't want to do if it wasn't merited.

So, I am not going to suggest that this is easy, but we are reconsidering this whole thing, because the whole point of the Best Pharmaceuticals for Children Act is to find the data and see

whether drugs work in children, and not putting anything in seems funny, so we are reconsidering that.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: Part of my question Dr. Chesney eloquently asked before, but I wonder if we can get access to the wording that you used for cancer drugs as perhaps a guide to us for our considerations.

My other quick question, I think back to one of the FDA group is am I hearing you right that if you have a drug that has been shown to be efficacious in a particular indication, that all trials requested in the future require an arm that includes that drug?

DR. TEMPLE: I am not ready to say that one would always do that, there are other ways to try to assure quality, but in this setting, it is reasonable to assert that we need to know whether your trial was an adequate test of whether this drug worked, and the only way we know to be sure that it is an adequate test is to have an active

control, and to have that active control be distinguishable from placebo. Then, you know this is a trial capable of showing things.

We have determined that our future written requests will include a requirement for a three-arm trial, because that's the only way we know to be sure that the trial is a trial that is capable of showing what the answer is, and we want to be sure we get the answer.

This comes up in written requests all the time, how much assurance do you have to have and how do you gain that assurance that the trial is a useful trial, and the reason it comes up is the one that everyone has alluded to, we don't think people are deliberately trying to mess things up, but the incentives to do a really good trial are greater when you have to win.

DR. PERRIN: I am a little confused. As a clinician, you know, typically, if I am looking at a new medication, I want to know that it is better than current therapy. I mean all of us are really interested in that.

There are a number of pediatric drug trials, not in the area of antidepressants that I am aware of, where new drugs come on the market, approved by the FDA, where there are only drug/placebo trials, and not trials comparing the new drug with currently approved FDA medications. That is where I am confused.

DR. TEMPLE: Good question. There are two possible uses for having an active control. One is where you want to compare the two therapies. Now, to do that, you would need a very, very large study, because you would be interested in even modest differences. That is not what we are talking about.

We are talking about the use of the third arm to show something about trial quality. Actually, a third arm is extremely common in depression trials now, because if the trial fails to show that your drug is better than placebo, there are two possibilities.

One is that your drug is no good, and the other is that the study was no good, and it is very

important to somebody developing a drug to know which of those two things it is.

If the trial shows that Prozac, say, works, and your drug doesn't, you get rid of the drug. If the trials shows that neither Prozac nor your drug works, you do another study. So, it is extremely important. But the two purposes of the trials are quite different.

To actually do a comparison and try to detect a small difference, you would need very, very large groups. That is an unusual thing for people to do, and usually, the drugs can't be distinguished. It is very hard to do that.

DR. GOODMAN: Dr. Temple, I heard you say before, if I heard correctly, that incentives are different when you need to win. Were you referring to the conditions of the six-month exclusivity arrangement, and if you were, if the incentives were different at that time, would you predict any difference in the design of those trials or the conduct of those trials?

The reason, let me say, I think that many

of us keep harping on this point, is not so much because we think that the suicidality data would have turned out differently. I think it is the absence of a benefit, the absence of efficacy that at least I am concerned about, because that is mostly what we have in assessing benefit or those trials, and we only have 3 out of 15 that are positive, so if there was something about the conditions in which those studies were designed or conducted that might have negatively impacted the outcome, I would like to know it.

DR. TEMPLE: Well, Russ and Tom need to respond, but we haven't seen anything in the design of those trials as written in protocols that makes them look any worse than any other trials. They seem to have reasonable size, so there is nothing obvious.

But, you know, this is an issue that comes up when you do so-called "non-inferiority" trials. The incentive, you know, the point of such trials show no difference between treatments, and as I have written repeatedly, that is not a good

incentive to give people.

It doesn't stimulate the kind of optimal behavior that you want, which is stimulated by the need to try to show a difference between treatments, and that is a problem here if you don't need to win, to gain exclusivity, and I don't disagree with the idea that you shouldn't need to win, the point is to get the data. That is why the BPCA was done that way.

On the other hand, you do want a good trial, and one way to guarantee that the trial is a good trial, however the drug comes out, is to be sure that it is capable of showing something we need to be true, namely, that Prozac seems to work.

DR. KATZ: Can I just add? One thing you need to remember about studies done in response to written requests is that they are very time sensitive, or at least it's possible that they are time sensitive.

What I mean by that is you only get exclusivity if your study reports, your supplements containing the data come in while you still have

some residual patent life left or exclusivity left. So, they have to be done within a particular time frame. In fact, the letters that we send, the written requests include a date by which the studies have to be submitted.

So, in some cases, there is at least potentially motivation to do studies rapidly, so that they are done and study reports are written, and the supplement, which includes these data, are submitted in time, so that they can still get their exclusivity.

So, one at least potential question that has been raised is enrollment so rapid or does it need to be so rapid into these trials that maybe not all the patients are adequately diagnosed, and maybe they have something other than depression.

It is very, very difficult for us, if not impossible for us, to be able to independently corroborate diagnoses in something, in conditions like these, so we, of course, take it on faith that they got the right patients, but maybe, for example, because of time constraints, they didn't

get the right patients, and that might contribute to a negative finding even if the drugs were effective in a true population. So, that is one possibility.

DR. GOODMAN: I think that is a fair answer. Anybody that wanted to comment specifically on that? Dr. Marangell.

DR. MARANGELL: Are you aware, is there a greater proportion of non-academic sites in these trials?

DR. MURPHY: I don't know that we have looked at that. I mean I know that there are definitely, in some of these studies, very, you know, academic sites that have been involved in numerous or actually well-known to us investigators.

I do want to make one thing again. One thing that every division within FDA is told, when writing their written requests, they are asked a number of questions - what is the public health benefit, what are the trials to get to that public health benefit, and you are not to take into

consideration--and most of the time they don't even know because you would have to go into a lot of patent law--they don't know or are told to not pay any attention to when the patents expire or the exclusivity marking would go out, they must look at it only from what are the trials that they need to have done.

Now, what is being told to you, though, is that--and we have written requests where the companies come back and say, well, that is not going to help us, because you put a date on here that it was due by 2007, and our patent expires in 2005, and we have said, you know, we are sorry, we need these kind of trials.

Now, would, in that situation, a company try to compress by getting more sites or, you know, whatever, would they try to do that trial in a different way? Yes, possibly.

I mean that is what we are trying to explain the balance between the way the process is set up, it is not to be driven by the time when the patents are expiring, the marketing exclusivity is

expiring, the divisions are to determine what the studies are that are needed to the best of their knowledge at that time. They are to design those studies to answer those questions.

Do we try to be reasonable and say, gee, we would like a 10-year follow-up study, but we don't ask that for other--you know, we have to be reasonable within the realm of what we would normally ask for, for an approval product.

Again, though, maybe we can be--we say we have to get this information because children grow and will go through a period where that might be effective.

DR. GOODMAN: Thank you, Dianne.

DR. MURPHY: So, you have to ask for additional information, you might not, for adults. I am trying to explain the process.

DR. GOODMAN: I will accept some questions out of order if they are on this specific topic.

Dr. Rudorfer, I think you had one.

DR. RUDORFER: I just wanted to follow up on Dr. Katz's comment about whether we are looking

at the right patients, which was an issue we discussed some yesterday.

Just one point that I want to follow up on. It is clear that in young people who present with major depression, there is a disproportionate number who go on to develop bipolar disorder, and I think one concern that we expressed yesterday was that the trials are very inconsistent in that especially in terms of accounting for family history, it sounded as if in some trials, a subject could literally be brought to the clinic by a parent who has bipolar disorder, and yet the child could be included in the trial.

I realize this question might be, as we said, a little out of the box. I would think that if there is any way to encourage the companies to actually try to find some of these thousands of young people and see what has happened to them in the 5 or 10 years since they were in the study, it could be tremendously informative simply in seeing whose longitudinal course has played out as what we recognized in young adults as major depression, who

developed bipolar disorder, who developed some other disorder, and go back and re-look at, for instance, those who after the fact are confirmed to have the diagnosis that we thought they did on inclusion.

DR. GOODMAN: Dr. Pfeffer.

DR. PFEFFER: Yes, I want to I guess continue on what Dr. Rudorfer is saying, because I think diagnosis is critical, and I think we can learn something about this that we have learned a little bit about depression in other realms, too, namely, that children are, in fact, different than adults.

So, what appears to be adult depression and what appears to be childhood depression may, in fact, be quite different, so that perhaps a lack of efficacy in most of the studies tells us something about the nature of the developmental course, first of all.

I agree with what you are saying about the potential for bipolar. That is one issue that is crucial, I think, in terms of maybe the adverse

response that children are having, but also if we think of the number who had some suicidal thinking, that also might be a subgroup of the children who are in these studies also.

The other part that I want to mention is that when I gave that talk last meeting, I talked about the complexities about what looks like depression in children, and not only course and family history, but life event circumstances, and that has not been looked at.

So, for example, children who might have been having immediate family turmoil and looked depressed, that is an issue that might have led to some resistance in response, for example.

The other point I would like to make is that we hear from some of our childhood psychiatrist colleagues yesterday who advocate to not ban use of these drugs, because they do see efficacy, and it may very well be that in their practice, with very careful assessment, careful diagnosis, they are selecting the subgroup of youngsters who potentially could respond, and

respond very, very well.

So, I think the question of diagnosis is crucial, which means that in terms of the study design, in a way, who has the most reliability to make a diagnosis, and what kinds of questions really are being asked and what data is being collected that might help us even look at predictability of response, and I don't think we have that, such as life events, such as family history, such as perhaps other issues that we would need to come up with and understand.

DR. GOODMAN: Thank you.

Dr. Gorman.

DR. GORMAN: A lot of us keep saying that children are different, and I don't think it should come to us, then, as a surprise that children may respond differently to medicines than adults do.

I think I would be more concerned about the efficacy of these trials if they were all unidirectional in the sense if they had all failed or they had all succeeded. I have heard nothing from the FDA to this point that says that the

playing field has been tilted in any way since one of these drugs in this class, which may not actually be a class, but it seems like it might be a class, actually works for children in the bar that the FDA sets up.

So, I am now going to address my single question to the rushing hypothesis. After Monday Night Football last night, I like the rushing hypothesis. There is one small question I have to ask.

Prozac was the first mover in this field, therefore, I assumed it came to market first, and probably then had the least time before its patent extension. Is that a safe statement?

So, it came to market first. Did it have the smallest amount of time? It was the first to go off patent, yes or no?

DR. TEMPLE: I believe it was the first one to go off patent by a little bit. It is off patent now, and only, I don't know, are any of the others off patent? So, we know it was the first off patent, which happened sort of a year ago.

DR. GORMAN: So, that would run counterintuitive to the rushing hypothesis, because Prozac had to get there first, and therefore, seems to have had the least time and would be the most likely to be rushed to get labeling.

DR. TEMPLE: Some of the trials were done before this program even started, I think, and they were done a long time ago.

DR. LAUGHREN: One of the trials was done by Emslie several years before, and the company obtained the data and submitted those data as part of that supplement. It was done in the early '90s, though.

DR. KATZ: Right. The studies that we asked for in the written requests don't necessarily have to be done or initiated after the written request is written.

If they have a study that is very old, but that meets the criteria that we put into the written request, they can use that, so they don't have to be done specifically in response to the written request, they have to meet the criteria

that we lay out, and it can have been submitted to us either before the written request.

But they could have done a study many, many years in advance before we even contemplated written requests. If they met the criteria, they can submit it in response.

DR. TEMPLE: But, also, remember it's a hypothesis. We don't know why those trials fail. It could be that children really don't respond. I mean we don't know the actual answer.

DR. GORMAN: Well, I would love to be in the position where I can say something nice about the pharmaceutical industry, because it sometimes seems to happen so rarely, but if Lilly did the trials before there was the potential for financial gain, because all they were doing was looking for labeling in children without the congressionally mandated reward for that particular behavior, and therefore had these studies in place, maybe the rushing hypothesis fails, but there is another hypothesis that could be generated from that.

DR. LAUGHREN: Again, in fairness, the

Emslie trial was funded by NIMH. This was not sponsored by Lilly. They went back and obtained the data, and they did subsequently an independent trial that also succeeded.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: I think Dr. Temple did a good job of explaining why, if you have an active treatment arm, the trial is likely to be of higher quality when asked to demonstrate that difference.

I wonder if another approach to motivating high quality studies would be to require that in order to get the exclusivity, that the trial be written up in a way that passes some sort of peer review and be published.

That way, even published on FDA web site, that way, if the trial is sloppy and finds the drug doesn't work, those results would not be buried, they would become public and that I think would provide some motivation to do a good job.

I am a little troubled. I wrote down a quote from Dr. Murphy. It said, "If a study is negative, we don't talk about it." I think if

that's the case, then, there is a lot less motivation to do a really good job on the study. Why not require the studies be published, be written in a way that it is of sufficient quality that they can be interpreted, and then maybe the quality would improve.

DR. MURPHY: But for peds now, we do. That is the difference. That statement was for adults. For pediatric studies, well, I should say it is for pediatric studies that aren't done under exclusivity, but for pediatric studies done in response to these written requests, we now are mandated to make them public whether they are approved, they are not approved, or even if they are withdrawn.

DR. TEMPLE: But you are also talking about a level of detail in the presentation sufficient for people to really get into was it a high quality study, and things like that.

DR. NEWMAN: Why not?

DR. TEMPLE: it is a fairly good question. We don't believe we have authority to insist that

things be published. We get full details, we get all the data.

DR. NEWMAN: But you could peer review, you could peer review them. You could send them out and say is this something that is publishable, and have people at FDA, who I am sure are very good at that, say no, this gets an F, you know, this is not good enough, send it back, or you don't get the exclusivity.

DR. TEMPLE: Well, our reviews, when we approve something, you get on our web site the contents of our reviews, so you get to see what we thought of all of the studies. If we do not approve, however, we don't believe we have authority to make those data public, so you don't get to see our reviews. That is our legal interpretation of what confidential commercial information is, and I can't rebut it or comment on it. It's a legal determination.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Just on that point, does the FDA now have the authority, if you wanted to, to

put negative studies in the pediatric label, do you have the authority or does Congress have to do something for you to get the authority?

DR. TEMPLE: We have authority. What I was saying before is--and we are, as I said, considering whether in the pediatric case, we should do that. In other cases, we would, too, if we thought it was important to point out the negativity, and the negativity was a true bill.

It is just the fact that if one study fails, doesn't necessarily say that something doesn't work, so we have been somewhat reluctant to just do that until it was convincing.

But as Dianne said, we are actively thinking about amending that policy for the pediatric setting where the whole point of getting the studies done was to see how the drugs worked in children, for the very same things that they have been studied for in adults.

It is a little different from novel use or something like that. The BCPA calls for studies of the exact same things that have been studied in

adults.

DR. MURPHY: And we are putting negative information in some of the labels already for other types of products, but because of the complexities that you have heard, it has been the policy for antidepressants for children not to do that at this point, but I think, as has been mentioned, it is being reconsidered.

So, we have, and I have got all the labels here that we have done, we are putting that information in some of these labels.

DR. POLLOCK: For the new approvals.

DR. MURPHY: No.

DR. TEMPLE: For where we grant exclusivity.

DR. MURPHY: Right. In other words, if a product comes in and doesn't work, we have put that information in some labels where we think it is very clear-cut, you know, eight more studies is not going to change this for whatever reason, and we put that in here.

We have also put in information where it

hasn't worked where there are safety issues involved, and we are not clear what those safety issues are, but we want to tell you about them. So, those are in the label, too, even when it wasn't approved for that indication.

DR. GOODMAN: Dr. Santana.

DR. SANTANA: I have a comment and then a question that really relates to a point that Dr. Chesney made about issues regarding the boundary of practice and FDA regulation.

My comment is that there was some comment related to oncology and issues, how we deal with some prescription and safety issues in oncology, and I think we have to recognize that pediatric oncology is unique in this country and that most of the trials, even the exclusivity trials, of which I have participated in some in oncology, are really under the umbrella of research centers and academic centers. Very little pediatric oncology is done in the private practice.

So, by force, you are now dealing with a group of individuals that are more specific and

more geared up to looking at issues that potentially could be relevant, whereas, I think in the other pediatric arenas that we are talking about, that doesn't occur.

So, I think it would be a misnomer to use pediatric oncology, maybe it should be the gold standard, but I think we need to recognize that it is kind of unique in the way it is practiced in this country.

Having participated in some of the exclusivity oncology trials, I can tell you that they are at the same caliber and at the same rigorous structure as any of our other oncology trials are in the cooperative group setting, et cetera, et cetera. So, that was just a comment to clarify the pediatric oncology issue.

I want to get back to patients and practicing physicians, because we have been talking a lot about study design and how to analyze data. I want to get back to the issue of patients, parents, and practicing physicians, and this boundary of what the FDA can regulate and cannot

regulate in terms of the practice of medicine.

I was struck yesterday by many of the testimonies from parents and families, and actually, there was even a gentleman who showed a slide, in which his child was given the medication as a free sample. I am not sure that all these whistles and alarms that we put in labels are really going to work unless somehow that practice stops for certain medications that we think potentially have a greater risk.

I wanted the FDA to address the issue historically. Is there any ruling that you guys can impose or potentially think about, about how these medications are given without prescriptions, that is, either free samples or in the marketing world, so you could comment on that.

Secondly, does the FDA have any historical data on successful programs? There was a mention that maybe a med guide to parents and families would be a way to address some of the safety issues and bring people to a better level of understanding.

Can the FDA comment on any successful programs that they can point where this has truly worked?

DR. TEMPLE: Just on the free sample thing, my understanding, but I don't really know, was that a physician did use a free sample to, you know, like start the child out. That is not without a prescription, it may not have been well done and may not have had adequate follow up, but I am not sure that it is the free sample that is involved, it is the lack of follow up that was described that seems like the problem.

It is not easy to know how successful our various endeavors have been, and Anne Trontell may want to comment on that. Some of them have effects that are not entirely what we wanted. She mentioned the program on dofetilide.

To start, dofetilide is a drug that is used to prevent recurrence of atrial fibrillation, but it is a drug that causes QT prolongation and Torsade de Pointes, and there is no doubt about it.

The recommendation in labeling, and it is

enforced by the need to give out various information requires that you come into a hospital or outpatient facility for a couple of days to see what your creatinine clearance is and to see whether you are a person who has QT prolongation to an excessive degree.

Then, after that you can go out and be treated with it for long-term use in preventing atrial fibrillation.

What appears to have occurred is that that is sufficiently difficult, so that people instead use sotalol, which doesn't have such a program, or quinidine, neither of which are an improvement of the situation.

So, people can avoid some of these things if they are inconsistent across the drug classes, so you always worry about that.

There is a very rigorous requirement for periodic measurement of liver tests with a drug called Bosentan, which is used for pulmonary hypertension, and although the drug was quite toxic when it was being developed, my most recent

information is that we haven't had any fatal liver outcomes, perhaps a testimony to the fact that people are indeed following up these patients.

Of course, this is a class of patients who are very sick and very closely watched. You don't know if that is typical how we are going to do.

Anne, you want to comment on some of the other programs.

DR. TRONTELL: Sure. On the issue of sampling, first of all, I think in some instances, at the time of product approval, there have been informal agreements, but no FDA authority to restrict sampling exists to my knowledge, but there may be agreement, you know, certainly, we don't sample oncology drugs. There are things that just don't happen.

On the issue of what is a successful program, I think we struggle in the agency, because good evaluations have not been done on a standard basis. We have the best information for those programs that are most restrictive, programs like clozapine or programs like the one for thalidomide

to prevent pregnancy exposures.

So, the available data to us to tell us what works tends to be only in those extreme cases where we have put, as Dr. Temple just described, for Bosentan, you know, very severe restrictions.

If you are asking for specific information about medication guides, I think we have in the general literature evidence to suggest that good education certainly facilitates good behaviors, but I don't think we have any evidence yet that it guarantees that they do take place.

So, if you had questions about the intermediate ones, I think for the most part, we don't have information about those specific educational programs or the reminder ones. Not uncommonly, education is applied in the context of these very restrictive programs that I just described, and again, teasing out what the education alone does is very difficult.

DR. GOODMAN: Dr. Katz.

DR. KATZ: You are hearing the difficulties that we think we have with regard to

imposing various sorts of restrictions although again, there are ways to do it although they may be very difficult to implement.

But it occurs to me that it might be particular difficult in this case because the use we are contemplating in all but one case is off label, and I don't even know what the implications of that are. Certainly, there are legal questions about what you can say and what you can restrict with regard to off-label use, and I don't think that we have thought through all the implications of that.

DR. SANTANA: So, as a follow up to that, since we last met in February and there was a recommendation to do something with the label that occurred and some warnings, has the Agency monitored the change in practice?

I heard a number yesterday of 10 percent. That is prescriptions, but has that been rigorously looked at, that there was an impact of that modification that translated to something very tangible?

DR. TRONTELL: I will ask either Michael Evans or Judy Stafford from the Office of Drug Safety. All we have really been able to monitor since the last advisory committee is volume of use, but they do have some information on how that has changed recently.

DR. GOODMAN: Ms. Griffith.

MS. GRIFFITH: I would just like to pursue this for a moment with respect to the patient and physician relationship. When Dr. Chesney was proposing perhaps some sort of a computerized programming or education, or even with respect to these med guides, when Dr. Temple suggested that perhaps there would be, you know, a mechanism much like you have for other drugs, that the patient and practitioner would be signing a consent form outlining the risks and benefits, I want to understand the reason that you thought that that might be too great a deterrent to pursue, simply because from my perspective as patient rep and parent, it seems to me that in the course of any treatment process for any severe illness, which as

we all understand depression is, you are often asked to look at the risks and to sign some statement to the effect that you understand what these risks are.

You even have to do that if you get a shot of botox, not that I know, but it just strikes me you have put the parents now in the position of actually doing the risk-benefit analysis. That is where we all are.

If by providing the families with the statement that these risks are indeed serious, I think that what we heard yesterday was how little awareness there was on the part of the parents that these drugs could be lethal in certain cases.

I am arguing for more information rather than less, not more restrictions, and I agree with the point that Dr. Santana made, that how often does a parent either open the box and read the information or understand it.

So, if it is very clearly stated between the doctor and the patient or the parent, I think it goes a long way to satisfying the need to know

for parents.

DR. TEMPLE: There are gradations of information, and we wrestle with how to do that without being an attempt to be informative, but not disruptive, so that, for example, a lot of drugs have what are called med guides. These are patient labelings that are actually, under the law, supposed to be given out by the pharmacist.

My own view is that if you don't make it part of the unit of use package, you might as well not bother, but in any case, we know that there are ways to get that information to patients either through the proper functioning of the pharmacy or by making it part of the package.

An enormous additional step, which has been done in some cases, but, you know, thalidomide is a level of risk that is sort of in its own category, where there is a requirement that the patient and physician discuss all these matters. That is a very huge step, and what you might think is reasonable for thalidomide, something that is used infrequently, you might find more disruptive

than you want or more difficult than you want for drugs that are much more widely used.

As Russ pointed out, it is particularly tricky when the recommended use isn't even in the label. How to write a med guide or something like that for something you are not really recommending and don't feel able to recommend yet, that may sound like a bureaucratic worry, but I think it's a serious worry.

You don't want to warn people and simultaneously recommend a use that you don't think is recommendable, and any discussion like that is tantamount to recommending the use. So, we will need to worry all of those things based on your conversation.

MS. GRIFFITH: Could I follow up? I understand that and I understand that there are all sort of issues involved, liability on the part of the physician, but I am suggesting, from the naive perspective of the parent, I think of depression as every bit as serious as the use of thalidomide posing birth defect risks or, as Dr. Santana said,

you know, the cancer example. Parents need to be informed about those risks.

I don't think that this is any different, frankly, and if it is an extraordinary measure to take, I think that it benefits both the practitioner and the patient parent.

DR. TEMPLE: For oncologic drugs, the label says you should be a properly trained oncologist. There isn't anything in there that says what you need to discuss. Patient med guides for oncologic drugs is by far the exception, I think because it is assumed that there always has to be such a conversation in the course of therapy.

I guess what is being discussed is whether there is a common practice of having that kind of conversation in someone who is depressed, and obviously, we all think that there should be such a conversation. The question is now to induce it and what to provide people to help them be sure they ask the right questions.

DR. GOODMAN: We have a representative from the Office of Drug Safety at the microphone.

Could you please state your name?

MR. EVANS: Michael Evans with the Office of Drug Safety.

With regards to drug use, comparing the first six months of this year to the first six months of last year, the market rose with all ages about 7 percent. Adolescents and children, in the first six months of the year, still comprised between 7 and 8 percent of that total. So, they are still widely used in children.

DR. GOODMAN: How up to date is that data? There must be some sort of lag time, isn't there, between when the prescription--

MR. EVANS: It is according to IMS Health, and this is January through June is what we looked at. This is outpatient prescription data, which comprises about 45 percent of all pharmacies in the country.

DR. GOODMAN: Let me make sure I understand. You don't see any significant drop?

MR. EVANS: No. I believe a woman mentioned yesterday that they saw a 10 percent

decline. We did not see that.

DR. GOODMAN: Dr. Irwin.

DR. IRWIN: Has the rate of increase remained the same or has it leveled off, or what is the direction?

MR. EVANS: In February, one of our colleagues, who gave drug use for 2002, that age group was still 7 to 8 percent of the total. It is still the same this year, first six months.

DR. GOODMAN: So, there has been no great change.

I will take again other questions out of order as long as they are directed to a representative from ODS.

Dr. Marangell.

DR. MARANGELL: Actually, a comment directed to this. I think it is really critical to this discussion that we keep in mind that our goal is to protect risk, but also that this is really a devastating illness, and I am not sure that I necessarily--I don't want to necessarily see prescriptions drop. These people need to be

treated.

What we want to do is make sure that people are educated of what to look for early on in terms of risk for those people that are at risk, children or otherwise. They are not necessarily the same thing .

DR. GOODMAN: Other questions for our speaker? Dr. Gorman.

DR. GORMAN: Is the data on the level of the class or is it on the level of individual drugs?

MR. EVANS: We looked at the class as a whole and then we looked at each individual drug in the class. That was according to IMS Health National Prescription Audit, and we also looked at the National Disease and Therapeutic Index from IMS Health, and tried to apply those percentages to outpatient projected prescriptions.

Only the players changed in that age group of children 1 through 17. Paroxetine was knocked out of the top five, but sertraline still is the market leader, followed by fluoxetine.

DR. GORMAN: So, the information, there seems to at this point only be one drug that is efficacious in this age range, moved it up the ladder, but didn't make it number one?

MR. EVANS: Not necessarily. This is what we observed when we were just looking at drug use in prescriptions outpatient, and the National Disease and Therapeutic Index is an office-based survey where a drug is mentioned during that survey and linked to a diagnosis.

DR. GOODMAN: Can you differentiate between the prescriber classes, whether it is a primary care physician versus psychiatrist?

MR. EVANS: We did look at specialty in MBA-Plus. Psychiatry was still about 65 percent of the specialty, pediatrics, somewhere between 15, 20 percent still.

DR. GOODMAN: Dr. Fant.

DR. FANT: Could you comment on the indications for the prescription, was it all depression or other off-label--

MR. EVANS: We looked at mood disorders,

anxiety disorders, ADD, and other disorders. In age group 12 to 17, it still appears there is not really any change. It is still mood disorders, which includes major depression, is still two-thirds of the indications.

It looks like in the 1 to 11-year age group, perhaps more shift to the ADD.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: I heard rather consistently yesterday a lot of concern about the direct-to-consumer advertising and the role that that has played in this, and it may not be the purview of this committee, but I am asking if we can address this aspect and how that plays with the implications of labeling, that if we do put, as was suggested, a specific negative label in terms of the indications and certainly as a warning, let alone a black box warning, that the amplitude of these warnings are heard.

I mean it is almost a penalty then for the intense direct-to-consumer advertising, which does play, as I understand it, a huge role in driving

sales for some of these antidepressants.

I just wondered if you could give us some indication, I mean is there a direct policy with D.D. Mack how these various gradations get translated into the few seconds that go on the tail end of a commercial.

DR. TEMPLE: They are certainly supposed to. The presence of a strong warning or box warning should be reflected right in the major statements that are made. The direct-to-consumer comes in two flavors, written and TV.

In TV, you can't give as much information easily, but it has to be available readily. You can argue about whether people make use of that availability. But the major statement would have to reflect the balance between those two things.

You know, I am sure people have views about whether that is done successfully or not. If it is written, then, the written statements have to show that balance. Any box warning has to be reflected in it.

So, yes, it is supposed to reflect the

balance of information that is in the labeling, so if the labeling changes, the direct-to-consumer advertising should change.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: Yes. Back to the ODS person. A number of the anecdotes yesterday suggested that people were put on antidepressants quite off label and probably not for major depression, but rather for minor depression and acute depression.

You said that you have the evidence on mood disorders that includes major depression. Can that be disaggregated at all into other non-MDD forms of mood disorders?

MR. EVANS: We could look at that. We didn't, we lumped them together just for a top-line statement at this time, because we wanted the focus to be more on suicidality than drug use.

DR. GOODMAN: Ms. Griffith.

MS. GRIFFITH: I wanted to know, since the data you got was January to June, and the Advisory didn't come out until late March, is it possible to look at the data that you got April to June to see

if there is a decline?

MR. EVANS: We did look at it monthly in those months, and there was not any decline. I mean it wasn't a change.

DR. GOODMAN: Are these new prescriptions?

MR. EVANS: These were total prescriptions, new and refill.

DR. GOODMAN: Did you separate out by new prescriptions in terms of the monthly rate?

MR. EVANS: We can, and we did, and we did not see much of a decline in those, as well.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: On the surface, this looks not bad in the sense that 65 percent are being written by psychiatrists, but although I am not here as a patient representative, I do have a daughter who has been on these medications, and I know for a fact that most often psychiatrists do not prescribe these medications.

My image is that at the end of the day, they take a whole packet of prescriptions--and I will be interested to have the psychiatrists

respond to this--a whole packet of prescriptions that have been written by social workers, pharmacists, psychologists, and sign their name.

So, I think when we are talking about educating primary care providers, looking at this, I am reassured, but I know that this does not represent who is actually writing the prescriptions.

MR. EVANS: Yes, this is a limitation of the data, too, the data is only as good as what the pharmacist inputs at the computer, and, you know, if that specialty is on there, hopefully, they will put that on there.

DR. CHESNEY: I am sure they don't, but I think this is very important in the educational issue, because the people who are prescribing this, on the whole, are not child psychiatrists, and they are family practitioners, they are ER physicians, they are nurse practitioners, they are pharmacists.

I mean I was appalled at what happened when we visited one of these pharmacists, but no disrespect to pharmacists, but this is very much

happening out there.

DR. GOODMAN: One last question for ODS representative from Dr. Wang.

DR. WANG: I was curious, has anyone studied what happened after the British contraindicated these in children, just to get a sense of what the impact of a labeling change, such as that, might be?

MR. EVANS: In February, they looked through 2002, the market between 2002 and 2003 group, 15 percent with no change really in the adolescent and children population. It was still around 78 percent, so I don't think there was a change much in this country.

DR. WANG: But you don't know of any data in the British--

MR. EVANS: We didn't look at that.

DR. GOODMAN: Thank you very much. You may step down.

We have six more presenters. I am not taking any more, that's it.

Dr. Leslie, do you remember your question?

DR. LESLIE: My question goes way back and is for the FDA. I think reading through the materials that we received from the public, two of the major concerns about the data that was coming in were suicidality, et cetera, being captured under other labels, such as emotional ability, and then also the issue about dropouts were people dropping out of either the placebo or the drug groups, that were having the kinds of adverse events that were of interest to us, and then not being counted in the data.

So, I had two questions. One was do you feel confident that the data you have received has addressed those two issues for the analyses that we looked at yesterday, and the second was what steps could you potentially take to address those drawbacks that were raised by the public in the written requests that proceed from here on out.

DR. LAUGHREN: I can respond to the first part of that. In terms of the data that we received, if you recall, we issued letters to companies in July of last year, which specified a

very clear research strategy for looking for adverse events that might be related to suicidality.

It included both preferred terms and verbatim terms. All these data are electronic, so it was a string search to look for events that might be possibly related to suicidality. In addition to that, we asked companies to look at all their serious adverse event narratives, any event that had been classified as a serious adverse event, they would have to look at and make a decision whether or not that might represent suicidality.

Then, later in the year, we issued additional requests to basically ask them to give us all the serious adverse event narratives, so that we could have Columbia themselves look at those data, and also, all accidental injuries and accidental overdoses to try and broaden the search, to make sure that we could capture everything that might be related.

Now, it is true, despite all of that, it

is possible that certain events that didn't rise to the level of being a series adverse event might have been captured under some other either verbatim term or preferred term.

The other question is whether or not the narratives that we received fully reflected the case report forms. The narratives are created by the companies. To try and address that, we have sort of a second level of this contract with Columbia that is ongoing right now.

We have done a 20 percent sampling of the case report forms for the narratives we have, to have them check the narratives against the case report forms basically to see whether or not they fully reflected, the narratives fully reflected what was in the case report form.

In addition to that, we have asked for the dictionaries. The dictionaries, basically, companies, when the code data, they subsume them under preferred terms, and once they do that, that creates basically, a dictionary.

So, we have asked for the dictionaries

from all these sponsors. Columbia is currently looking at those dictionaries to see if there are any other additional adverse event terms that might be of interest to look at, again to answer that question whether or not all relevant events have been captured.

That is a very tedious, time-consuming process, but it is ongoing right now.

Dropouts, Dr. Hammad addressed that yesterday. We did look at dropouts, and as he suggested, it is true, many patients were dropping out for these events. In a sense, it was almost a surrogate for that endpoint.

DR. GOODMAN: Dr. Posner, did you have a comment?

DR. POSNER: I just wanted to say that, in addition, because we asked for all of the accidental injuries, and that would be the most likely place, that all of these events involved some type of injury or another, that you would find events that were missed, so we can feel reasonably confident that this body of data represents

everything we would want to look for, but we are doing these additional steps, as well.

DR. GOODMAN: Dr. O'Fallon.

DR. O'FALLON: Yes, this sort of follows up. We are back to what I am concerned about, the people who came here, they are worried about the side effects, the toxicity here. Right from the beginning, when you told us back in February about this study, I was worried about what wasn't recorded in the drug companies' records, for whatever reason.

I think that is still, no matter what we do going forward, we have got to address the issues there. So, what I am wondering about, I would like to propose, and you shoot at and tell me that these things are not feasible, but it seems to me what we really need are somehow a standardized suicide monitoring procedure or whatever for future studies in mental illness, any kind of a drug that is targeted toward the mind, we should be looking for this type of thing, the suicidality side effect.

Then, I think we are going to have to have

some sort of standardized suicide coding. They have done it in adverse events, not great, but it could be done better for suicide coding because of the work that has been done here.

I think this has been a wonderful outcome in terms of the coding issues.

Now, here is one that is going to kill everybody, but you can make suicidality a goal, a primary goal in, say, mental illness or maybe depression more specifically, where you really think that this side effect or toxicity, this adverse event is also a symptom of the disease.

In cancer, they have had to struggle with the issue of distinguishing side effects from symptoms of the disease for decades, some way of going after that.

Just one more comment. This is a comment. I believe that there was a 40 percent--in the stuff I saw before I came out here--I think I saw 40 percent placebo effect in TADS, the TADS study.

If that is true, this is a major issue. That is one of the reasons why we really do need to

have placebo arm in these different studies, because if 40 percent of this population will have a beneficial effect due to sugar pills, to try to tease out true effectiveness of these medications given their severe side effects, it is very important that we have a placebo arm even going forward.

I know that you are not thinking of it, but I think some of the people in the room are wondering why we have to go with sugar pills.

DR. LAUGHREN: Let me comment on the last point first. We clearly agree with you about placebo, but it is not just the act of giving a pill. In all of these trials, there is a lot that happens that results in improvement.

DR. O'FALLON: Yes, I know that.

DR. LAUGHREN: There is a lot of attention, the patients have a lot of interaction with staff. That is really the placebo effect.

But the other point you are making, I completely agree that ascertainment is ultimately the issue. If you don't collect the information,

it doesn't make any difference how carefully you search the database, if it wasn't collected, it's not there, so ascertainment is key.

Again, that is one of the things that we hope to get out of this effort with Columbia is a better guidance document for future trials to make sure that suicidality is properly ascertained, but it is an evolving thing in the field. I mean there is not at this point in time an optimal way of doing that, so we hope to get an instrument that we can apply for future trials.

Again, I agree with you that coding of data needs to be standardized, and again that is one of the things that we expect to come out of this.

DR. POSNER: Could I just add to that? We are very committed to addressing the question that you are referring to.

DR. GOODMAN: Would you bring the microphone closer.

DR. POSNER: I said we are very committed to addressing this issue in terms of suicidality

adverse event monitoring, and Dr. Laughren mentioned guidelines that we are going to write and measures that we actually have developed that we can implement in all trials, that will help us collect the right data and then be able to use these consistent definitions to classify events, so we can make sense across all of these trials.

What is important to note is that we are working on a National Institute of Mental Health study called TASA, Treatment of Adolescent Suicide Attempters, which is very focus on this issue of adverse event monitoring, and it is wonderful because it is helping us inform the process, so we have developed very, very rigorous standards of how we ask these questions, what measures we use, and how to do it consistently, and that will help inform the guidelines and the measures that industry and everybody else can use.

So, we have made a lot of progress in that, I think.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I just want to follow up on

the last discussion. It seems to me there are two, somewhat separate things, and I would be interested in people's views.

One is to make the periodic routine question better than it is. There is a suicide item on the score, but that didn't show anything. Maybe that will never show anything because when it happens, it happens abruptly and you don't happen to pick it up at the two-week period, but it does seem as if a better questionnaire on that question, done routinely, might be useful.

The second part of it is how to characterize events, what questions to ask about those, what to write down. Is that what you are thinking, they are two somewhat different things?

DR. LAUGHREN: I agree, they are two separate things. There is the suicide item that is part of every one of these instruments and sort of standardizing how that routine information is elicited, but then when an event occurs, you have to ensure that the appropriate questions are asked to flesh out that situation, so that someone down

the road who is looking at the data is able to make sense of it.

DR. O'FALLON: But I would like to point out that the monitoring procedures, especially for, say, the first two weeks or something like this, should include a real collaboration with the children and their caregivers, their parents, whoever they are living with, to be on the watch for those and to report them immediately, and that those things would be part of the data.

DR. LAUGHREN: Let me just respond to that quickly. Basically, you are switching gears to a clinical setting, I think, other than a clinical trial.

DR. O'FALLON: You guys can write the regulations for the clinical trial, right?

DR. LAUGHREN: Right, but obviously, the points that you are making apply to clinical practice, as well.

DR. O'FALLON: Yes, but they would apply I would say in the clinical trial, because I think that you are not possibly getting all your

information. If you don't come in for two more weeks, people forget that they were scared 10 days ago.

DR. LAUGHREN: Absolutely, I agree.

DR. POSNER: I just wanted to add that we are also working with the CDC just on this question, what are the right one or two questions that need to be asked in any trial or clinical setting to get this information to be able to classify it appropriately, which is exactly what we are talking about, and it is not necessarily the best questions on the measures that were used in this trials, but that is exactly the pertinent point in clinical setting or in research settings with the increased monitoring that you are referring to.

DR. GOODMAN: I am going to need to wrap up the remaining questions in the next five minutes.

Dr. Irwin.

DR. IRWIN: The question I wanted to ask specifically was related to the one that is on the

table right now. Yesterday, we heard from several families and individuals about really homicidal behavior and more violent behavior outwardly directed, not internally directed.

Of concern to me is that the focus has been so much on suicide, but what I wanted to know is what kind of monitoring or what kind of tools are in place to really measure that phenomenon in these trials, because it seems to me that we don't have any data that has been shown to us at least on adverse experience or events with the clinical trials.

DR. LAUGHREN: Our focus here clearly has been on suicidality, and not on hostility and violence. There was a lot less of that in these trials than we had suicidality, and we have not come to grips with that yet, but it is a whole other area that needs to be fleshed out and developed in the same way that suicidality has been fleshed out because again we have included in our database information on whether or not these individual patients at some time during the course

of treatment were coded as having hostility or agitation as a preferred term.

If you go back and look at what got subsumed under that, I am sure it is going to be quite different depending on different sponsors, and it really requires a parallel development to try and understand what that means.

Again, all the things we have been talking about for suicidality apply to that domain, you know, how do you ascertain for it, what kind of questions do you ask to flesh it out, it is a real problem.

DR. GOODMAN: By the way, the placebo response rate from the TADS trial is 35 percent. Looking at the paper again, I see 35 percent.

DR. O'FALLON: Okay.

DR. NEWMAN: Just to clarify, that is much or very much improved in the TADS trial.

DR. GOODMAN: I don't think that one is based on the CDRS, right, that is what you are saying, it is based on the CGI?

DR. NEWMAN: The dichotomous outcome was

were they much or very much improved, so if you said just improved, reasonably, it would have been a lot more.

DR. GOODMAN: But that is the standard, I mean it has to be much or very much improved to be a responder. That is pretty much across all clinical trials.

Dr. Pine, please.

DR. PINE: I want to return to a point that was raised by Dr. Goodman and just call the committee's attention to a couple things that he said and then also raised a couple other issue relevant to the discussion about 10 or 15 minutes ago with FDA.

That is the issue of both how perplexing, but also how important it is to think very carefully about the efficacy data and the difference between the data for fluoxetine, on the one hand, and all the other antidepressants, on the other hand, and how do we understand that.

Number one, just to underline that I agree that the importance of that point cannot be

overstated. I guess there is a couple of issues that were not discussed 10 or so minutes ago in sufficient detail, and really two points to raise.

One is that I do appreciate from a regulatory standpoint that it is very difficult to specify exactly how one is to do an appropriate study. We talked about a lot of the details that we don't need to go over again except one thing was not discussed, and that was a discussion of the level of rigor that goes into both the training of the investigators who are going to ascertain the samples and document the diagnosis, on the one hand, but then also follow the response of the patients throughout the trial.

Then, I think the last thing to say about that specific point is that when we look at the data that have been published, and probably the most extensive data are from the sertraline trial as opposed to the TADS trial, with the sertraline trial being a pharmaceutical-sponsored study that appeared in JAMA, and the TADS trial being an NIH-sponsored trial that was also published in JAMA.

There are some fairly clear signs that the manner in which investigators were trained, that the criteria for enrolling patients for the process of evaluating the response as it was manifest throughout the trial was quite different in those two studies.

Again, when we come to the issue of how important it is to compare the data for fluoxetine and the data for the other agents, I think we need to acknowledge that there are already signs in the data that have been published in the reports that have appeared in peer review, that the quality of the studies appears to be different.

I think it is also important to note that if we were to look at the efficacy data by industry sponsor versus federally funded, there have been, to the best that I can recall right off the top of my head, two federally funded SSRI trials, both are positive.

So, we are 2 out of 2 on that score, whereas, if we look at all the others, we are basically 1 out of 13 or 1 out of 14.

DR. GOODMAN: Those two are both in fluoxetine, isn't that correct?

DR. PINE: That's true, so, you know, we have a confound between federally sponsored and the compound, but those are the data that we do have, and I think given the issues that I just discussed, you know, we are going to be very hard pressed to say this is a funding or design feature issue, which it might be, or that this is a medication issue, which again it might be.

DR. GOODMAN: I want to make sure I am clear on the source of the fluoxetine data for the clinical trials. I think it was mentioned before that some of the data that contributed, I don't know which of the positive studies, but one of the positive studies at least, was actually a study that had been conducted by Dr. Emslie, and that, in fact, was a federally funded study, is that correct?

DR. LAUGHREN: Yes, the Emslie study was funded by NIMH, but there was another independent trial that was funded by Lilly, that was also

positive. The TADS trial was not part of our decisionmaking, that came later. So, there was another positive fluoxetine study that was done entirely under Lilly's sponsorship.

DR. GOODMAN: Dr. Rudorfer, did you have a comment?

DR. RUDORFER: Just on this last point, I think that was back in '80s, am I correct, that the Emslie study was first done?

DR. GOODMAN: No, '97.

DR. RUDORFER: Because we have in our material, a fluoxetine clinical trial that goes back to the '80s.

DR. PINE: That was a very small study, at least as I understand it from reviewing the material. Maybe you want to comment on the 1980 study.

DR. LAUGHREN: I am not familiar with that one. I think the Emslie study was maybe early '90s, but we can probably check. I am sure it is in Dr. Dubitsky's review.

DR. PINE: Well, in the material that we

received, there was a study that was described, that I recognized just from the description as a study that was published in 1990 by Simian as the first author.

DR. LAUGHREN: That was probably, I think it was HCCJ. That was the study that was terminated early. I think there were only 40 patients in that trial. That was not one of the trials that was the basis of our approval of the claim in fluoxetine.

DR. RUDORFER: Could I insert just another quick safety-related question? We were talking before about if there is a way to judge the impact of the label change that was made in March, since that would seem important to us in terms of whether an additional change would be helpful.

I am wondering if the Med Watch Program offers any clues there in terms of reports from the clinical community of adverse events, whether there has been a change in 2004 versus last year, for instance.

DR. TRONTELL: We haven't looked at that.

The Med Watch Program, just to be very precise, has two components. Med Watch itself involves reports that come directly to the FDA, and don't come through the pharmaceutical manufacturers. That is actually a minority of the reports, 5 or 6 percent.

The Adverse Event Reporting System, which Med Watch and the manufacturers feed into, is much larger. The challenge was reports that came to the agency spontaneously, that you actually can, in fact, see a paradoxical increase in reports when these events become known to the public, so it is not a reliable way to tell you whether or not things are changing, because we know not every report comes to us and the factors that influence reporting are changing dependent on scientific and media attention.

DR. RUDORFER: So, within the agency, do you see any index that you can use to judge the impact of the label change in March?

DR. TEMPLE: The only thing that you could measure properly is use, so if the warning sort of made people think twice, and decided to watch and

wait instead of treat, you could detect that through the data that have been described.

But the adverse events are unpredictable. We know that not all serious events are reported, you know, various estimates go from 1 percent to 10 percent to higher, but as Anne said, if you change public attention to something, you can get increased reports without having increased numbers.

It is very hard to know that, to know about those things. What you can think about is looking at databases that have reports of these things, the kind of thing that Jick did and others, but the events in question, first of all, you are not sure how well they are described, you are not sure whether they get into the reporting system. It is very difficult territory. You know, epidemiology is difficult enough, this is particularly difficult, because you don't know how they are classified and it is really hard.

DR. TRONTELL: Just to follow up, if you want to see a change, you may actually have to wait some time before you see a change in the outcome.

If you wanted simply to see if prescribing practices are different, I think you might have to go even beyond the use data we have, even beyond, say, new prescription to see if starts on these products are changed, to actually do some active surveillance and survey clinicians or survey patients to find out if, in fact, there is a different process for introducing these products.

DR. GOODMAN: Dr. Marangell, did you have a question? Okay.

Dr. Fant.

DR. FANT: I just want to follow up on that and the comments and questions that were raised by Dr. Chesney earlier.

One of the things that I was struck by yesterday and hearing the testimony of the families, and from my own personal experiences with friends and family members, much of the discussion here has been focused on the use and efficacy and outcomes of these drugs related to major depression in the trials that have looked at that, but the off-label use of these medications is fairly

promiscuous, and the prescribers extend well beyond those that are trained in the care of the mentally ill.

I think that is a real problem when you have ob-gyns prescribing it and giving it away for ladies who just may be a little moody, you know, when they come in, or feeling a little down, and without having any consultation or evaluation by someone who is specifically trained to evaluate that, I think that is a problem and I don't think that represents an isolated incident.

I think any labeling change considerations really need to not necessarily be directed to regulate how medicine is practiced, but to somehow influence or disincentivize that kind of unrestricted free-lance approach to how these medicines are used.

I think that has to be kept in mind, and I would just like to emphasize that.

DR. GOODMAN: Dr. Perrin? Dr. Irwin.

DR. IRWIN: I would just like to respond to that. I mean I agree with you that the

distribution of these medications by individuals who aren't trained is really a worrisome fact, but I will tell you in San Francisco County, to find an individual who is trained to see a child with a mental health disorder is virtually impossible unless someone walks through the door with $175 in hand to give to a psychiatrist.

So, I think that what has happened, and it's a fundamental problem that we are dealing with, and it is not the purview of this committee, that the issue of mental health problems in children and identifying individuals to care for them or finding individuals to care for them is really very, very difficult, and it pushes primary care clinicians to prescribe and make judgments, and provide medications when they probably should not be without appropriate consultation.

So, I think it is a real major crisis.

DR. FANT: I agree 100 percent, and I make those comments fully cognizant of the fact that the mental health arm of health care in this country is probably in worse shape than health care in the

broader context.

Certainly, in terms of its availability, certainly in terms of its coverage by health insurance plans, it is not sufficient to do what it needs to do. But I think it is important not to make it easier for bad medicine to be practiced under those conditions, but to somehow create conditions that kind of force, at least under those suboptimal conditions, some better protections and better practices.

DR. GOODMAN: Drs. Pfeffer and Wang, and then we are going to take a break.

DR. PFEFFER: I would like to just go to another area of our discussion and that is to focus on what I will call the real world issues. I think that the speakers yesterday in their own way gave us a representative view to some degree of that, and I am wondering, someone mentioned, I think Dr. Pine, about prescriptions and can they be a little bit more either regulated or I will say focused.

I am wondering if we might consider the option of when a physician writes a prescription

for a medicine, such as an SSRI, that what is also included on the prescription is the diagnosis, so that we would have the kind of data that we just heard, but amplified by some knowledge at least of what the clinician is thinking about the rationale for the prescription.

I know we do that in New York relative to controlled substances at times, or other, in the clinics, for example, the prescription forms actually have that on their forms. So, I don't think it's any greater violation of patient's privacy than to say a patient is already on a medication.

It might provide us with some additional national-like real world practice ideas.

The other comment I would like to make is that I think it was Dr. Zito who mentioned yesterday about a proposal of having sort of a more widespread, sort of service oriented approach to study the issues also.

So, I think while we are talking about constructing drug trials that are carefully

controlled and carefully defined in terms of the population, given the fact that the prescriptions are being used much more widely, it might be helpful for us to have a view, a focus, and how can we study these issues also, and the studies need to be done obviously in different ways.

DR. GOODMAN: Dr. Wang, did you have a question?

DR. WANG: No, it was covered.

DR. GOODMAN: I would like to take a 10-minute break and then we are going to return for a presentation, and we need to at least handle one of the questions before we break for lunch.

[Break.]

DR. GOODMAN: We are about to begin. Please take your seats.

If you recall from yesterday, when Dr. Wysowski was presenting, she said she had some additional data that was provided on the Jick study, and we asked her to defer until today to present it. I think she should be able to do that pretty quickly, also give you an opportunity to ask

her any other questions that you think are relevant to today's discussion.

At the close of that presentation, we are going to get down to business in addressing these questions sequentially. In the course of doing so, I am going to ask you to, as best as possible, to restrict your comments and the discussion to the question at hand. Otherwise, I may defer that to later in the course of our discussions.

So, with that, Dr. Wysowski, could you go ahead and present the data. Maybe you want to give us a little bit of a sense of the context first.

Diane Wysowski, Ph.D.

DR. WYSOWSKI: Right. I don't know how important or relevant this is at this point in time, but I am going to ask you to switch gears from the clinical trial data and think back to my presentation yesterday morning, which was on patient level controlled observational studies.

I talked about two studies, the Jick study that was published in JAMA, and the Valuck study, but I am going to have you focus on the Jick study

and recall that it was a case-controlled study. It was done in the United Kingdom and the General Practice Research Database, and it examined the use of four antidepressants - amitriptyline, fluoxetine, paroxetine, and dothiepin in suicidal cases versus non-suicidal controls.

In their original analysis, Dr. Jick and his colleagues used dothiepin as the reference category.

At FDA's request, Dr. Jick and colleagues kindly re-analyzed their multivariate data for nonfatal suicidal behavior using amitriptyline rather than dothiepin as a reference category.

The data are controlled for age, sex, calendar time, and time from first antidepressant prescription to onset of suicidal behavior. Now, in the lefthand portion of the slide, you see their original analysis with the risk ratios and 95 percent confidence intervals with dothiepin as a reference category.

On the right, with amitriptyline as a reference category, the risk ratios for both SSRIs

increased and became statistically significant at the 0.05 level. The risk ratio for dothiepin was 1.21 with a 95 percent confidence interval that included 1.

For fluoxetine, it was 1.40 with a 95 percent confidence interval of 1.03 to 1.91, and for paroxetine, it was 1.55 with a 95 percent confidence interval of 1.11 to 2.16.

Now, the investigators asked that their interpretation of these results be presented verbatim to the committee. We advised that these post-hoc analyses be interpreted with caution. They were not the preplanned primary analysis, and the p-value and confidence intervals are not adjusted for multiple hypothesis testing.

We think conservative interpretation requires that p-values lower than 0.05 or confidence intervals with coverage greater than 95 percent would be necessary to assert that these results are statistically significant with overall 5 percent Type 1 error.

These results are consistent with the

interpretation in our report that the risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin, and that a possible small increase in risk bordering statistical significance among those starting the newest antidepressant paroxetine is of a magnitude that could readily be due to uncontrolled confounding by severity of depression.

Moreover, we did not observe an increased risk of suicide itself for the users of amitriptyline, fluoxetine, or paroxetine compared to users of dothiepin.

So, that is their supplementary analysis, it was a post-hoc analysis, and that is their interpretation of the results. It did increase the two SSRIs to the level of statistical significance at the 0.05 level.

DR. GOODMAN: Now, dothiepin is not a medication available in this country. It is also a tricyclic antidepressant, as is amitriptyline,

isn't that true?

DR. WYSOWSKI: That is correct, but again, the choice of the reference category makes a difference in the results.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: I think it is very helpful to have these additional analyses. I really had, though, a couple methodologic questions about this and the Valuck study that I think are fairly quick.

One is, in the British database, how valid or reliable are these measures of suicidal behaviors, not achieved suicide, and similarly, how good were the measures in the Valuck study of--I can't remember the terminology they used off the top of my head--but of suicidal behaviors given the kind of database they had to work from?

DR. WYSOWSKI: Well, one of the concerns that I had, which I expressed yesterday, was that the possibility of missing data and incomplete ascertainment, and misclassification, and when you are talking about suicide ideation, which is a softer, more subjective diagnosis, it is difficult

to know how many people actually come forward and report that. I guess if it's a serious concern, they come forward and report it.

One of the things that I think Dr. Jick says is that there is some possibility--the general practitioners on which the data are based, they make these notes, and it looks like they get entered into the computer about 90 percent of the time is what I figure from what Dr. Jick says here.

So, if there is some misclassification in that way for the 10 percent that don't get entered, of the missing data, you would be concerned.

DR. PERRIN: But it requires that the general practitioner actually puts it in his or her notes for it to get even possibly entered. There must be substantial variability in that phenomenon.

DR. WYSOWSKI: Well, they do have computers, and these people were trained, and so they achieved a level of training success to be entered and qualified for this database, but it sounds to me like--it says here, "Information on patient referrals and hospitalizations available in

the manual medical records in the general practitioners' offices was recorded on the computer more than 90 percent of the time."

So, that implies that about 10 percent of the time you are not going to find the data there. It was in the manual record, but not on the computer. So, there is some possibility for some error there.

Now, how that actually works out into the results, don't know really.

DR. PERRIN: For the Valuck study, do you have information on their measure of suicide attempt?

DR. WYSOWSKI: The Valuck study was based on paid medical claims data and of 70 managed health care organizations. I talked to Dr. Valuck about that, and he said that he thought that the PharMetrics integrated outcomes research database that he used, which is the 70 managed health plans, that the data was very good and very complete, but one of the things that is a problem with his study is that he cannot go back and validate through

medical records the information that he has on the computer, so that is one problem, but he said that was better than most Medicaid databases.

DR. PERRIN: Most Medicaid databases are very poor for analyzing children's mental health services.

DR. WYSOWSKI: Right.

DR. GOODMAN: Dr. Ortiz, did you have a question?

DR. ORTIZ: I just was wondering if Dr. Wysowski could clarify the risk ratio for this. Is it suicidal behavior, suicide attempts?

DR. WYSOWSKI: It is nonfatal suicidal behavior, which includes ideation and attempts.

DR. GOODMAN: I believe in reading the Jick paper, there was reference made to 15 completed suicides in the entire population.

DR. WYSOWSKI: Right.

DR. GOODMAN: And they go on to point out, those 15 were within the 10 to 19 age group, in fact. There were others obviously outside that range, but that none of the 15 in that younger age

group were on antidepressants.

DR. WYSOWSKI: Right. Actually, they include suicides in their study, and there were 17 cases and 157 controls, but also I think Dr. Goodman is referring to the fact that, yeah, there is some information on children that committed suicide, and it was somewhere on the order of about 15.

But that makes me wonder. I wasn't able to determine whether that 15 is a reasonable rate or not, so, you know, whether that is under-ascertainment or not, we don't really know.

DR. GOODMAN: That, in part, was my question. I wasn't sure from reading the paper how they ascertained it, but it still was striking that none of them were on antidepressants.

DR. WYSOWSKI: However, they do say here that causes of death in particular are routinely recorded, so you would think that they would have pretty good data on deaths, but you don't know, and all the suicides, but you don't know.

DR. GOODMAN: Dr. Gibbons.

DR. GIBBONS: Most statisticians view large-scale naturalistic observational studies as statistical atrocities. I am not one of them. I think there is a great deal to be learned from naturalistic observational data.

Having said that, I think it is very, very important to protect oneself from bias due to selection, and it appeared to me here that, you know, there is all kinds of selection bias as to who gets on to what kind of medication.

I guess, first, there is a question, well, first, there is a statement. These are sorts of cases where things like propensity score matching and other sorts of methods that have been around for a long time for the analysis of observational data are critically important.

Covariate adjustment typically, which I imagine was done here, can be very misleading, because it assumes linearity, and many of these relations aren't linear, and, in fact, the biases cannot be overlapping. You could have situations where the people who got on to one drug, don't look

anything like the people in the other, and, in fact, the use of covariates in a general linear model will be more misleading than helpful.

Have they made any attempt to do this simple analysis using some form of propensity score matching to ensure that the likelihood of taking the drugs is consistent between the two groups?

DR. WYSOWSKI: Yes. Dr. Jick did not, but Dr. Valuck did, and I presented those results yesterday. In the poster, there was no increase in risk for any of the antidepressants, but they had classes of antidepressants, as you recall. They are not individual antidepressants.

For the expanded study, which was based on 24,000 patients with diagnosis of major depressive disorder, they did find a relative risk of about 1.58 for the SSRIs, but it was not statistically significant. They did include a propensity matching adjustment.

DR. GIBBONS: Given that we are seeing this consistent 1.4, 1.4 through a lot of the analyses, it would be very interesting either to

have them do those analyses or perhaps the committee would think about performing such analyses if we could acquire the data.

DR. GOODMAN: Thank you very much.

DR. WYSOWSKI: You are welcome.

Discussion of Questions and Vote

DR. GOODMAN: It is time to roll up our sleeves. I would like you to pull out the questions before us. It was given out attached to the agenda for the meeting, on one page, or you can use it as represented in the slide handout that Dr. Laughren gave earlier today.

Let me make a few comments first, before we begin to address these questions. For the most part, they are focusing on risk, specifically, risk of suicidality, and it seems to me it is not until Question 4 that we need to be thinking about ratio of benefit to risk.

So, I think for the most part, the first three questions focus entirely on risk, but in order to come up with some recommendations in terms of regulatory actions, we do need to consider the

balance between risk and benefit.

Also, in talking about suicidality, there are some definitional questions that have come up all along, and I think we need to be, among ourselves, as clear as possible what we mean when we say suicidality. Maybe there will be some benefit from the work that the Columbia group has done to help us make sure that we are using the same language.

Also, I think it behooves us to try to translate what suicidality means to the general public. In looking at some samples of the morning papers, front page New York Times, front page USA Today, there are headlines about how it has been concluded already, based on yesterday's discussion, that the antidepressants increase suicidality in children.

I am trying to imagine. I would be interested in how a parent, in reading that, what they would think, what do they mean by suicidality. My guess is that they are going to think that it is suicide. As we discussed yesterday, this includes

suicide, it includes suicide attempts, but our definitions also includes preparatory actions and ideation.

So, I think we need to be very clear that we are using the same terminology, and maybe Dr. Posner will be able to help us along the way in that.

As I said a little bit earlier, that we are going to try to keep very focused on the question at hand, so I may defer some of your questions until later in the day. I would like very much to be able to answer at least one, perhaps two, questions before breaking for lunch, so that the reward will be lunch to get some of this work done.

My sense is that Question 1 may be the easiest question, and then they may get increasingly more difficult, so I think we need to pace ourselves accordingly.

Also, just as another kind of overarching statement is that for the most part, at least in the beginning, we are asked to focus exclusively on

the clinical trials, but as we begin to deliberate on issues of risk and benefit, then, we have to then begin to consider data from outside those clinical trials and therefore, our task becomes more difficult and more complex.

Any questions about process before we begin our comments?

MS. DOKKEN: Just before we start on the specifics of Question 1 or 2, as someone new to the committee, who is trying to listen and learn about, I do have a question related to guidance from both the Chair and the staff, and I would feel more comfortable hearing about this, I guess, before we even get into Question 1, which is I hear still some discomfort about the data.

On the one hand, the options of labeling and black boxes, et cetera, but I hear another theme, too, which was articulated in particular by Ms. Griffith, and that is, even though we are two advisory committees only, and even though the FDA is regulatory, is it within our purview, and more so, do we have a responsibility to go beyond

something narrow like that, like labeling, and also talk about the issues.

As I said, Ms. Griffith referred to education, not just of clinicians but of the public, and how much time, you know, can we allocate time to that, as well.

DR. GOODMAN: Dr. Katz.

DR. KATZ: One response to the last part. I think when we get to the appropriate time in the meeting, I think you should discuss in a very freely ranging way what provisions you think would be a good idea to institute in order to use these drugs safely.

I wouldn't worry so much about the nuances of what your responsibility is or what we can do from a regulatory point of view. If there is something that you recommend, and we have already talked a little bit about this, if there are things that are outside our purview and we are incapable legally of instituting, we will get back to you on that or will let you know, but I think we really want to hear a relatively wide-ranging conversation

about what sorts of things you think might be useful. If we can't do it, we will let you know, but we would like to hear about it.

DR. GOODMAN: Any other comments about process?

I also noticed behind me that we have Question No. 1 projected, so you don't need your reading glasses to address it.

Let me read it. Please comment on our approach to classification of the possible cases of suicidality. Here, by parentheses, that word has been defined. Suicidal thinking and/or behaviors, and/or analysis of the resulting data from the 23 plus 1 pediatric trials involving 9 antidepressant drugs.

Another thing I probably should mention is that in terms of the questions we vote on, clearly, No. 2 is one we are going to vote on, and a yes vote then would lead us into No. 3. I am not sure that No. 1 requires a vote. You are asking for comment.

Are you asking for a vote on this

question?

DR. KATZ: No, we are not asking for a vote, just comments, just a general sense of the committee.

DR. GOODMAN: I was going to actually start and try to answer the question first, to go out on a limb, since this is the easiest question, I thought I would take a stab at it, in my opinion. But if there are other comments, and I will be going around the table, so that each of you will have a chance to comment, so unless it's really a process question, you will get your chance.

It is a process question.

DR. NEWMAN: This is a process question. It seems to me it might not be a good use of time to go around the table and have everybody comment on it. I mean I just think they did a great job, we should praise them, and move on to some more substantive issues that are important.

DR. GOODMAN: You stole my words, now what am I going to say. I do like to go around the table even if the comment is ditto, just to give

everybody a chance to speak.

Let me start. I would agree that I think that given the inherent limitations of the data, it was a very rigorous examination, very carefully planned, involved leading experts. There was appropriate blinding, more than adequate training. We saw, too, that we had further vetting by agreement with an independent study that was conducted by the FDA in a subsample.

I think there is always room for criticism, but I think most of my criticisms would be regarding the inherent limitations of the data itself, not what was accomplished by first the Columbia group and then the FDA's re-analysis of the data.

So, my comments are very favorable and I can't see that there is much room for improvement. In fact, I am impressed with how much they accomplished, and I was somewhat skeptical in our last meeting, and very impressed with the outcome and attention to detail.

So, let me now go around the room starting

with Dr. Fant.

DR. FANT: My only comment, I agree with everything that you just said, my only comment is in the same spirit of my father, when I would come home with a 98 on my test, and he would wonder why I didn't get 100, and I guess my question to Dr. Posner is, is this scale applicable across various cultures and racial groups in terms of behaviors and actions that may be significant with respect to the endpoint that may differentiate one group from another, that may be useful in trying to explore and develop those, validate this tool in different groups?

DR. POSNER: The answer is yes, and most of the studies that these concepts are based on have a lot of heterogeneity in terms of race and general populations, so absolutely.

DR. FANT: So you feel comfortable that this tool would be just as useful in an inner city, predominantly African-American clinic, as well as one that serves Southwest Hispanic community versus one that serves Native American kids on the

reservation?

DR. POSNER: I think that the definitions and the classification, the underlying concepts in the classification that were represented in what you saw yesterday, absolutely, and again were based in just those populations.

In the NIMH study that I referred to earlier, for example, there is a range of all of the populations that you just mentioned, and those are exactly the kind of behaviors we are looking at and the samples that we are looking at.

Again, it's overarching concepts and the behaviors are similar across all those groups.

DR. GOODMAN: Dr. Pfeffer.

DR. PFEFFER: I think this is an excellent scale as a classification. I think that it's a wonderful beginning and carried out with real data regardless of the quality of the data.

I wanted to make some points just for clarification, and I think that is what Kelly was just pointing out, too, in a way. This is a classification, and I don't know that one can yet

extrapolate this to, let's say, use with patients.

This is a secondary means of focusing individuals in terms of their behaviors or thoughts, but not yet to gather the data about them, and I think that is important to emphasize, so that much work I think needs to be done to create the kind of an instrument that could be used reliably and validly to assess directly from the patients what the nature of their thinking is and the nature of their intent, as well as the behavior itself.

The other point I would like to make is that this classification does hold across all age groups generally, but in creating a method of interviewing and establishing the information, what is also necessary is to consider developmental perspective, because we do know that children's cognitive capacities of understanding the nature of their planned behaviors are quite different than adults.

I will go back to the example that tends to be thrown out, and I would agree it should be

thrown out, but the child who slapped herself, for example, that was one of the illustrations.

You know, if you have a child that has problems or immaturity and cognition, one might not quite know what she was intending to do, and a slap or a hit with a piece of glass or whatever, it all can mean something quite different in the mind of a child, so that much work needs to be done to tease this out I think from a developmental perspective.

DR. GOODMAN: Dr. Pfeffer, I would certainly agree with your point that the assessment, the prospective assessment of the patient is a different matter, but with regard to the narrower question, as I interpret it, in terms of the classification data, the process of classification, would you have any additional comments?

I think yours are more comments in terms of what would be the next steps in implementing the system, administering it to subjects in a prospective study.

DR. PFEFFER: I think the classification

is excellent. I would also raise the question, the children and adolescents who couldn't be evaluated, was it due to the data itself, was it due to questions about what category the child might fit into, which I tend to doubt because they actually solved those issues by discussions.

I think, generally, this is a wonderful classification.

DR. GOODMAN: Dr. Posner, you had a comment?

DR. POSNER: I just wanted to respond to your first point, which is you are absolutely right, and all of that work has been going on simultaneously. So, we are quite well prepared and enthusiastic actually about putting helpful assessment tools into future studies now that ask the right questions to be able to put events into these kind of categories. So, there are two separate questions and both being addressed, I think.

I think your next question has to do with our No. 3, the kids where we knew they hurt

themselves, but we couldn't say why--am I correct--and the reason was because of the limited data about suicidal intent.

So, these were narratives that said superficial scratch on wrist, and that's it, and, of course, not enough surrounding information to infer any kind of intent, so again, that is why that category was warranted. This is important, we know they hurt themselves, but we just don't know why. As the FDA told you, they put that into a worst case scenario, sensitivity analysis, which I guess looked very similar to the primary outcome.

Did that answer your question about those cases?

DR. GOODMAN: Yes. Dr. Fost.

DR. FOST: No further comment, thank you.

DR. GOODMAN: Dr. Ortiz.

DR. ORTIZ: My comments I think are more on the line of what Dr. Pfeffer had to say. I think what Columbia has done is a wonderful start for the pharmaceutical companies to improve their identification of suicidal behaviors, and I think

the FDA has done a superb job of further analyzing the 24 studies.

However, the 24 studies excluded children who had suicidal ideation with the exception of 4 studies, and the vast majority excluded children with history of family bipolar.

So, again, my concern is in regards to the testimony yesterday that we also need to think about families and the clinician out there practicing, the pediatrician in Farmington, New Mexico, who has a mother with a 12-year-old who comes in, who says, "I want to die."

I think we need to also be thinking about issues of side effects, of agitation, hostility, delusions, mania, and violence, which this particular population, I mean I think for a classification system, it is great, but there is other issues related to side effects and clinical practice that I think affect suicidality profoundly.

DR. GOODMAN: Thank you.

Dr. Malone.

DR. MALONE: I agree that the combined study was done very well, and I think it is encouraging that the original FDA study pretty much agrees with the second study, and I think gives it more validity that way.

DR. GOODMAN: Thank you.

Dr. Nelson.

DR. NELSON: I just have one comment, that I think a reasonable topic for discussion going forward by the Pediatric Advisory Committee might be to think through what lessons have been learned by this experience for the ability to compare information across different drug development programs within drug classes, because I suspect this issue might exist in other areas.

So, I think that is worthy of focusing on at some point in the future, just to get that on to the docket.

DR. GOODMAN: Thank you very much.

Dr. Perrin.

DR. PERRIN: I think the classification is great, and I would like to know a little more about

the discordant cases between the FDA and Columbia, but I think that knowing more about the discordant cases would not change the findings at all.

DR. GOODMAN: Thank you.

Dr. Grady.

DR. GRADY-WELIKY: I agree with everything that has been said. I would just like to follow up a bit on what Dr. Nelson said, which is that the Columbia study actually showed us a great deal about the role of narrative reporting, and I would think it is very important that we look at, for future studies, guidelines for those narratives so we have further information.

DR. GOODMAN: Thank you very much, Tana.

Dr. Ebert.

DR. EBERT: I also agree, that the classification I think was reasonable, and I commend the investigators on that. As far as the analysis, just one brief comment, and that again I think the analysis was appropriate, but again we have the caveat of the studies themselves being of somewhat questionable quality, and the variability

of quality probably is hard to establish.

Having said that, when the studies are analyzed, they are analyzed based on weighting those studies on their size, which therefore gives the greatest weight to the larger studies, not necessarily knowing whether those are the highest quality studies.

DR. GOODMAN: I like your last point.

Dr. Gibbons.

DR. GIBBONS: Clearly, there has been a lot of excellent work done both in terms of the classification and in terms of the analyses. I think in terms of the integrity of these data, the classification has gone about as far as you can milk the data for, and I am not sure that we really need to do much more in that regard.

In terms of the analysis, I think that the analyses are very thoughtful, but I don't think they have addressed the critical question that they were intended to address.

I am reading from the summary minutes of the February meeting, that "Since we are in the

preliminary stages of designing an appropriate analysis of patient level data"--blah, blah, and then it goes on, the analyses that are presented so far are not really analyses of patient level data. They are combinations of risk ratios in a meta-analytic framework from study to study. They are not patient level data.

The survival analyses that were done, to some extent, are patient level analyses, but those analyses are not adjusted for the effects of covariates, and I really think there may be more to these data than what we have seen, and would offer that we should have a look at the data, and I would be happy to do that.

DR. GOODMAN: So, you are making a suggestion that there is opportunity for continued mining of the data, and maybe we can put that in sort of our parking lot and return to it as we get to the recommendations.

DR. GIBBONS: Yes.

DR. GOODMAN: Any comments from the FDA regarding the analytic questions that were raised

just now?

DR. LAUGHREN: We would be happy to share the database, it is not a problem.

DR. HAMMAD: Regarding the fact that there is no apparent patient level data, examining the confounding on trial level was done based on the patient level data, and also, as you said, time to event also utilized the patient level data. Also, examining the interaction in all trials by the certified analysis used the patient level data, but there might be some other things to be done putting everything together.

DR. GIBBONS: I don't have necessarily any expectation that a different analysis would yield a different result, and I don't have any criticism of the analyses that have been done. In fact, given the time frame that were available, you have gone way beyond any of my expectations, but I do have a few ideas of how the data could be analyzed in a different way, that might shed a slightly different light.

DR. GOODMAN: Thank you.

Dr. Pine.

DR. PINE: Beyond the general comments about the outstanding nature of the work, I guess I would make only one other comment, and that relates to some discussion between the last meeting and this meeting, about the degree to which these analyses were necessary or appropriate, and I guess I would only just speak for myself to say that I found them both helpful and in some ways necessary to really inform on the next question that we are going to deal with.

Again, just speaking for myself, I feel far more comfortable being able to talk about the second issue concerning is there or is there not a signal, having seen the outstanding quality of the work that was done.

DR. GOODMAN: Jean Bronstein.

MS. BRONSTEIN: I have nothing further to comment about the study although I really thought the analyses done with Columbia really helped me better understand this issue than I did in February.

I do at some point want to speak about warnings and what I heard from yesterday's testimony, and I think it really comes under the next question rather than this one, so I will hold that for then.

DR. GOODMAN: Thank you.

Dr. Rudorfer.

DR. RUDORFER: I would like to second the excellent quality of the classification project. I wonder if there is room to more formally include informant information.

I am thinking particularly in some of the coding, which have been described as softer, for instance, suicidal ideation, should there be a subcategory of suicidal ideation that is validated by a family member as having been expressed as opposed to just expressed by the patient.

DR. POSNER: Ideation is not typically one of the categories that you would feel even the need to be validated by a family member, because it is what is going on in their head, so usually, the most valid indicator of it is the child or

adolescent.

I understand what your comment is in the narrative. Some of the narratives said, you know, mom said that he said this, or the doctor just said, you know, indicated what was said, but there is no way to further break that down at this point with the limited information that we have.

Again, I think it becomes more relevant just from our assessment standpoint in terms of behavior than ideation, having the supplementary informants.

DR. RUDORFER: Thanks. The only other thing I would add is just to re-emphasize--and again this is not a problem with the classification, this was a problem with the underlying data--that your outcome was only as good as the data that were available, and I think we are all faced with that conundrum that those data seem to be rather incomplete and inconsistent.

DR. POSNER: It is true, but I wanted to highlight, in your handouts, you see the first example I gave yesterday of the suicide attempt

that was clinically impressive, where the patient took 100 pills, you have a very detailed narrative in your handouts.

It is important to note that every one of these narratives, many of the narratives had a lot of supplementary information, and that was what was so crucial about having suicidal experts, because they can take all of that supplementary information and say, yeah, this looks like a suicide attempt given everything that we have.

So, I just think it is important to highlight that there was a significant amount of surrounding information even though stated intent was very often not there.

DR. RUDORFER: Right. No, I appreciate that, and I commend you for that. My concern remains with, say, the placebo-treated subject who walks in and verbalizes no complaints, and then the rating process goes on and no one ever discusses any surrounding issues because there doesn't seem to be any cause for it.

DR. POSNER: Right, we can never make

sense of something that is not there.

DR. RUDORFER: Right.

DR. GOODMAN: I have already rendered my opinion, I will just add by saying that I was not prepared to answer Question 2 at the last meeting, but I am now based upon the reclassification.

Dr. Chesney.

DR. CHESNEY: The good news is that I have no further comments about the analyses other than what the rest of the panel has said.

I was struck yesterday, as I was in February, by the reports of the parents of a number of children who never expressed suicidal behavior or ideation, and yet proceeded to commit suicide, and my second point has to do with other injurious behavior.

We have looked at self-injurious behavior, we have looked at obviously suicidal, but we haven't looked at aggression, hostility, all of those aspects of the activation syndrome that we talked about in February.

The thing I feel relatively good about,

however, is that I think, had we looked at those, it would have only strengthened the results that we have already seen, so those are my only comments.

DR. GOODMAN: Thank you.

Dr. McGough.

DR. McGOUGH: I just agree with the Chair's comments.

DR. GOODMAN: Ms. Griffith.

MS. GRIFFITH: I would endorse that, too, and I agreed with Dr. Gibbons that the classification has gone about as far as it could, but I have a very quick question for Dr. Hammad, because at the February meeting, you raised the possibility that the data might not be robust enough to render any conclusions, and your formidable presentation yesterday, I suspect gives you confidence, but I would just like to know if you, indeed, feel that this is robust enough. I am asking you a very subjective question, I am sorry to put you on the spot.

DR. HAMMAD: Yes, you are right, it is subjective. Of course, it depends on what do you

mean actually by "robust" here. I think if you look at the individual trials, for example, you feel that there is nothing going on, there is nothing significant on its own, but when you see how consistent the signal is coming from most trials, putting this in the context of what the rest of the process is, which is the fact that we know now we have every event that is out there, as well the public testified, and you still see it, then, you can feel more comfortable about the findings.

So, I agree with the comment that were said before about the level of comfort that is definitely much better than it was in February.

Also, the sort of things like the information we have on discontinuation, for example, also about the history of seratin [?], I mean these two factors alone could have made the results one way or the other, and if we did not have information about those, and we had not tested them, we would have spent a long time trying to speculate how much actually impact we have.

So, we also got this out of the way, the obvious, clear potential explanation for the apparent risk. So, I think what we are saying now is true.

MS. GRIFFITH: Thank you.

DR. GOODMAN: Dr. Leslie.

DR. LESLIE: I just want to say thank you for the work you did.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: In terms of classification, I just want to second what most of us have said, which is that I think the FDA and the Columbia group did as good as they can with the data that they had.

Just two comments. One is that in terms of going forward, and Dr. Posner might obviously have ideas about this, is that the Columbia classification was obviously done in terms of what you could get out of very limited data, and in the future, sort of going forward in a prospective sort of manner, you might have a different classification or you might have a scale that had

additional items which might be very important, which you couldn't get from retrospective data.

So, I think we still need to think about that you can, for prospective studies, do something maybe that is even better.

DR. POSNER: I just want to clarify one thing, and it is a very important point. This classification scale and scheme really is about concepts and definitions, so we defined, suicidal attempts were defined like this. We took the data and put it into that category using that definition.

Then, there are the measures that you use, the tools, to ask the questions to ascertain that information to be able to know whether that definition applies. So, we do have those measures and tools that aid in this classification that will hopefully inform all of the studies going forward, as you are pointing out.

So, the whole system really involves two elements, right, the tools in which people and clinicians and industry need to use to ask these

questions of these patients and families to find out whether or not, where they go in this classification scheme.

Does that clarify it somewhat?

DR. ROBINSON: Yes, but, for example, like in preparatory acts, you have preparatory acts where the person stops themselves versus somebody else stops themselves, and often from a clinical point of view, you know, it is like my child had the rope up and I saw them and I stopped them, as a clinician, that has a very different thing than somebody saying, well, I was going to do this, and I got the gun out, but then I told myself, no, that is wrong, and I went to my family.

Again, for going forward, you might make some refinements. I am just saying not necessarily have this set in stone, because this is obviously done for something that is sort of retrospective.

DR. POSNER: But what I am saying is we have an assessment tool, for example, where all of those questions, the clinician has those questions in front of them, so have you ever done anything to

hurt yourself where you wanted to die, have you ever started to do something and stopped yourself, and then they get that information with those definitions and the probes and the questions, and then they can then go and decide there was a preparatory behavior or there was a suicide attempt.

So, all of those distinctions and questions and helpful aids, we have certainly been working on and intend to hopefully distribute and even have guidelines and training days, so that people can start to use these in their studies.

I just wanted to add to two comments I heard about we have to look broader at more of the other symptoms that we are talking about and worrying about, like akathisia, agitation, and aggression.

The study that I keep talking about, for example, the Adolescent Suicide Attempter study, that is NIMH-sponsored, we are working very hard on measures and tools to look at all of these side effects that are associated possibly with SSRIs

including all of those things - how to ask the questions, how to collect it, so hopefully, we can have tools and we can also answer some of these related questions.

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: I would agree that the reclassification and analysis were both clinically and scientifically appropriate. I found them to be rigorous. I was impressed with the blinding procedures and would echo the thought for future randomized, controlled trials, in conjunction with the FDA, that there be some type of standardized classification that is mandated across all studies.

DR. GOODMAN: Thank you.

Dr. Irwin.

DR. IRWIN: I agree and I would just like to second what Dr. Chesney raised in terms of the issues of aggression and violent behavior. They don't seem to be a part of this instrument right now. Thanks.

DR. GOODMAN: Ms. Dokken.

MS. DOKKEN: I agree with the intent of

the previous comments.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: I do, too.

DR. GOODMAN: Dr. Wells.

DR. WELLS: I think we have done about as well as we can do with the reclassification and with the re-analysis. We recognize, of course, that the data aren't perfect, having largely to do with how they were elicited.

I don't think that there is very much more that we can do with the data, although there may be a little bit more. I recall that Dr. Mosholder, for instance, had recommended that we might want to do an analysis using inpatient hospitalization as a primary outcome and see what is picked up there.

We remain troubled by the inconsistencies across the studies, even for specific drugs, we don't understand what accounts for those inconsistencies, but I think at this point, we need to move forward and see if there is some decisions that we can make with the data that we have.

DR. GOODMAN: Thank you.

Dr. Pollock.

DR. POLLOCK: Yes, it's a question was there ever or is there any plan for this kind of patient level, at least to sample, because of the concerns about ascertainment in the adult studies, if there was any contemplation or has there been any probing at all of the quality of that data.

I mean we have some confidence in your overall conclusion, but we don't have confidence, or at least the public doesn't have confidence for some of those adult studies, what was actually recorded, and if it might be certainly in the public's interest to conduct at least a quality sampling using the same methodology in the adult studies.

DR. LAUGHREN: As I indicated yesterday, right now our focus is on the completed suicides that we have in this very large database, and we can consider this second issue, but I think right now we are going to try and finish up with looking at the completed suicide data.

DR. GOODMAN: Dr. O'Fallon.

DR. O'FALLON: I agree with what has been said by the rest of you, I am not going to argue with any of you, but I am still--I think there are a couple of issues here.

One of them is that I don't think that this re-analysis has done very much about looking at that question about the association between adverse events and dose changes. I think there may have been problems. At least I didn't see very much about that. Maybe I was missing it.

I think I am still very concerned about the possibility that we might be underestimating the incidence of these adverse events, the suicidal ones. I am afraid of it because if we get the answer wrong, we could have a very bad effect upon medical practice. That is always the issue here with doing research.

Obviously, there wasn't very much power to detect, I mean it's a rare event, thank God it's a rare event, suicidality, but there isn't a whole lot of power to pick it up under the best of circumstances even with the meta-analysis.

I think I have asked this question twice, and I think the FDA needs to address upfront the charges that I heard over and over again that the FDA doesn't have all the data, that somehow or another the companies are holding back data or suppressing it from you.

I think that is something that has to be made clear to the public. You have said no, if they put in an application, we get every shred of data they ever had even if it was 25 years old. But there is a perception out there that I think the FDA has to address.

DR. GOODMAN: I am not sure if those comments are germane to the question at hand. You may want to hold them for later.

DR. O'FALLON: Okay.

DR. GOODMAN: Dr. Santana.

DR. SANTANA: I also agree that clinically and scientifically, you have done the best that you can with the data that you have. I do want to move forward, though. I mean this classification system is an event-based, outcome system, but it really

doesn't get to the issue that I would have if I was a practicing physician in this area, which is, is this toxicity or is this lack of response, does that lead to that common outcome.

So, as you develop your new tools, your new questionnaires, whatever you are going to do to validate this classification and take it forward to new studies, I would want you to pay some attention to try to dissect how that common outcome is related to either toxicity or lack of response, because I think that would be important and would address some of the issues that the parents and families had, you know, that they were attributing it to toxicity, whereas, some of us may interpret that it actually was a lack of response.

DR. GOODMAN: Thank you very much.

Dr. Wang.

DR. WANG: I agree these were very strong process and results. I do have two small suggestions to bound the lingering questions we have about case ascertainment. The first is how many cases may have been missed by the sponsor's

screen and never sent, and for that, you might consider an audit of what was not sent, you know, a sample of that.

The second is the potential ascertainment bias due to this unblinding by side effects, and you could check for this by seeing whether an adverse event known to be unrelated to antidepressants was elevated in the antidepressant versus placebo arms. It would just at least give us a sense of the potential magnitude of either of these two problems.

DR. GOODMAN: Dr. Gorman.

DR. GORMAN: I would like to echo the generally positive comments about the reclassification as being helpful to especially myself to understand the data, and that would then lead to a compliment to the Office of Drug Safety both at the global level and the individual level for recognizing the signal through all the noise when the data was not classified in a way to make it as clear to them as it is now to us.

The ascertainment of the cases, I think

would make the signal stronger in general. I think all the errors we are worried about, in general, about how much information has been presented in the narrative, might, in fact, make the signal stronger and therefore, while I recommend to the FDA as a comment to this that I hope this classification system becomes generalized across all your therapeutic areas, that the active ascertainment for suspected or serious adverse events in all classes become active and done in a way that allows us to not be arguing whether we have got as much of the signal as there is to get.

DR. GOODMAN: Thank you.

Dr. Maldonado.

DR. MALDONADO: I just have a couple of questions, but I agree with the general consensus, and the questions are based on these tools that have been developed. As you know, the tools are as good as the ones who use the tools. It is still not very clear to me who is going to be the end user of the tool.

I actually congratulate Dr. Iyasu for

doing the reproducibility and reliability within the FDA. I am glad to see that the FDA is doing its own studies, too. And then who are going to be the end users, is it going to be the medical officers on DDP who are going to be doing this classification, or is it going to be the requesters from the sponsors, or even primary investigators?

The more you spread that, the more variability you have to expect, and then the study that Dr. Iyasu did might not be relevant depending on the user.

The other thing, maybe Dr. Posner can tell us, where the publications for the validity of these questionnaires and classifications are, because again these tools are so dependent on their validity. I am not in this field, so they may be published and people know, but I have never seen them, or maybe if they are not published, are they going to be published, so people know the validity of these two tools.

I am not just referring to a classification, but also to the questionnaires that

you mentioned.

Thank you.

DR. GOODMAN: Dr. Mehta.

DR. MEHTA: I think the FDA has done a great job of classifying data with very poor case of confirming information. I would go one step further, and that is, request FDA to design a case that could confirm suicidality and also together with a set of instructions, and give it out to every sponsor from now on, because I suspect that this issue we will be revisiting 10 years from now.

I think Dr. Gorman and Dr. Posner also commented essentially the same thing.

DR. GOODMAN: Are you going to give the references?

DR. POSNER: No, I was just going to reiterate that we have commented many times that we are going to write guidelines just to do that for industry and everybody else.

DR. GOODMAN: We can't hear you.

DR. POSNER: I was just reiterating again that we, in collaboration with the FDA, are going

to write guidelines for better ascertainment. I think we should also have training meetings. We discussed this yesterday. Whatever we can do to make this consistent across everybody who is going to be doing this kind of work.

DR. LAUGHREN: Right, and that applies to both the classification and the ascertainment.

DR. POSNER: Right.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: A classification scheme like that is presumably what a company would do, probably with a special group set aside to do it in a blinded way, to evaluate the data they have got.

One other observation I want to make is that one of the ways we try to focus on things that are important is to look closely at all the people who leave a study prematurely in association with an adverse reaction, and the narratives associated with that are one of the things medical reviewers look at most closely.

We also get a fair sample of dropouts that were said to be for administrative reasons to see

if underlying those there is actually an adverse reaction, because sometimes you want to check those things.

So, that is one of the ways you go looking for things you don't know enough to expect, see what happened in those people.

DR. GOODMAN: Thank you.

I want to conclude our discussion. You can take a seat. Thank you.

There, you have our comments. I think it is pretty straightforward. There was a great deal of agreement that you can't imagine a better job being done given the starting point.

Naturally led to discussion about what to do in the future, and I think there are some excellent suggestions there, not only for the FDA, but the field in general in terms of improving our ability to detect, ascertain suicidality and perhaps other symptoms that might be relevant and help us sort out whether we are dealing, as was said before, with toxicity versus an indication of ineffectiveness.

So, I think that in the future, hopefully, we will be ascertaining and classifying these data in a prospective fashion, and obviously, a lot of the details need to be worked out about who will be doing what part of that job.

With that, we should head to lunch, return at 1:00 p.m. to tackle the remaining questions. A reminder, once again, this should be ingrained. Do not discuss meeting questions during the lunch.

Thank you.

[Whereupon, at 12:02 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.

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

[1:00 p.m.]

DR. GOODMAN: Would everyone take your seats.

First, a housekeeping matter. Anuja Patel will be passing around a sign-up sheet, so that we can know if you need a taxi and at what time. I assume you want that returned to you, Anuja, after it has made its way around the table.

We are now entertaining the second question before us. It is presented there up on the screen. I will read it.

Do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients?

Now, what I would like to do is first have a discussion of the question, give you an opportunity to ask any further questions of individuals from the FDA who presented yesterday that have bearing on this question.

Then, we will, following that discussion,

go around and ask for your votes. You choices are Yes, No, or Abstain, and you are permitted to have 30 seconds, not much more, to explain the rationale for your vote.

So, first, we are going to have a discussion. This will be the opportunity to see if we can extract any additional information. I also wish to point out that there are four members of the committee at the table who are non-voting members. We welcome them to participate in the discussion phase, but obviously, will not be participating once the vote commences.

Their names are Dr. Mehta, Dr. Maldonado, Dr. Gorman, and Dr. Wang.

In posing this question, I had a few comments, and maybe a question to the FDA in terms of clarification.

First, I had mentioned earlier that there is some lack of clarity about the definition of suicidality. In fact, as we can see on the other screen, although there is quite clarity there, you can set the brackets either narrowly or broadly in

terms of what we mean by suicidality.

For the most part, in the analysis that was presented yesterday, the definition of suicidality corresponded to Outcome 3, which included evidence of suicide attempt, preparatory actions or suicidal ideation.

So, I think before we take a vote on that question, there should be some discussion and maybe some guidance from the FDA, as well, is which definition of suicidality are we adopting for the purpose of that vote.

Second, I wanted to note that if we are basing the information exclusively on the clinical trials, as stated explicitly in the question, we have no instances of suicide, so we would not be concluding anything about suicide, only the risks of suicidality, not completed suicide.

My feeling is--again, I pose this to the FDA--we cannot ignore the other information we heard from the public testimony about cases of completed suicide, and obviously, those are not from the trial, yet we can in some ways extrapolate

from the ideation and behaviors in the trials to the risk of completed suicide that perhaps would exist in the absence of a carefully controlled environment, such as is the case in a clinical trial.

So, maybe I could start by posing the two questions to the FDA. One has to do with which definition of suicidality should we be entertaining, and, secondly, should we limit this answer to what we know from the clinical trials.

DR. LAUGHREN: Our intent was that you focus on Outcome 3. That was our primary endpoint in the trials, so that is what we intended by suicidality. I think for the purposes of this question, we would like you to focus on the clinical trials.

I mean you can subsequently address data from other sources, but we are primarily interested with regard to this question on the clinical trials. I agree with you that it applies to suicidality, not completed suicide, because obviously, there weren't any completed suicides in

these trials.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: The difficulty in dealing with the question of completed suicides is that while, unquestionably, some of the cases reported sound pretty interesting and persuasive on the point, you have no idea how persuasive the decrease in suicide that other people alleged, how large that is.

So, how to say whether there is a net benefit or harm on completed suicides certainly is unclear to me. Those data are very hard to analyze quantitatively. That is not the same as saying that some people don't seem to get worse when they are on these drugs, but some people seem to get better also. So, how to put that in numbers that addresses that question, increasing, say, the risk of suicide, that seems very hard to do.

DR. LAUGHREN: I guess another qualification here is that obviously, this is a very small window in time that we are looking at. These are short-term trials. I think it has to be

focused on that window in time for which we have data. I mean in my view, that is really the question.

DR. GOODMAN: Other comments from the committee?

Dr. Nelson.

DR. NELSON: The question I had, let me just be clear, because I think might have been answered by your response, because the way the question is framed doesn't say anything about the timing of the suicidality and some of the discussions of early versus late, and questions of late decreases, et cetera.

So, by restricting the answer to this question to the data at hand, the way I would interpret it is it is to speak directly to the early possible increase in signal that is seen, not to the broader questions, which then would come in to play perhaps in tackling Question 4, where the risk-benefit becomes an issue.

So, I state that as a comment, I guess, in order to make sure that I am interpreting what you

have said correctly, because I was going to ask about how this would be focused on the early versus late kind of issue that has been part of this discussion.

DR. GOODMAN: Dr. Ebert.

DR. EBERT: Just another clarification for my purposes, and when we talk about this, I am assuming we are talking about an increasing risk compared with placebo as opposed to an absolute increase in risk, because obviously, that would also take into account the potential efficacy of the drug.

So, in fact, we might be, if the drug is efficacious, seeing a net reduction in suicidality, but we are talking here about comparing it with a placebo.

DR. GOODMAN: I would agree with that interpretation.

Dr. Irwin.

DR. IRWIN: Is there a word suicidality?

DR. GOODMAN: Every time I write it in Word, it gets red underlined.

DR. IRWIN: It seems to me, I mean to me, I am not certain anyone really knows what it is that we are saying and what you are voting on, or, to me, I would like to know what suicidality is.

DR. GOODMAN: I don't think it is in an Oxford Dictionary either.

MS. GRIFFITH: It is not in Webster's.

DR. IRWIN: In a sense, it confounds things by, you know, the front page of the paper today, I think may lead to kind of a misrepresentation.

DR. POLLOCK: Can't we just use the explicit language?

DR. GOODMAN: That is, in part, what I would favor, is that if we use it, I think we need to at least parenthetically define what we mean when we are answering the question.

Dr. Temple.

DR. TEMPLE: Yes, that is what we do. I think that is what we actually did in labeling. Whether we should coin a new word is debatable, obviously, but it means suicidal behavior plus

suicidal ideation. That is what we use it to mean as those items.

DR. GOODMAN: Would it be fair for us to slightly modify the question, or do we have to take it as it is, because what I would say, if we could use the definition that corresponds to Outcome 3, I would feel most comfortable, because that corresponds to the reclassification and the way you approach the dataset.

So, suicidality, suicide attempt, preparatory action/or suicidal ideation.

DR. KATZ: Yes, you can certain amend the question. We called it suicidal behavior and ideation, but it is clearly what is embodied in Codes 1, 2, and 6.

DR. GOODMAN: I think we have a clarification on that and hopefully, the public will understand what we mean, too, and that, I think we will leave it to the press to do their job in trying to best define what we mean and don't mean by that term, specifically, that we are not talking about actual completed suicide if we are

restricting our deliberations to the clinical trials, because there weren't any instances.

Dr. Perrin.

DR. PERRIN: I would like to ask a related question to help me understand how to approach this vote, which is really not the analysis, but the trials themselves and some I think fairly brief questions.

My understanding from reading the reviews in Dr. Dubitsky's presentation yesterday, and from Dr. Hammad's review, that these are very diverse populations in these trials, only variably well described, so we don't really know what percentage of these young people actually had major depressive disorders even in the MDD trials.

We know very little about comorbid or co-existing conditions in them. Although they describe what the inclusion/exclusion criteria are, we know relatively little about the concomitant treatments for them.

Again, as I read the descriptions, they are a lot of drugs that they might have been on

were excluded, on the other hand, about three-quarters of all the samples were on some concomitant treatment of some sort or other.

So, I take it, if I am reading this right, a very diverse, hard to consider similar populations across the multiple trials, which might be the explanation for why nefazodone had absolutely no events in 450 subjects.

I am really asking the question, am I right in this reading, and, if so, because that would help me understand more about the strength of the signal given incredibly diverse samples.

DR. GOODMAN: Perhaps Dr. Dubitsky, is he here, could answer that.

DR. DUBITSKY: I am not quite sure how to even begin. It is a very complex question, and it is very relevant. The diagnostic criteria did span anywhere from DSM-III up to DSM-IV, including DSM-IIIR, but beyond that, I think as I alluded to yesterday, you know, some studies did use more extensive diagnostic screening procedures, and it is to me very unclear as to what role that may have

played in creating some diversity among the trials.

I think you mentioned the issue of concomitant treatments, and it is true that most of the patients did receive some kind of treatment, be it something as simple as aspirin or another antidepressant during the trial.

I think, in general, the treatment with concomitant antidepressants other than the study drug was fairly rare, but you can go on from there, because you do have antipsychotics and all kinds of other non-psychotropic medications, non-psychiatric medications that do have psychotropic effects, and it becomes very, very complex trying to sort that out in terms of what the medication was, what the actual psychotropic effect was, what the timing was, how that may have influenced the outcome of interest.

So, I don't have a good answer for that.

DR. GOODMAN: I think there were some differences you pointed out and the degree of structured interviews that were conducted, so that may account for some heterogeneity.

I think even if the criteria were uniform, the inclusion/exclusion criteria were uniform across the studies, which they weren't, I do think there is a great deal of heterogeneity, which has to do with the limits of our ability to characterize major depression in children.

DR. PERRIN: In that context, I think it is also, we have heard the real difficulties in distinguishing major depression and bipolar disorder in these populations.

I guess the point that I think you are supporting is very diverse populations, nonetheless, a very persistent signal despite very different populations.

DR. DUBITSKY: I think it is quite possible that the population was very heterogeneous. Again, to what extent that is actually the fact, I don't really know, but there is a distinct possibility.

DR. GOODMAN: Thank you.

I want it to be clear and make sure that we all agree at this point and understand that as

we answer this question, we are restricting our data to the clinical trials. I think that is the intention of the FDA. I think that is reasonable as long as we understand which question we are asking.

We are not asking the broader question based upon other data that has been brought to our attention, strictly what can be gleaned from the clinical trial data.

But I will entertain any discussion of that point.

MS. BRONSTEIN: As I listened to the reports on the studies and also listened to the public testimony, I think some of the public testimony really highlights the necessity to look carefully at the trials.

The public is asking us very succinctly to warn them, and I think we have done some since last February, and I think we need to even do more in the way of maybe even informed consent and using family members as partners even more than we have in the past.

But I want to harken on what Nami talked about a little bit yesterday and some of the clinicians that spoke. I am most concerned about access for children to all of the kinds of things that are available even with the known risks.

I guess, as somebody who is very concerned about the consumer, I really want to focus on what the signal is in terms of giving warning, not necessarily restriction.

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: I certainly agree with, for example, the next question focusing on the clinical trials, that really is a clinical trial question of what we know from the current data.

I think when we get to broader questions, for example, should these antidepressants be contraindicated in children, I think it is almost impossible to address that question without bringing in a broader database beyond the current clinical trial.

DR. GOODMAN: I think that is a fair statement.

I want to make sure before we try to answer the question that we are clear about the question. I think we are at this point.

Any further clarification needed?

[No response.]

DR. GOODMAN: Dr. Newman, I think you wanted to add a little bit to our dataset. I will give you an opportunity to do that.

DR. NEWMAN: I made a slide during lunch. If I could have the pointer, too. When the FDA staff presented the results of the pooled analysis of the clinical trials, what they presented were the relative risks and the 95 percent confidence intervals, and although if you have a lot of practice, you can look at those confidence intervals and see what the p-value is, that does take some mental arithmetic.

It is kind of hard to do those logs in your head. So, these are the four risk ratios. They are all about two, meaning that people who were assigned to SSRI treatment in these trials had about double the risk of these suicidality events,

and these are the lower and the upper 95 percent confidence intervals, and the p-value is sort of the measure of the strength of the signal meaning how, if SSRIs did not cause suicidality, how often would you see a signal this strong or stronger.

Just to show you that my little spreadsheet way of doing it works for the people who know some statistics, if the 95 percent confidence interval just exactly hits 1, the lower limit, then, that means the p-value is 0.05, which it is here or reasonably close.

You can see that the p-value, that is the chance of observing a signal this strong or stronger, the highest one is about 0.04, and this one here, which is the lowest p-value, because the sample size is the biggest, because we are looking at the possible events, as well as the definite ones. This is Outcome 4, and in all the trials, not just the MDD trials, is about 5 in 100,000, so this is a signal strength that would occur by chance about 1 in 20,000 times.

I think this is important because many of

the concerns that have been expressed by members of the committee would be to a loss of power, they would lead to we are not capturing all the suicides, we are not sure that all we have is suicidality, and heterogeneity, and maybe they didn't even have the right disease and sloppiness, all of those would tend to make the p-value higher.

So, I actually think the way the question is phrased, which is does it support the conclusion is actually a little bit weak. I think we could phrase the question, it would be much stronger about the data.

DR. GOODMAN: Thank you.

Dr. Nelson.

DR. NELSON: Thank you for doing that, but I got the impression yesterday when you suggested that, that a little statistical skirmish broke out, so I am interested in hearing from the other statisticians around the table just what they think of this approach.

DR. NEWMAN: Actually, I talked to Dr. Hammad ahead of time. Did you want to comment?

Okay. If the other statisticians would like to look at this, or I could open up the spreadsheet and show them, but I really, I don't view this as controversial. If there are people that do, then, I would like to hear from them.

DR. GOODMAN: Dr. Gibbons.

DR. GIBBONS: The computation is based on the fact that these are asymptotic confidence intervals, that is, you are assuming large sample theory and assuming normality of the risk ratio, and that is how Dr. Hammad did the computation, so the probability values fall directly out of it.

Of course, it makes sense that when you are right on the boundary of 1, the probability should be 0.05 or close to it based on the 95 percent confidence of the asymptotic normal limit.

So, these p-values are reasonable, but be careful about p-values. One of the reasons why people use confidence intervals is to describe an effect size, and a very small difference in an effect size in a large sample will give you a probability value that is very, very tiny.

So, don't interpret the difference between 0.05 and 5 times 10 -5 as being a huge difference in effect size, but at the same time, if you are worried about things like multiple comparisons, like, hey, they went out and did a bunch of tests and some of these are probably happening by chance alone, you look at a value of 10 -5, you can do an awful lot of comparisons.

We are all born with a fixed number of degrees of freedom, and if you use them up too quickly, you die a painful death, but that protects you pretty well.

DR. GOODMAN: Thank you very much. That is the best explanation I have heard of that yet. Thank you.

Other committee members? Dr. Katz.

DR. KATZ: I just want to comment on the last comment. It is true, I suppose, that 5 times 10 -4 or 10-5 protects you against a lot of multiple comparisons, but 0.04, which is the p-value, the normal p-value for Outcome 3 for SSRIs and MDD, and we haven't yet gotten to the point to which a

population should any conclusion apply, but the 0.04, in the face of lots of multiple comparisons perhaps is a different kettle of fish.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Tom, maybe a follow-up. As far as the p-values go, if I humbly understand it, you know, worrying about Type 1 error, we are worrying about calling something different when it is not, but I think the problem is the other way.

I mean I am more concerned of missing something that is there. I am more concerned about Type 2 error, and is there any light to be shed on that, or are we just comfortable enough that we have got a signal, we keep the signal, or is there some way we can infer if we are missing a signal?

DR. NEWMAN: The Type 2 error refers to that you have failed to find something which is really there, and I would submit that these p-values are very, very low, and so we have found it, and it is there. When the p-value is 5 times 10 -5, power is not the issue at all. You had abundant, abundant power to find that because you

found it with such a very, very high level of statistical significance.

DR. GOODMAN: Is there any more data that people feel they need to see before answering this question? Again, the data from the clinical trials, not research you would like to see conducted.

Dr. Pine.

DR. PINE: Just two brief comments, one related to what you just asked and another related to the other issue, and it relates to a conclusion that Dr. Laughren gave when he was summarizing his kind of directions to the committee, and that is the idea that one might use a different statistical threshold when making conclusions about safety as opposed to when making conclusions about efficacy, so while 0.05 has become kind of a magical number for whatever reason, that is usually in the discussions about efficacy, and I just wondered if he would, you know, comment if his statements really apply to this exact situation.

DR. LAUGHREN: My interpretation of the

regulations is that we don't need the same level of certainty, so I think it applies directly here.

DR. PINE: Then, the only other comment I would make, and this might affect the question or it might not, and it relates to your statement about other data from other trials.

As far as I know, there are no other randomized, controlled trials of SSRIs in pediatric depression. There are other trials of pediatric anxiety disorders, and, you know, discussing them for safety right now, I know is not really the issue before the committee, but I think that there has been a hint from the analyses that have been done that perhaps the signal, so to speak, is particularly strong in children who are suffering from major depressive disorder.

I would just think it would be important, if we were to go beyond major depressive disorder, to be sure to look at trials that have not been discussed, that are federally-funded trials in particular as opposed to industry-sponsored trials.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: The analyses that Dr. Hammad presented include all of the trials we know about including trials that are not in major depressive disorder, only 15 of them, or one more with TADS, and the signal, as the previous slide showed, actually looked slightly stronger when you add the trials that are not in major depressive disorder.

What that means, I have no idea, but that is how the numbers sort of come out.

DR. GOODMAN: Basically, I want to echo that. Maybe I should clarify this point. As I understand this question, it applies to all the clinical trials, not just the major depression ones.

Although the numbers were admittedly small for some of the other anxiety disorders, like OCD, they were very small numbers, but when you aggregate the data, it adds to the evidence of suicidality.

DR. TEMPLE: One of the things the committee could think about is whether some of those trials are more germane to this question than

others. The main analyses Dr. Hammad did included them all.

For one thing, there is a lot of overlap in these things, and maybe the people have more than one disease, but that was the primary analysis, and there are, of course, more data, more numbers, more trials, so you have somewhat more information on those than you do on the others. Those are all good questions.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: I just wondered if before you bring this to a vote, if it is possible to rewrite this, so that we are absolutely clear what we are voting on, and it is not only--my concern is not only that you define suicidality, but also this may to some members appear redundant, but pediatric, as well, that we actually talk about clinical trials between ages of, you know, we fixed that, because the way the warning came out, at least into the field and into practice, in the last few months, was all patients, that there is a risk of increased suicidality sort of across the age

spectrum, and this caused a little bit of consternation.

While it is important that the efforts towards monitoring and that people be alert in all ages, where we have the evidence and where we are specifically voting, I think today is about the evidence base that we have in those specific trials conducted between certain ages, and that is where the data is.

I would just again feel better if we could just frame this question very explicitly, so it is not subject to distortion.

DR. GOODMAN: I certainly agree that we should further reference what is meant by "these trials" in the question. Perhaps this list that was supplied by Dr. Dubitsky covers it, but let me make sure that we are voting on the right set of trials, are they the ones that are listed here? I am interested in a little bit of guidance about how to properly reference the studies.

DR. TEMPLE: It is clearly the trials we have presented to you. They are all pediatric

trials. If you feel that you have to say that in there, go ahead and say it, but we will understand it.

Those are the trials you are talking about, and the database relates to suicidality in pediatric patients, however, the warning you are referring to was quite deliberately not intended to apply only to pediatric patients, because it didn't have anything to do with whether there is an increased risk of suicidality. That was considered good advice for any person getting these drugs. You should know that sometimes people get worse and you should monitor them closely.

So, you might want to comment on that, but that was our intent.

DR. POLLOCK: It was conflated with this stuff.

DR. TEMPLE: No doubt.

DR. GOODMAN: Any other data you want to see, or discussion, before bringing it to a vote? Dr. Laughren.

DR. LAUGHREN: Just again for

clarification, Question 2 is intended to follow Question 1. Question 1 clearly states that it's the 23 plus 1, 24 trials.

DR. GOODMAN: I apologize, I wasn't paying attention.

DR. LAUGHREN: I am just pointing out that Question 2 is intended to follow directly from Discussion Point 1, which focuses on the 24 trials for which we have presented data.

DR. GOODMAN: So, you know what we are referring to, we now know what we are referring to, so I think we are okay.

Ms. Griffith.

MS. GRIFFITH: But will the public know what we are referring to, and when this is extracted for the press, it better be as clear as it can possibly be. Also, if I could just reference your web site, you need to have something very directly speaking to this and outlining it in detail on the web site ASAP.

DR. GOODMAN: Further discussion before we bring it to a vote?

Dr. Pfeffer.

DR. PFEFFER: Yes, I would agree with what you just said in the sense that the question almost alludes to a generalizability, and I am not yet sure, given the discussions we had this morning, that we are fully ready to have very generalizable statements about the last part of the question, suicidality in pediatric patients.

I think we have some datasets now, and we have discussed how much they have potential problems, but this is the existing data that we currently have. So, as of today, this is our knowledge base, so to speak, and we feel from what we said this morning that we need more information ultimately and gathered in different ways.

So, I am not sure we can say this is a generalizable issue yet. So, that is the caveat I would like to address.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I am not sure what the reference to generalizability is. This question refers to the 23 plus 1 trials and to the evidence

that they do or don't provide about the risk of suicidality, defined properly, in pediatric patients who were the subject of those trials.

We don't think those trials have any reference for adults. We don't know about the risk of actual suicides, it is a fairly narrow question because those are the new data we got. Those are the result of the pediatric trials, and the question is have they told us something.

DR. GOODMAN: I understand.

Dr. Pfeffer.

DR. PFEFFER: I guess what I am trying to say is that what I mean by generalizability, I am not talking about other ages, but specifically, I don't yet think that it clarifies all pediatric patients would be at risk.

DR. GOODMAN: I don't think that is the implication of the question.

DR. PFEFFER: I am talking about the general public.

DR. GOODMAN: It means in the trials that were listed and presented to us.

DR. TEMPLE: And there could be differences among patients in the trials. That is true for every effectiveness trial that has ever been done. You don't know as much as you would like to. It's in the pediatric patients that were in these studies, not all pediatric patients.

DR. GOODMAN: Tana.

DR. GRADY-WELIKY: I just wanted to comment that the amount of discussion we are having about what the question means or doesn't mean is important to at least acknowledge and, you know, we are a group of experts in this area, so when it comes to the public, I think the fact that we are struggling with it is needed to be commented on, and I would agree with Dr. Pollock that I would like to see the final version of the question before voting.

DR. GOODMAN: Dr. Katz.

DR. KATZ: I just want to get back to this question of generalizability, because we do clearly want to be able to say something at the end of the day about whether or not these results apply to any

identifiable population of pediatric patients.

If you were to conclude that, yes, the data show that there is an increased risk of suicidality in these specific particular pediatric patients who enrolled, but we can say nothing about, for example, pediatric patients with MDD, in general, or patients with psychiatric disorders, that would be quite problematic.

Generally speaking, we do take control trial data and we convince ourselves that the results apply to some relevant population that was not studied in the trials. If all our conclusions only applied to people in trials, we wouldn't have very much to say about drugs.

So, there is a question we are asking. You can take this stepwise if you like, but we will ultimately want to know whether or not you think that these data demonstrate that there is a risk of suicidal behaviors or suicidality, as defined, in some identifiable population who in the future or who are currently being treated with the drug or drugs.

DR. GOODMAN: I don't think the main text of the question needs to be changed, but I do say that it needs to be footnoted, so that what I would suggest is that the statement--the question we are answering reads as follows:

Do the suicide data from these trials--and we should put Footnote 1--as listed in--what shall we call this, Dr. Dubitsky? Appendix A, presented by Dr. Dubitsky? Somebody give me another way of describing that.

DR. TEMPLE: You could refer to it as the 23 plus 1 trials referred to in Question 1.

DR. GOODMAN: Okay, that is fine with me.

So, the 23 plus 1 trials referred to in Question 1. Somebody is bound to ask me which 23 plus 1 trials those are, and those are in Appendix A listed, provided by Dr. Dubitsky. We are getting like lawyers here.

DR. MARANGELL: All available randomized control trials in pediatrics involving antidepressants.

DR. GOODMAN: I think we are beating a

dead horse, frankly. I think we all know at this point what we are voting on, and hopefully, when it gets translated somewhere that the press and others will be attentive to exactly the appropriate references.

Any other discussion? I want to get off the question and on to information relevant to arriving at an answer.

Any other discussion that we need to have before you are prepared to make your vote?

If not, I am going to start, not with myself this time, I am going to start from that end of the room from my first voting member, Dr. Santana, and then I am going to remind you--yes, it's you--yes, no, you can abstain, but obviously we would encourage you to be definitive with a yes or a no, and up to 30 seconds in comment although that is not necessary, a simple yes or no would be sufficient, and we are going to be recording your vote.

DR. SANTANA: That is why I am here. My vote is yes, and I have no further comment.

DR. GOODMAN: Dr. O'Fallon.

DR. O'FALLON: I am going to abstain. I am looking at this data, and I don't see that clear signal that everybody sees.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: Yes.

DR. GOODMAN: Dr. Wells.

DR. WELLS: Yes.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: I would vote yes and I would even say that I think this particular question is weakly phrased to say support the conclusion, and I would also vote yes if it said do the suicidality data from these trials prove beyond a reasonable doubt--

DR. GOODMAN: Now, we are really becoming lawyers.

DR. NEWMAN: -- increase the risk of suicidality, because I really think it is definitively shown.

DR. GOODMAN: Ms. Dokken.

MS. DOKKEN: Yes.

DR. GOODMAN: Dr. Irwin.

DR. IRWIN: Yes.

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: Yes.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: Yes.

DR. LESLIE: Yes.

DR. GOODMAN: That was Dr. Leslie.

Gail Griffith.

MS. GRIFFITH: Yes, and I was convinced by the signal exposed in the TADS data.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Yes.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: Yes.

DR. GOODMAN: Dr. Goodman, yes.

Dr. Rudorfer.

DR. RUDORFER: No. May I take my 30 seconds, please?

DR. GOODMAN: Yes, please.

DR. RUDORFER: In my opinion, most of the trials we reviewed were scientifically flawed.

None were designed to address the question of suicidality. What they were designed and powered to address, namely, efficacy, most failed to do in the major depressive studies.

I believe that we saw evidence of many suicidal-related events, however, to assign causality, I think that was not shown. I think that, as we have discussed, to show a differentiation between active drug and placebo, I don't believe that the studies were properly designed to do so, and we have no other corroboration that the ascertainment of events was equivalent, and the question of switch into mania and akathisia, and whether those adverse events and complications could, in fact, have resulted in or coded as suicidal events, I think remains a real possibility, and we simply don't have the data to disprove that.

DR. GOODMAN: Jean Bronstein.

MS. BRONSTEIN: Yes.

DR. GOODMAN: Dr. Pine.

DR. PINE: Yes.

DR. GOODMAN: Dr. Gibbons.

DR. GIBBONS: Yes with a brief statement. I think the effects are very small. I think they are consistent across the studies, but no more so than the actual data show in the simplest of views. The rate of these events, Outcome No. 3 is about double in the drug arms relative to the placebo arm, and most of the analyses tend to corroborate that.

Nevertheless, looking across these studies, looking at the TADS studies, looking at the naturalistic studies, we see a preponderance of evidence in favor of rejecting the null hypothesis of no difference.

I would not be totally surprised, though, that in further analysis, we might find some confounding factor, such as initial suicidal ideation that might be biased across these studies. Nevertheless, these are randomized studies, and randomization is a very important tool, hard to ignore.

Thank you.

DR. GOODMAN: Dr. Ebert.

DR. EBERT: Yes, with a footnote that we are looking at the data collectively as a whole.

DR. GOODMAN: Dr. Grady-Weliky.

DR. GRADY-WELIKY: I also say yes with a brief statement that yes to the question as revised with the appropriate footnotes and definition of suicidality as suicidal behavior and/or ideation, and I would agree with Dr. Gibbons' eloquent comments about the fact that it seems to be a minimal risk, but something that we should agree to.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: Yes, and I feel that the data are really quite compelling given the incredibly diverse, relatively poor studies, and that we find a strong signal arising despite the inadequacy of the studies is very compelling to me.

DR. GOODMAN: Thank you.

Dr. Nelson.

DR. NELSON: Yes.

DR. GOODMAN: Dr. Malone.

DR. MALONE: Yes, although I would like to add the caveat that I think if you look at some of the data we saw, that, in general, both drug and placebo had a decrease in suicidality over the course of the trials.

DR. GOODMAN: Dr. Ortiz.

DR. ORTIZ: Yes.

DR. GOODMAN: Dr. Fost.

DR. FOST: Yes.

DR. GOODMAN: Dr. Pfeffer.

DR. PFEFFER: Yes.

DR. GOODMAN: Dr. Fant.

DR. FANT: Yes.

DR. GOODMAN: Anuja is going to tally the votes.

You don't get to vote, Dr. Temple.

DR. TEMPLE: I don't want to vote, but I would like to ask a question.

DR. GOODMAN: Let me give the tally first.

A total of 27 voting. 25 Yes. 1 No. 1 Abstention.

Dr. Temple.

DR. TEMPLE: The committee obviously finds these data quite convincing. I was just curious about Dr. Rudorfer's reservation.

Do I understand that you think there may have been an ascertainment bias, that certain clues might make people more inclined to call this in the treated group than the other group, is that the nature of it?

DR. RUDORFER: That is part of it. In terms of ascertainment, as I was mentioning at the end of this morning, there was no systematic way of collecting these data. We have no idea what questions were asked in which study.

It seems to me plausible that a placebo-treated patient, who was not volunteering, say, somatic or other complaints, might be subjected to less interrogation beyond the rating scales than someone, for instance, who came in complaining of GI side effects or other SSRI typical side effects, and I was concerned about the blind there.

My other larger reservation is that I

thought we can't have it both ways. Either we think that these drugs are effective or they are not, and if they are effective, then, we are looking at a collection of studies which, for the most part, are showing a lack of efficacy, and I thought that is not the appropriate context in which to evaluate the adverse effects, especially one which we know is integral to the illness under study.

For instance, if we were looking at, say, a cardiovascular measure where the illness date wouldn't necessarily be relevant, I would be less concerned.

DR. TEMPLE: The TADS study, of course, showed both effectiveness and an increase. That is just one study, though.

DR. RUDORFER: I agree with you, on one hand, yes, it is just one study. The other is that TADS is specifically designed as an effectiveness study, meaning very few exclusion criteria, with the aim of following upon, but not replacing, efficacy trials, and I am concerned that we really

don't have a collection of good efficacy trials to evaluate.

DR. GOODMAN: Because of the overwhelming affirmative vote to the last question, we don't get to skip the next one.

Let me turn to Question No. 3 and read that.

If the answer to the previous question is yes, to which of these nine drugs does this increased risk of suicidality apply? Please discuss, for example, whether the increased risk applies to all antidepressants, only certain classes of antidepressants, or only certain antidepressants.

Dr. Katz, do you want to clarify?

DR. KATZ: Yes, I do. The other grouping, which we haven't explicitly described in this question, would be what indications, as well.

DR. GOODMAN: I was going to add that. I agree that I think that the other possibilities would be the sorted or quarantine indication.

In terms of how to approach this, this is

a little bit more data intensive. In order to come with an affirmative answer to the last one, you only had to be convinced that the association was true for one of the drugs. Now, we need to I think have some reference and I wonder again if the handout from Dr. Dubitsky would be appropriate to make sure you all have handy as we take a look at individual compounds and trials.

Again, I think this is going to be a little bit more labor intensive.

Dr. Nelson.

DR. NELSON: It would just be helpful for me to clarify the intent behind No. 3/4, because one way of answering 3, when you get down to small numbers in single trials, is to make a pragmatic decision that you should then apply the grouped data to individual drugs rather than just a database decision that, in fact, you have enough evidence, because I think we are going to take a big group divided up into many small groups, and the answer may be no, no, no, no for a number of drugs where you would still decide that you would

want to have a class risk assessment.

So, it would be helpful. I guess I am concerned that we don't get to the real question, which is what to do, if we just spend time on nine different drugs and three different indications.

DR. GOODMAN: I think that is a good point. I also think there is a statistical question embedded in it, in that I think it is easier to answer in the aggregate, because that is where we still have the stronger significance, but if I am not mistaken, when you get down to individual drugs or individual trials, although the numbers may be higher, the relative risks may be higher in the drug versus placebo group, it doesn't reach the levels of statistical significance.

So, I would also like to have some input from our statisticians on how we should approach the individual trials or studies.

Dr. Katz first.

DR. KATZ: I just want to reiterate that that is exactly what we are asking. We are asking about the individual drugs. We want to know, the

numbers are small, the estimates are variable, none of them really, for the most part, are statistically significant on their own, but you have already heard two sponsors with different drugs.

One said everybody ought to get the same label. One said the labels ought to be drug-specific. So, we anticipated that outcome by asking the question as we did.

DR. TEMPLE: We are asking for your best interpretation of the data. We already know each of the drugs is different, each of them can't be considered statistically significant, but in the face of that, given the whole data, what do you think the best interpretation is.

DR. GOODMAN: I think, generally, when I hear a class, I am thinking chemical class rather than particularly how they are used. There is certainly a great deal of similarity among the SSRIs in terms of they all share high affinity for the serotonin transporter.

When you get to the different

antidepressants, there is some variability. Some have direct interactions with the serotonin receptor, some do not, but then some experts in the mechanism of action of antidepressants might argue it doesn't matter what their acute receptor binding profiles look like.

It has to do with what changes they induce in the nervous system during chronic administration, and some would argue that a commonality or changes in serotonin system is independent of the beginning.

So, I think we could get very much bogged down on exactly what we mean by chemical class, so perhaps, I think we are going to have to do it by individual drug and maybe by indication, but I would be open to other suggestions.

Dr. Pine.

DR. PINE: I guess I have a couple thoughts, two main ones. Looking at the known effects on brain neurochemistry of all the medications that we have before us, one of them is definitely a bit of an outlier in that Wellbutrin,

by most accounts, has clearly different chemical effects than all the others, and I think that is the only strong point I would make in that regard, number one.

Number two, I think a number of people, both yesterday and today, said the following, which I would agree with both from the FDA and also on the committee, that I think a lot of people had a reasonable sense that fluoxetine was the one medication for a lot of reasons that, you know, might not have this effect, and yet we see the data from the TADS trial that suggests that might be the case.

So, to the extent that you are really going to force us to say anything specific about any medication, at least me personally, my feeling was that the only feeling that one might have had coming into the meeting was that the outlier, besides Wellbutrin, would be fluoxetine, and I think at least with respect to fluoxetine, the data from the TADS trial, you know, takes that away at least from my opinion.

DR. GOODMAN: Well, maybe this raises also a question. We said that we were going to focus on the clinical trials. Does that mean we should not include the data from the TADS study? That's the Plus 1. You were right, Tana, we should have been very explicit. That's the Plus 1. I was forgetting that that was the Plus 1.

Dr. Fant.

DR. FANT: You spoke to the question in terms of defining what do we mean by class and how to address the drug issues, because, you know, one looks at Wellbutrin, but if it was an SSRI, I might be inclined to be biased in a direction of safety to sort of lump it in with the others, and look at it as a class effect, but I am not sure if I am willing to sort of roll that in without any input from anyone else to tell me that that's off base with the effects that we are seeing with Effexor.

DR. POLLOCK: Right, exactly, and going the other way, Remeron is clearly not an SSRI also, and we have data on that.

DR. GOODMAN: You have to wait until you

get called, because I have got other people waiting here.

DR. POLLOCK: I am sorry.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: I think we, in approaching this question, need to be clear. Are we answering this question as an interpretation of data issue where you could simply take out the slides that were provided and look at confidence intervals, much as what we did as opposed to do we think regardless of the data, we should apply a class label for warning against suicidality, however that is defined, which is really Question 4.

In answering this question, I think we just need to be clear that it is an interpretation of data. Even if I said that the data doesn't support it for one drug, I may still support a class warning. In the interests of efficiency, I think we just need to run to get to the real question, which is what to then do.

DR. FANT: Again, how are you defining class, are you defining class as "antidepressant"

or chemical class?

DR. NELSON: All of the drugs we have been talking about. I mean I am not a psychiatrist, so all of the SSRIs.

DR. FANT: The reason I asked that is because, like the Chair, I mean when I think of class, I think of class based on mechanism of action as opposed to therapeutic.

DR. NELSON: Correct. Simplistically, I think of class when I go into Hippocrates or My Palm, and it says SSRIs and has a name next to it. That is how I think of class.

DR. GOODMAN: But there is overlap. The point I was trying to make is that there is some overlap.

Certainly, there are some differences and that the SNRIs, like venlafaxine, also have potent effects on the norepinephrine system, but they share, they overlap, at least at some dosages, have high affinity for the serotonin receptor, or we don't understand exactly how bupropion works.

What I was alluding to also is their acute

properties may not be as relevant as what their impact is on the adaptation of the nervous system during chronic administration, so there may be some independence between the initial effects and the ultimate final pathway of the effect, because obviously, the nervous system is functionally coupled. These are not distinct systems for the most part.

Dr. Marangell.

DR. MARANGELL: I think all those comments are quite valid. I imagine that many people group SSRIs together and will probably want a class statement of SSRI Yes/No, antidepressants Yes/No, and then whether or not you want to break out SNRIs and Remeron and Wellbutrin as others.

DR. GOODMAN: I would be comfortable with that approach.

Dr. Perrin.

DR. PERRIN: I would encourage that approach. It seems to me, looking at the data, that the ones that raise questions to us--to me, I am sorry--are Wellbutrin and the nefazodone data

where there are basically no events.

You might argue that these are really different drugs in that context, but my sense is the Wellbutrin one, probably simply because this is only kids with ADHD, and there are no kids with depression in that population, at least to the degree we can define it, we can't define it very well. There certainly could have been some kids with co-existing depression.

The nefazodone, I would like to have us understand more about it. That is why I have asked about it, but my guess is it is also a population-based finding that has nothing to do with the drug, because there were no events in the placebo group either.

DR. GOODMAN: Dr. Gibbons.

DR. GIBBONS: I think that really this ends up being a statistical issue. Dr. Hammad has shown very clearly that these studies, even combined within drug classes, are insufficient to have reasonable power of rejecting the null hypothesis for even a fairly major effect. You

know, we are out at about a risk ratio of about 4 to have reasonable power, and so I really don't think that we have the data to be able to make drug-specific statements, period.

Now, if the committee wants to make statements that there is clear heterogeneity among the effects across drugs, and even point to those drugs that show less of a signal than others, that seems totally reasonable to do, but to use these limited data for a particular drug to make an informed decision about whether or not this already small signal has anything to do with one drug, but not another drug, I think is reaching beyond the available data.

DR. GOODMAN: Dr. Malone.

DR. MALONE: Yes, I agree that we have to look at all the drugs, and I think if you look at, say, the difference between the TADS study and the other studies, I think the other studies were not set up to look at suicidality very specifically, but my impression was that the TADS study did look at it more systematically.

When it was looked at more systematically, you came up with a finding in fluoxetine that you didn't have in the less systematic studies. So, missing a signal or having a lower signal might really just be ascertainment, and I think for that reason, you have to look at it as a class.

DR. GOODMAN: Could somebody remind me, in the analysis of SSRIs alone in major depression, did that reach the level of statistical significance for showing elevated risk level?

Could you please come to the microphone, Dr. Hammad.

DR. HAMMAD: Yes, it did. I can get you the actual number. Yes, the overall risk for SSRI/MDD, it was 1.66, and the confidence interval was 1.02, the lower limit, and the upper limit is 2.68.

DR. GOODMAN: So, that included fluoxetine, paroxetine, sertraline. What am I missing? It wouldn't be venlafaxine, it's SSRI, right? Citalopram, I am sorry, citalopram.

Let me go back to Dr. Gibbons for a

moment. Given that, assuming we were just voting, not voting, but we were just commenting on a class of SSRIs in major depression, would you be comfortable drawing a conclusion based upon the data we have?

DR. GIBBONS: I think you can make the statement within this class, you have reached statistical significance, but I don't think you have the data to make the statement that among the other drugs you don't have statistical significance. So, that's the rub.

Again, I think in all of this, you have to explain as clearly as possible what are the limitations of the data, so that you are not misinterpreted as saying there isn't an effect or there is an effect.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: I was taught 20 years ago when we were in the tricyclic era that when you initiate treatment of depression, there is an increased risk of suicidality, and I think since the SSRIs don't cause cardiac arrest when you

overdose, everybody forgot that need, and that is one big problem.

As many other people have said, I think we don't have the data based on these small, miserable studies to say that they are safe.

The last thing that I thought of, we had a strong argument yesterday for differential labeling, and I think companies go to great lengths once things are marketed to show an advantage of their drug over their competitors, and there are always pretty much sham studies that are set up, so drug reps go around that can say one is better than the other.

I don't want to let the wolf into the henhouse by letting any company say that since my drug hasn't been shown to cause suicidality, there is an advantage to it compared to that other drug over there. I think that would be a terrible, terrible mistake.

DR. GOODMAN: Dr. Fost.

DR. FOST: Just a point of order. I am not clear whether we are discussing Question 3 or

Question 4, and I want to second Skip Nelson's suggestion that we focus on Question 4, because if there is agreement on that, then, I don't think there would be much value in going through it drug by drug, condition by condition, unless somebody wants to subtract--

DR. GOODMAN: You may be right. Let's all take a moment to look at that.

I think the heart of the next question is what recommendations we are making. Isn't that really the thrust of No. 4, is the regulatory recommendations.

DR. KATZ: Yes, I think including, more or less, some specific recommendation. We don't need exact language, but, in general, what concepts ought to be conveyed in labeling, and then, of course, any additional regulatory actions besides just changing labeling are on the table.

DR. GOODMAN: I still think we need to answer Question No. 3.

DR. TEMPLE: I think you are having the right discussion about 3. Three is asking you, in

the face of limited data, what is the best interpretation of these results. We already know you don't have enough data on Effexor or any individual drug, we knew that, and if that was the question, we wouldn't have asked you.

The question is in the face of these limitations, what is the best interpretation, and I think you are having a good discussion of that question.

DR. KATZ: But for our purposes, it is useful if you are going to say something like, well, we believe the findings generalize to all the drugs, it would be useful to have some comment on, for example, some of the drugs that have no events. It would be useful to consider why you think those should be included, as well.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: I guess as a summary position, I certainly don't see any reason to question the data that has been put before us, and I would probably just follow the confidence intervals as a fair neophyte.

So, I have to defer those to my psychiatric colleagues about the other drugs without events and how those may or may not be included. That is really an issue that I wouldn't be able to address, but I think if we are going to just follow the confidence intervals, like most of us did last time, we should just sort of say that and then move on.

DR. GOODMAN: Could I ask Dr. Hammad or Dr. Laughren, which of the medications were free of a signal, just remind us?

DR. LAUGHREN: Do you have my slides from this morning? Slide 8 shows that there were no events in the Serzone, the two Serzone trials. These were trials in major depression. There were no events in the Wellbutrin, the one Wellbutrin trial, which was an ADHD trial.

DR. GOODMAN: Dr. Gorman.

DR. GORMAN: As one of the least sophisticated statisticians around the table, I harken back, as someone else did, to their early training. I once asked a statistician what to do

with a zero numerator, and they said whenever you see a zero numerator, you can always write a 3 in there, because mathematically, it works out that way. Don't ask me for the mathematical proof, I am sure someone here can do it for me.

So, even in the small trials, when there is a zero numerator, I think we can do some interpretations. I will bring the reference for the next committee meeting.

DR. GOODMAN: There are special circumstances surrounding the Serzone trial that could explain it besides the drug itself. Are there any that could explain that outcome?

Dr. Malone.

DR. MALONE: I think we have already talked about these studies not being designed to look at suicide, so ascertainment could have been different in that study than any other study, and lack of ascertainment could be the reason they have no events. It is really hard to know.

DR. GOODMAN: And the Wellbutrin study was in ADD, wasn't it?

DR. MALONE: Yes, and I don't think in ADHD, I am a child psychiatrist, I am not sure that suicidality becomes a clinical focus, so in the visits, it may not have been asked about as much, or even paid attention to as much. I am not surprised that in the Wellbutrin you didn't have any events.

DR. GOODMAN: Dr. O'Fallon.

DR. O'FALLON: I looked in the back of this book. We didn't see all those follow-up slides, but I looked at them last night, and they are rather useful. On page 35, the diagram, for SSRIs, as a class in the MDD trials, and those are the four, and you take a look in here, and it comes up with the right confidence interval down at the bottom.

But you can take a look and see that the confidence interval for the whole class just barely clears 1, so we are looking at a 0.05 level here. Actually, the verification using the other modeling doesn't quite even--it kind of takes away from that a little bit.

DR. GIBBONS: I believe the random effect in this case a little more than the fixed effects.

DR. O'FALLON: So, that puts the 0.05 up a bit, like 0.052, or something like that, but at any rate, you can take a look at that. It does show you where your signal is in the SSRI trials in MDD.

If you look on the next page, at the top, there is a similar diagram for I believe it's the SSRIs in the other indications, and you can see the signal there. That signal fails to be significant in suicide, and that is on the key endpoint that you were talking about, 1, 2, and 6 as the endpoint. Does that help?

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: A couple of points in response to recent comments. One is what is different about Serzone. Perhaps it's not the methodology. I mean you could hypothesize that mechanistically, Serzone has a 5HT2 antagonist which has been at least theoretically associated with a decreased early agitation and early anxiety realm of side effects, but pragmatically speaking,

the manufacturer has stopped producing that drug because of other issues.

So, in terms of the use of our time, it might be of academic interest, but I am not sure it is going to make a clinical difference to the people that we are trying to help.

The other point is that one of the things I think the TADS trial very clearly indicates is if we had the same discussion prior to that single, relatively small, but very helpful study, we would have said fluoxetine looks like it doesn't have a signal.

So, the point is that one very small group of patients can dramatically alter these numbers that we are talking about. So, I think to finally dissect them at the level of whether there is or is not a statistically significant signal with these very small numbers is likely to lead us in the wrong direction.

The public and the FDA want something about SSRIs versus all antidepressants, if you just look at statistical significance of that, you could

probably pick any four of these drugs at random and come up with something similar, I mean since you have drugs that have a signal and don't within that same class.

DR. GOODMAN: As it has been discussed, in fact, this led to at least one of the abstentions, and also some of the other comments, is that even in aggregate, there are limitations in these data. When you break it down to the individual drug, the numbers get vanishingly small.

It would seem to me, my sense at this point, it would be premature to identify a particular drug that should be exempted from this warning, the reason being, in part, that if we were to exempt one, it would conceivably have the unintended consequence of steering traffic in that direction prior to us having sufficient knowledge about the true risk, and we may inadvertently then learn that there was a risk there at our next meeting.

So, I think given the statistical concerns, the small numbers, and my own clinical

impressions, that for the most part, when I have seen at least--thank God I haven't seen suicide--but I have seen suicidal behavior, suicidal ideation, I have seen the activation syndrome, for the most part, I have seen it with most, I am not saying all, but with most of the antidepressants, and I have not seen it limited to major depression.

I have seen it in the treatment of children with OCD, and there is, in fact, evidence of that in these trials, that it occurred in the OCD patients, as well, with fluvoxamine, although the numbers were very small.

So, unless I think there is a very good reason for us to do it, I think we are best off talking about the class, not on a chemical basis, but as antidepressants used in the pediatric population.

But you can take shots at that position now, but that is where I am leaning.

Dr. Pfeffer.

DR. PFEFFER: I would agree with that, and

I would just like to highlight again, on the blue pages that we have, two issues that I would like to highlight.

First, many of the studies did not exclude a family history of bipolar disorder, and I think that is an important design issue that we need to keep in mind in even considering comparing, first of all. In relation to Serzone, to be specific, interestingly, they did exclude a family history, but they also excluded history of a suicide attempt.

So, there may be other issues besides the chemistry, as you are saying, but could be confounding this. When you put everything together as a class, I think that is an interesting and important issue, because it may say to practicing clinicians, be wary of the SSRIs in general, but there may be specific populations, then, that they need to identify, for example, family history.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: Also, even mechanistically, mirtazapine also has a 5HT2 blocking effect, and it

is clearly in our group, and I am concerned about the sloppiness of saying SSRIs, because practitioners will say, you know, in a telegraphic fashion, that, well, does that mean since I know that mirtazapine and Effexor are not SSRIs, that that might be safer.

So, I just second your idea that if we are going to do it, then, I think on the basis of the available evidence, I would rather not see it as, quotes "SSRIs," unless you are entirely explicit about the other couple of drugs, or if you just say antidepressants, my preference is for the class in that terms rather than trying to make it mechanistic.

DR. GOODMAN: Dr. Ortiz.

DR. ORTIZ: My comment is that I also agree that I think we don't have enough information to say that particularly the bupropion is safe and that we should stick to antidepressants. I am wondering if we are not moving into kind of research design recommendations, and if we shouldn't at this point. It seems like we have

talked enough about 3 and 4 to vote on them.

DR. GOODMAN: Just procedurally, I am not sure we need to take a vote on this. We haven't been asked to take a vote on it, but I am open to discussion.

Dr. Katz.

DR. KATZ: I think it would be useful to have a vote. I mean the sentiment, at least the few people who have expressed one explicitly, seems to be that this signal should be considered to apply to all of the drugs, for all of the indications.

But I think it would be very useful for us to actually get a vote on that particular proposal.

DR. GOODMAN: Would you like to pose the question, Dr. Katz?

DR. KATZ: Well, I think I sort of did.

DR. GOODMAN: We need to hear it again. See if you can do it again.

DR. KATZ: I will see if I can do it under pressure now.

DR. GOODMAN: We will give you a few minutes.

DR. KATZ: Should the signal of increased risk apply to all drugs studied or all antidepressants including all indications studied, words to that effect.

DR. TEMPLE: You actually proposed it. I don't remember your exact words, but probably someone does. I think you said something like the best interpretation of these data is that it should be applied to all drugs used for pediatric depression and other conditions.

DR. GOODMAN: All antidepressants.

DR. TEMPLE: All antidepressants when used for all of these conditions, not that we know that to be true obviously.

DR. GOODMAN: Psychiatric conditions. We have heard I think some examples from the open public forum where it was used for non-psychiatric. It may be when used in the pediatric population for all indications, and, of course, there are very few indications.

DR. TEMPLE: All the studies were for indications pretty much that the drugs have.

DR. GOODMAN: Okay. So, we will limit it to the indications that are under study, all the indications, psychiatric indications.

Would somebody put that question together for me?

In the meantime, Dr. Marangell, as we try to draft it.

DR. MARANGELL: I was going to try and draft it for you.

DR. GOODMAN: Please.

DR. MARANGELL: I move that we vote that the committee's opinion is that the increased suicidality, as previously defined, pertains to the use of the nine antidepressants listed for all indications studied to date.

DR. GOODMAN: I like that.

DR. McGOUGH: Can I ask a question? I don't want to lose sight of other drugs approved for depression. There are tricyclic antidepressants, there are MAOIs, and I think part

of the decision is do we include all those, as well, and is this a general recommendation for any drug that is indicated for depression.

DR. PINE: Can I make a comment, too, about both of those comments?

DR. GOODMAN: Dr. Pine, go ahead.

DR. PINE: I would feel more comfortable, and again maybe nobody agrees with this, but I would be interested in your thoughts, if you made the statement more of a negative, since I think it more accurately reflects the data.

In other words, none of the agents should be excluded from this warning, because I feel more comfortable and can confidently make that statement, whereas, when you make the statement that it applies to all, you know, particularly agents where there is no event, I am kind of left--

DR. GOODMAN: I think that is the corollary, but I think it would be hard to translate the corollary into practice.

DR. PINE: The first statement was something about a warning that we just voted on

already, Question No. 2, and then the second one was no agent should be excluded from this warning--

DR. GOODMAN: Let me return to Dr. McGough's comment for a moment in terms of whether we should be expanding our considerations to tricyclics and MAOIs. I don't think we can because if we look at the history of this process today, we are focusing on the clinical trials, although I would agree with you that based upon clinical experience, one would suspect similar kinds of problems with tricyclics.

In fact, we saw that in one of the studies based upon the British sample showed no significant difference in relative risk between dothiepin, which is a tricyclic.

DR. McGOUGH: I think there are actually other reasons in addition not to use those other classes, and I don't even think they are used very commonly.

DR. GOODMAN: Because of cardiovascular concerns, yes. I hear your point from a clinical standpoint, but I think based upon the data under

consideration, I would agree with Dr. Marangell's rendering of the question.

Other comments? Dr. Newman.

DR. NEWMAN: I like the phrasing except that I wouldn't restrict it to when the drugs are used for the indications for which they were studied, because we heard of one girl who got one of these drugs for migraines, and I would just say when given to pediatric patients, and not restrict it to the indication studies, because, you know, also, people are getting it for sleep.

So, I would just make it very broad, when given to children, they can increase suicidality.

DR. GOODMAN: I have to agree with that.

Dr. Gorman.

DR. GORMAN: Agree.

DR. GOODMAN: Dr. Gorman, you agree also?

DR. GORMAN: Agree.

DR. GOODMAN: Tom.

DR. LAUGHREN: Just a thought. Clearly, when you are moving from Questions 1 through 2 through 3, going from 1 to 2, clearly the focus is

on the 24 trials that we looked at. I think as you move towards 3 and 4, I personally don't see any problem.

I mean if you have reached a conclusion that you can expand this claim to the antidepressant class, in other words, you are willing to ignore findings of no events for certain trials, I don't think it is so unreasonable to consider expanding it to the whole class, and here is my reasoning for that.

I think there is a great risk in steering clinicians back to using the tricyclics as an alternative to a safe group of drugs, which all of us know are not, so it is just something to think about.

DR. GOODMAN: Dr. Marangell, could you restate that question now including all antidepressants in the pediatric population, could you try it?

DR. MARANGELL: I can try. I move that the committee adopt the position that antidepressant agents, when given to pediatric

patients, defined 7 to 17 years old, increases the risk of suicidality as previously--no?

DR. GOODMAN: Let her finish and we will get back to the age range.

DR. MARANGELL: I move that the committee consensus is that the risk of suicidality, as previously defined, applies to all antidepressants when used in pediatric patients.

DR. GOODMAN: I like that. Was there a desire to not qualify what we mean by pediatric, or to qualify differently?

Dr. Leslie.

DR. LESLIE: I just feel that 7 to 17 is not a good direction to go in.

DR. GOODMAN: So, it is sufficient to say pediatric?

DR. LESLIE: And I just wanted to add the other reason I would say that this is important to say broadly is we have got Cimbalta and other things coming out, and you don't want someone saying, well, Cimbalta doesn't have this warning, so you ought to use it instead of Luvox, et cetera.

DR. GOODMAN: Did anybody transcribe that? I am comfortable with the statement. They are on it. We are about to project it.

Dr. Katz.

DR. KATZ: I would just like to hear a little bit more discussion about applying the warning, whatever it is that we apply, at least applying the result to non-psychiatric indications.

We don't have any trial data in that population. We have reports of individual cases, and clearly they are used for other things, but I would just like a little more discussion or hear what people think about extending it to all possible indications for which these drugs might be used.

DR. GOODMAN: Once Tom gave us some freedom to not confine ourselves to the clinical trials, I think led us to consideration of all antidepressants and all possible indications, but, sure.

Dr. Nelson.

DR. NELSON: In looking, for example, at

the current labeling, I think the restriction to major depressive disorder is potentially falsely reassuring, and it would concern me if it was listed only for psychiatric conditions, that the same thing would happen with the off-label use in non-psychiatric conditions.

Even though there is no data suggesting that, by having a warning associated with the drug, and not with the condition, the way a clinician could possibly read this would be here, I am giving you this drug, but since you are not depressed, it is not going to happen in you, so therefore, it is safe, and we can't say that.

That is the way it would be read, so I think by not listing it to the drug, you open up that possible interpretation to a clinician, which, in the absence of evidence, I think would be a danger.

DR. GOODMAN: I agree completely, and I think, although we haven't discussed this at great length, and I don't know how many people would agree with this statement, but I think at least I

do, and I have heard some other mention the fact that our hypothesis of the mechanism here is some sort of behavior toxicity that may be compounded by an interaction with an underlying proclivity, such as bipolar diathesis.

It may have to do something about metabolism or drug levels. There are a number of other factors that can contribute, but once I saw the data in the OCD trials, although it is only a few cases, I began to think, and also based on my own experience, that this isn't strictly worsening of depression or ineffectiveness in treating depression, especially since in a number of the cases, it seems to happen so early in the course.

So, I would agree completely that I think, in part, our recommendations reflect a working hypothesis that what we are seeing, although a rare event, may represent behavioral toxicity that can occur in individuals other than those already diagnosed with depression.

We have the revised question up on the screen--no, we don't.

DR. TEMPLE: That is my revision, it is not exactly the same as others, and you don't have to take it.

DR. GOODMAN: We are going to have to change it.

Dr. Marangell, what do you think?

DR. MARANGELL: If you say the best interpretation of the results of the 23 plus 1, then, it would be the indication studied. If you say what is our, you know, kind of interpretation of where we go with those results, then, it is a little bit broader.

DR. GOODMAN: I would like to go with broader. I don't know if we can change it on there.

Other comments? Dr. Chesney.

DR. CHESNEY: When you introduced applying this principle to all antidepressants, this is a whole new ballpark for me, because I don't know anything about them, and we don't have any data, and maybe I misunderstood, but if I didn't misunderstand, could somebody explain to me why we

should extend whatever we decide about what we have heard about, to things that we have heard nothing about?

DR. GOODMAN: What is it that we haven't heard about?

DR. CHESNEY: All the other antidepressants. What I heard was that we extend this, not just to SSRIs, that we know about, but to all other antidepressants, and I don't know anything about them.

DR. GOODMAN: We have covered most of the field, but I would let others--

DR. MARANGELL: There are two areas of extension in regard to the revised Question 3. What I was actually just referring to was the extension to pediatric use or any use in pediatric patients as opposed to just the uses that were studied, and the rationale for that portion is, you know, clearly it is beyond major depression for those of us that think that there is a consistent signal, you see that also in some of the non-major depression indications, such as the OCD trials.

So, that is the reason to extend that, and then the feedback we got, that I heard from the rest of the committee was that even beyond those trials, there may be other indications, and we don't want to try and give the signal that it is limited to, you know, if a doc wants to use an agent for a pain condition, that we wouldn't expect to see it there.

In terms of other antidepressants, the tricyclics and the MAOIs are older agents, and my understanding is that they have never been studied in pediatric patients, so we have no data, is that correct?

DR. TEMPLE: It is not a bad idea to take those questions in sequence. First, think about the drugs that were studied and what is the best interpretation of them, and then, you know, we might approve a new antidepressant, and is it going to be the only one that doesn't bear that label? Do you like that idea? We will get to that.

DR. LAUGHREN: Actually, a clarification. Some of the older drugs have, in fact, been

studied, but FDA has not seen the data, they have never been submitted. There are at least 12 trials in tricyclic antidepressants in pediatric depression that I am aware of, but I don't know how well those patients were ascertained or suicidality, I know nothing about the safety in those trials.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Again, I think when you treat depression, there is an increased risk of suicide. Most of this is off-label, so to restrict it to indications is kind of an illogical event, that somebody would get Zoloft for insomnia is beyond anything I can understand.

So, I think really the purpose of this, I think is to really put physicians on notice that this group of medicines can cause these problems for whatever they think of. To be safe, I think we are really putting the physicians, you know, the real attempt is to inform them that they need to be concerned, they need to monitor for whatever they are using this for.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: One of the things that I took away from a lot of the public testimony yesterday was how much the people said they wanted to have known things before they got into a treatment.

I think one of the things that we have to deal with is that we do not know a lot about some of the other drugs, like the tricyclics, the MAOIs, we just don't have the information because they were done so long ago.

Now, I personally think that it would be a great tragedy if clinicians went from using SSRIs to tricyclics, which have a much lower overdose. You can kill yourself taking much, much fewer pills.

But I think we also have to be humble enough to say, you know, there are certain things we don't know. We don't know about the risks for tricyclics, we don't know about the risks of SSRIs used for these off-label non-psychiatric indications. We just don't know, and there is no

information.

In some ways, that is the most accurate thing to tell a prospective family thinking about these drugs, is we know for certain indications, it has an increased risk of suicide. For this stuff, we don't know, it might be a lot worse, it might be better, we just don't know, but take this into consideration.

DR. GOODMAN: Before I get to you, Dr. Temple, I actually don't think it is such a bad question. I think that by answering this question, it allows us to put Question 3 behind us, and then I think a lot of the discussion that we are having is then what should we recommend in terms of further regulatory action, and I think that is really getting it to Question 4.

Would that be a reasonable way of sorting out where we are right now, to try to maybe answer the one that is up there, and then we can talk about whether, in our recommendations in terms of further warnings, that maybe that issue should be expanded further, but this would be a good

transitional question, as I see it.

Dr. Temple.

DR. TEMPLE: There really are two parts. The first part in some ways is I think what most people have given their answer to that. The second part I just was writing quickly referred to tricyclics, but it is worth thinking a little bit here about whether the best interpretation is that it applies to some study, some new drug like we just approved one that hasn't been tested yet.

We are going to surely have to come to grips with that question, too, so it says tricyclics, it could have said MAO inhibitors, it could have said duloxetine.

That is the second question, but I think that follows the first.

DR. GOODMAN: I would like to take off after the second bullet for a moment. Unless there is further discussion, I would actually like to vote on that question that is up there.

Dr. O'Fallon.

DR. O'FALLON: Again, on page 34 of the

thing we got yesterday, there is a nice diagram that shows the relative risks and their confidence intervals for all of the nine drugs, all of the indications, and what you will see, when you look at it, is that every drug has at least one trial that shows an increased drug.

You can make the argument that there is some evidence for every single one of these.

DR. POLLOCK: If we are saying the nine drugs, it includes Wellbutrin, which isn't one of these.

DR. O'FALLON: Perhaps, but what I wanted to point is that every single one of these drugs has at least one, some more, that show an increased--okay, eight, whatever--it says all drugs.

DR. GOODMAN: Unless there is further discussion, I would like to put this to a vote. The reason, why do I want to answer this, because it is our job to try to answer the questions that were presented before us.

I think that if we don't answer this, it

is not clear from our last vote whether we were thinking of just one drug or many drugs. So, this is the natural sequence that we are making it clear by this that we are talking about in aggregate when we look at the data. We are not exempting any of the drugs for any of these pediatric indications.

So, I think we need to answer this question, and it should be put to a vote.

Yes.

DR. FANT: Just another way of phrasing that which may be more palatable. If things are just transposed a bit, to say is the best interpretation of the results of the 23 plus 1 trials, that none of the drugs examined can be excluded from the increased suicidality risks that has been shown da-da-da.

DR. GOODMAN: Let me ask a statistician and then a wordsmith. Any statistician want to weigh in on that?

DR. GIBBONS: I don't think you want to draw an inference beyond the data that you have.

DR. GOODMAN: So, are you supporting the

way it is currently phrased or suggesting it be different?

DR. GIBBONS: I am supporting the last statement.

DR. FANT: Basically, what it says is that the data--it is more difficult to say the data applies to all nine, and for me, it is easier to say that based on the data we can't exclude any of the drugs.

DR. GIBBONS: The non-exclusion, yes.

DR. GOODMAN: I would find that more palatable, too, I would agree.

Does somebody want to try that?

DR. NEWMAN: I will take a stab.

DR. GOODMAN: Okay, we are working on it. In the meantime, we will entertain other comments.

Dr. Newman.

DR. NEWMAN: I guess I will have to see it, but I am concerned that that does sound quite a bit weaker to say that we can't tell for sure that this drug doesn't cause suicide or suicidality. It is true, we need to apply this warning to the whole

class, but there is sort of a double negative there, and I think it would be clearer to say the warning applies to the whole class.

DR. GOODMAN: What I was suggesting before is that this isn't the warning per se. I think we can still construct the warning. I think it would be more along the lines of what Dr. Marangell had drafted earlier. This is just to answer the specific question to indicate that we are not talking about just one drug and then we can get beyond Question 3.

Lauren, do you have something?

DR. MARANGELL: The data in aggregate indicate an increased risk of suicidality. Although there is variability in the results, we are unable to conclude that any single agent is free from risk at this time.

DR. GOODMAN: That's good. Do you want to do that one more time? You may get the Chair of this committee soon, you know that.

DR. MARANGELL: No, thanks.

Okay. Data in aggregate indicate an

increased risk of suicidality as previously defined. Although there is variability in the results, we are unable to conclude that any single agent is free from risk at this time.

DR. GOODMAN: Give it a chance to be keyed in.

DR. TEMPLE: From our point of view, any of those are fine, because they point directly to what the next question is going to address, so it's okay.

DR. LAUGHREN: As long as it includes a mention--it would be better to see it in writing, but I didn't hear mention of pediatric patients in all indications.

DR. GOODMAN: We are working on it over here.

Tana.

DR. GRADY-WELIKY: Along those lines, I wanted a point of clarification about are we talking pediatric use indications or are we talking pediatric use?

DR. GOODMAN: We are talking about the

studies. We are back to talking about the studies. In a sense, this is the second part of the previous vote, and what we are indicating here is that are affirmative as already voted by the majority of the committee, indicates concern about all the drugs in aggregate or at least that we can't exempt any one of them individually. Otherwise, as left, the vote could look like we were just concerned about one of the drugs.

DR. MURPHY: You could just say the data in pediatric patients.

DR. GOODMAN: Dr. Irwin.

DR. IRWIN: I just wanted to be certain in terms of the definition of pediatrics, what do we include with that, because it can vary. Does FDA have a definition of that?

DR. MURPHY: Yes, we have a definition that allows you to be very flexible depending on the state and country from which your data is derived. Again, later, when we get to the warning, we can be more specific, but I think right now the phrase "pediatric data" would be sufficient.

DR. GOODMAN: Isn't the NIH definition up to 21?

DR. PINE: It matters what it is being applied for, less than 18 for some definitions, and less than 21 for others.

DR. MURPHY: Ours is not up to 21.

DR. GOODMAN: Yours is not up to 21?

DR. MURPHY: It is up to 18 in some guidances.

DR. GOODMAN: In these particular studies, were they all up to, but not exceeding, age 18?

DR. MURPHY: Yes, they were. Most of these studies included 17.

DR. GOODMAN: They included 17, but not 18?

DR. MURPHY: Is there an 18 in one of them?

DR. GOODMAN: I am sorry, I can't hear.

DR. MURPHY: I think they say to 18. That is where you get into argument.

DR. PERRIN: There were a couple of studies where a couple kids got in over age 18 by

mistake.

DR. HAMMAD: May I say something?

DR. GOODMAN: Yes, please.

DR. HAMMAD: I think I had 85 patients that were 18 years old out of 4,000, but I did have it up to 18.

DR. GOODMAN: Up to and including 18?

DR. HAMMAD: Exactly, including 18.

DR. IRWIN: The reason I asked that is because much of testimony we heard from the public, a lot of that was in young adults that were beyond their 18th birthday.

DR. GOODMAN: Again, that is for our next statement.

Ms. Griffith.

MS. GRIFFITH: I agree. I think that is problematic in that it varies from state to state. There are legal definitions of how long a parent can have control over a child in terms of what that child will not have to agree to by way of intervention.

So, I would even recommend we go up to 21

because, as of 18, in most of the states in the U.S., children no longer have to comply with pharmaceutical interventions, and I think a lot of people would dismiss the advice once a child turns 18, and it is not warranted.

DR. GOODMAN: Any further wordsmithing of the question? I am satisfied with it.

Dr. Newman.

DR. NEWMAN: I just think this phrasing is quite a bit weaker than it was before because when you say you can't conclude that an agent is free of risk, you can never ever conclude that any agent is free of risk, so this just doesn't say very much.

I would rather state it more affirmatively. Although there is variability in the results, we believe these results apply to all antidepressants in this class.

DR. GOODMAN: Before you change it, we need to have some other input on that.

DR. ORTIZ: This is not the warning. This is what we are going to vote on, and it seems like there is a lot of consensus that this is what we

can vote on.

DR. GOODMAN: Right.

Dr. Fant.

DR. FANT: If we put the comment in there "within this class," I am just concerned, you know, it is going to restrict it to say SSRIs, and the whole point of this is to include, you know, to be cognizant of potential risks in drugs that really, as poor as the data is with other drugs, there is even less data.

So, the increased risk, we can be as strong as we want in affirming that and emphasizing that, but I agree with the whole concept that no company can enroll 70 kids and say we didn't see anything, therefore, you guys ought to use us instead of the other guy. I think we should not facilitate that.

DR. GOODMAN: Dr. Katz.

DR. KATZ: A couple of things. First of all, I think you have to say something about what kind of agent we are talking about. I think if you said any single antidepressant agent, we would know

what you mean, which brings me to my second point, which is this is not language for labeling or anything else, as someone said. This is to guide us, to give us a sense of what you believe about which sorts of classes and indications the risk applies to.

I believe it is fair to say that if you vote on this question, and you add the word "antidepressant agent," we will know what you mean.

So, I don't know that we need much more extensive discussion on fine-tuning the question. We know what you are getting at, I believe, and if you vote on this with just the addition of the word "any single antidepressant agent," I think that would be perfectly fine for our purposes.

DR. GOODMAN: That is the change I would recommend, if we could just punch in that "any single antidepressant agent."

DR. MURPHY: Dr. Goodman, when you go around and each person votes again that 30-second statement, they can make it clear if they have a problem with the statement.

DR. GOODMAN: That is correct, and we are talking about the antidepressants that were in the trials.

DR. TEMPLE: That's correct. I thought that is what you were referring to.

DR. GOODMAN: That is what we were referring to.

DR. TEMPLE: So, we will have a second question either now or in the next one, it doesn't really matter about what to do with the drugs that weren't in the studies.

DR. GOODMAN: Right.

That is going to be the last comment before the vote.

Dr. Perrin.

DR. PERRIN: I am just wondering whether a slight variation on that issue of risk could be, and I can't quite have it in front of me now, that we are unable to conclude that any single antidepressant agent has particularly low risk of suicidality at this time. It might be a more accurate statement of where we are.

DR. GOODMAN: Is free of increased risk maybe. It is free of increased risk.

DR. TEMPLE: Fine. That is what that means. When say "free of risk," it means free of increased risk, otherwise, it has no meaning.

DR. GOODMAN: That's it. We are going to go for a vote, and if you have further comments including about the wording of the question, you can state them in the 30 seconds that I am going to allow to be included.

Let's start at the opposite end of the table this time, first, with Dr. Fant, could you indicate Yes/No.

We did not add increase because Dr. Temple said it was implied.

DR. FANT: Yes. No additional comments.

DR. PFEFFER: Yes. No other comments.

DR. FOST: Yes.

DR. ORTIZ: Yes.

DR. MALONE: Yes.

DR. NELSON: Yes.

DR. PERRIN: Yes.

DR. GRADY-WELIKY: Yes.

DR. GOODMAN: Wait, slow down. Let me do the name first. I think we are eager to cast a vote.

We have Fant Yes, Pfeffer Yes, Fost Yes, Ortiz Yes, Malone Yes, Nelson Yes, Perrin Yes, Grady-Weliky Yes.

Ebert.

DR. EBERT: Yes.

DR. GOODMAN: Gibbons.

DR. GIBBONS: Yes.

DR. GOODMAN: Pine.

DR. PINE: Yes.

DR. GOODMAN: Bronstein.

MS. BRONSTEIN: Yes.

DR. GOODMAN: Rudorfer.

DR. RUDORFER: Yes with a comment. First of all, I wonder if--I guess it's too late to go back, but--

DR. GOODMAN: You guessed right.

DR. RUDORFER: --if a clarification of the phrase "increased risk" would be helpful. Again, I

think we have agreed that an increased risk is likely to be small, and I wonder how that should be conveyed, because "increased" covers a fairly wide range.

The other thing, if I have a few seconds left, just to reiterate my concerns. I agree certainly with the spirit of this statement, that we have seen that signal across all the drugs.

My concern relates, if I may use an example, to the two citalopram studies we reviewed. An American study found efficacy in major depression in a pediatric sample, and found no suicidality signal.

The European study combined data from seven different countries, which I did not find methodologically attractive, found no efficacy compared to placebo, and did find a positive suicidality signal.

S-citalopram, we have no data on the related compound. So, again, my overarching concern remains the fact that I think this is very much still a work-in-progress.

Thank you.

DR. GOODMAN: Thank you.

Dr. Goodman, Yes.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: Yes with the understanding that this statement applies only to the SSRI agents that we have been discussing. It doesn't say SSRI anywhere.

DR. GOODMAN: Let me clarify. It applies to all the compounds that were studied in the trials, which includes several non-SSRIs. When you add the non-SSRIs, the hazard ratio gets bigger, for what that is worth.

DR. CHESNEY: In other words, we are including imipramine and--

DR. GOODMAN: No, no, just the ones that were involved in the clinical trials that we reviewed, that were part of Hammad re-analysis.

DR. CHESNEY: Which were the non-SSRIs?

DR. GOODMAN: Venlafaxine.

DR. CHESNEY: All right. The answer is Yes.

DR. GOODMAN: I am sorry. Let me re-ask your vote, Dr. Chesney, based upon that clarification.

DR. CHESNEY: Yes.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Yes.

DR. GOODMAN: Griffith.

MS. GRIFFITH: Yes.

DR. GOODMAN: Leslie.

DR. LESLIE: Yes.

DR. GOODMAN: Robinson.

DR. ROBINSON: Yes.

DR. GOODMAN: Marangell.

DR. MARANGELL: Yes.

DR. GOODMAN: Irwin.

DR. IRWIN: Yes.

DR. GOODMAN: Dokken.

MS. DOKKEN: Yes.

DR. GOODMAN: Newman.

DR. NEWMAN: Yes.

DR. GOODMAN: Wells.

DR. WELLS: Yes.

DR. GOODMAN: Pollock.

DR. POLLOCK: Yes.

DR. GOODMAN: O'Fallon.

DR. O'FALLON: Yes.

DR. GOODMAN: Santana.

DR. SANTANA: Yes.

DR. GOODMAN: It was unanimous this time. We had 27 respondents, all Yes.

Do people want a short break? Yes.

[Break.]

DR. GOODMAN: I think we have made a great deal of progress. We have two remaining questions.

As currently constructed, neither of those questions require a vote.

Dr. Katz.

DR. KATZ: Yes, it is very important for us to have you vote on an extension of the question you just voted on, which is whether or not this should apply to all other antidepressants or whether you simply want to limit whatever warning or whatever conclusion we draw to just the ones that were studied.

My understanding is that in this question, the one you voted on, you limited it to consideration of the drugs studied.

DR. GOODMAN: That is correct. Let's have a discussion and see if others around the table agree.

Dr. Gorman.

DR. GORMAN: For future drugs that are coming down the pike, the Food and Drug Administration, under the Pediatric Research Equity Act, has the ability to demand antidepressant studies in children prior to their release.

I don't think there can be any doubt after the numbers we heard today that they will be used in more than 50,000 patients and have the potential to give a significant therapeutic advance, because at this point, we only have one drug that is approved.

So, I think for drugs coming down the pike, I think there is the ability within the FDA to ask for that information, and since I am not a voting member of the committee, I will leave the

discussion about what to do with the previously approved drugs alone.

DR. GOODMAN: Dr. Wang.

DR. WANG: Yes. It seems if you exempt any drugs, new or otherwise, you set up this perverse incentive, particularly for the new drugs, to either do no studies or to do poorly conducted studies where they don't ascertain cases or underpower them, so I think to prevent that perverse incentive, you have to put the onus on them to show that they are the exception.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: While I might want to have a similar strategy across all antidepressants, I think it is really not appropriate for this committee to take a stand against antidepressants for which we have not reviewed the data.

I am very uncomfortable saying that we know much about them when we really haven't seen the data on them.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: Although agreeing with the

prior point, my concern would be the message that would be sent if you didn't apply this across all drugs, and my own preference would be to have a class risk warning and then any preferential treatment ought to be on the efficacy side, so that you then have drug-specific labeling under the efficacy component, which would then begin to differentiate, so that individuals can be informed about the risk-benefit ratio by looking and comparing those two sections, which would be one way to direct people appropriately as opposed to inappropriately.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: Just again, what we are talking about here is patient safety, and I think it is appropriate that we err on the side of being in favor of that, and even though we haven't reviewed data specifically, I think it is an unanswered question, and as such, I think it is appropriate to apply it generally to the class of antidepressant drugs.

DR. GOODMAN: Dr. Laughren.

DR. LAUGHREN: Just to clarify what we are planning to do with the general warning that we have already implemented for 10 newer generation antidepressants, we are planning on extending this. In fact, it has already been extended to some of the older drugs, some of the tricyclics.

Our plan is to extend it to all, and the question here is whether or not we should also, if we are thinking about adding new language to that warning, suggesting that we have now established causality, whether that new language should also apply to all antidepressants.

Again, I think this concern has been expressed by several members, that if you don't do that, you are, in effect, directing clinicians to use those older drugs.

DR. GOODMAN: Dr. Leslie.

DR. LESLIE: Again, my concern is not just the older drugs, but the newer drugs, because Cimbalta, which is coming out, is most comparable to Effexor, which had the highest relative risk, and I again would be very concerned with the

marketing directly to patients and the heavy marketing to clinicians, that it would be marketed as the only drug of this class without a label, and would thus again push clinicians in that direction.

DR. GOODMAN: Dr. Marangell, did you have a draft of the question that we were composing before, that represented more of a general warning? I don't think we keyed it in. I don't think it was saved.

I think where we are in the discussion, let me remind people, we are in Question 4, and we are talking about recommendations regarding additional regulatory actions.

Since the last meeting, warnings were issued about a group of symptoms that may be part of what some have labeled inactivation syndrome, that were proven to be precursors of suicidality.

So, I think, in part, the question before us is whether we want to extend that now to conclude that there is a suicidality risk. In the last warning that was issued, it said that there was no established connection between the

medications and suicidality, and we have obviously been deliberating and voting on that question.

We are really talking about what additional warnings need to be posed that go beyond the activation symptoms or syndrome that was defined previously.

Dr. Temple.

DR. TEMPLE: Whether you do it as part of Question 3 or part of Question 4, we unequivocally, as you have already indicated, need to know whether the warning, if it is modified, needs to be in the labeling for all antidepressants or just the ones that were in the study including tricyclics, MAO inhibitors, duloxetine, and so on.

So, I don't know whether that is a 3 question or a 4 question, but once you answer the question about any additional warning language, we have to know who you think that applies to.

DR. GOODMAN: Dr. Malone.

DR. MALONE: I think it applies to all of the drugs. Was it the Jick study that really didn't find any difference between the risk for

different classes of drugs. I think that is one reason to apply it to, say, the tricyclics which were included in that study.

Also, some of the older drugs, like the tricyclics and MAO inhibitors, are much more dangerous, so if you did become suicidal, you would actually have the drug with you, that you could use to commit suicide easily.

I agree that new drugs, as they come on the market, you wouldn't want to automatically give them this undue edge that they don't have this warning.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: I would just like to say that when I made my comment before the break, I wasn't thinking of all these other factors, and on reconsideration, I think that these are excellent points.

I think that the wording was correct that it is well recognized that suicide and suicidal behavior emerges during the early stages after treatment, and because we don't have the specific

studies that address this issue, it may be reasonable to assume that this would apply to all antidepressants at this point in time until proven otherwise.

Somebody made that point, put the onus on the company to show that they did not fall in that ballpark. So, whereas before the break, I was very alarmed that we were going to be asked to do some things we knew nothing about, I think I now understand the reasoning.

Thank you.

DR. GOODMAN: Thank you.

Dr. Pine.

DR. PINE: I think it is important to recognize, speaking again as a child psychiatrist, that there is a very legitimate concern about discouraging people, and physicians in particular, from moving away from the 23 plus 1, the agents that we have been discussing, to tricyclics antidepressants.

I think that, at least from my own perspective, I think we want to think kind of

ahead, and I think we do obviously based on what the FDA said, and based on other information, say something about the use of those agents.

Historically, there actually is a fair amount of data on those agents, although not nearly the amount of data as we have reviewed for SSRIs, and it is current standard of care in child psychiatry not to use those agents, and that is really based on two things.

That is based on, number one, the fact that a number of meta-analyses have shown that the agents are not effective over placebo, and there has not been a single study that demonstrated efficacy for a tricyclic antidepressant or an MAOI, number one.

Number two, there was a lot of concern in the 1990s about the cardiotoxicity of these agents in children, not only the cardiotoxicity in overdose, which I think there is little debate about, but even questions about cardiotoxicity when the agents were used appropriately in therapeutic doses.

So, I think, on the one hand, it is very important to say that it would not be good if physicians were to move from the newer agents to the older agents, on the one hand, on the other hand, probably the strongest thing we could say would not be to say, well, we don't know whether these drugs cause suicidality or not, the strongest thing we could say is that there are plenty of reasons to discourage this.

One of the might be that the agents are associated with suicidality like the SSRIs, however, the cardiotoxicity and the lack of efficacy data, I think are stronger reasons not to move that way.

DR. GOODMAN: Dr. Gibbons, did you have another question or comment?

DR. GIBBONS: This is a very tricky issue. The issue is we don't want to go beyond the data that we have, but on the other hand, with the exception of one of these agents, we haven't shown any adverse effects on a drug-by-drug basis.

Now, a new drug comes out on the market.

Given current regulatory practices, there will not be enough data to show a risk ratio of 1.5 in that drug, so the conclusion will be that there is no association, and they may get an exemption.

On the other hand, you know, so what you are doing is you are holding a much higher standard to the drugs that were looked at in these 21 studies, for which we were able to pool over drugs and show an effect.

I suppose you could set up a situation in which a new drug or an old drug that was not part of the 21 could, in fact, be removed from the list if the study was powered, if there was enough data, so that they could, in fact, identify a risk ratio in the magnitude that we are looking at here, in the 1.5 range or so, but they would have to get a hell of a lot of patients to do it. It might not even be practical to do that.

So, it is really a conundrum of what to do.

DR. GOODMAN: Dr. Fant.

DR. FANT: To address the question that

was posed about extending to other drugs, I think based on the data that we have looked at here, at least from what I have seen it is impossible to tell if the endpoints that we saw, if the signals that we saw were due to drug-specific effects or if they were due to factors intrinsic to the disease process in the patient that was perturbed by treatment by whatever mechanism.

It is kind of hard to sort out which is the major factor in that regard. Until that can be sorted out, until you have some information that suggests, on a mechanistic basis, that it is related to a drug-specific effect, I don't think you can exclude any drug that impacts on depression.

DR. GOODMAN: Take a moment and look at the question or the statement, not a question, but the statement as it is proposed.

DR. TEMPLE: Is that intended to be labeling language?

DR. GOODMAN: My understanding is that it is not our job to write the labeling language for

the FDA. That is one of the reasons I wasn't sure that we needed to take a vote, because I don't think that we should be writing these for you, but I think it does help to have something in writing here to communicate to the FDA how broad our concerns are.

Dr. Temple.

DR. TEMPLE: So, is this your proposal?

DR. GOODMAN: Two committee members have proposed this.

DR. TEMPLE: My initial response to that is it doesn't really say that you should assume this risk applies to all drugs. It says you should use caution in pediatric patients. Well, we have sort of said that already. It doesn't quite say you should worry about that risk in pediatric patients.

We can work on it, too, but we are interested in some view of how explicit we really should try to be even if you don't write the exact words. That one is not so explicit perhaps.

DR. MARANGELL: I think we are just trying

to put forward, kind of the broadening concept of including both prior agents and future agents that are categorized as antidepressants and where to go from there.

DR. GOODMAN: Dr. Katz.

DR. KATZ: Fine. I think we certainly get the thrust of that, we appreciate it. One question that I think we would like you to explicitly address is whether or not you think this is the sort of thing that belongs in a black box, which is sort of another level of communicating risk.

Right now it is a warning, the major language is in the warning--the language is another section--but the major language is in the Warning Section. Do you think this arises to the level of a black box warning?

DR. GOODMAN: Let me ask Dr. Nelson to comment.

DR. NELSON: Let me comment on that, and then just make a comment on the language of the second sentence. I think the difficulty with a black box warning, at least my interpretation, and

maybe it is based on my practice, is if I see a black box warning, I just don't do it, for example, propofol for long-term sedation in pediatric ICUs, no longer done because of the warning.

So, I think a black box warning may drive people away from drugs that they might otherwise appropriately use as opposed to a warning that is placed upfront in the Warning Section.

My difficulty with this language, and I know we are not going to talk language, but I would try to be more specific. I mean one of the more difficult things to communicate, I think even to physicians, is risk data, and I kind of liked the slide that we were provided, that could even in this case, communicate data where you could have something like out of 100 patients treated, 2 to 3 patients on average will have an increase in suicidal behavior or ideation after initiation or changes in treatment, period.

So, people say, well, what does this really mean, it means that if they give 100 people the drug, they have got to watch out 2 or 3 times.

That, to me, is useful information, and I would advocate labeling that provides that kind of information.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I am just trying to interpret the last statement, which is that we should give some quantitative estimate of what the nature of the risk is.

DR. NELSON: Well, it is more than that, because I think it is an issue of percentage. I mean there is a lot of literature on whether risk is best communicated as numbers out of 100 versus percentages versus other things, so I am explicitly saying I find the most useful thing is real people out of a real cohort of people helps me know what the universe is.

DR. TEMPLE: I would add that we should probably tell people what the baseline risk is and what the increase compared to baseline is.

DR. NELSON: I would also link this to similar kind of data under the efficacy, so you are right.

DR. GOODMAN: Dr. Rudorfer.

DR. RUDORFER: A couple of questions. First, about the tricyclic issue. My recollection is there is some language already for the older antidepressants related to risk of possible clinical worsening early in the course of treatment. I mean I am just wondering, if something doesn't exist, or even if it could be moved within the labeling to be comparable to placement, say, of the newer--

DR. GOODMAN: Tom.

DR. LAUGHREN: Again, let me reiterate what I suggested earlier. Our plan is to extend this current, much broader warning statement that is now only in these 10 current generation drugs to all antidepressants including all the tricyclics, all the MAOIs. Some of them actually already have it.

So, you are right, there is that old language in the tricyclics. That is going to be changed to the newer language, and really the question here is whether you are comfortable with

us extending this additional view, that now we have established causality for suicidality to all antidepressants, not just these nine drugs that were studied in these trials, and pediatric patients.

DR. RUDORFER: Do I understand correctly, Tom, in the newer warning, that is where the description of the behavioral activation is mentioned, because again, what I am wondering is, if that specific language really should be applicable to the tricyclics.

I mean at our February meeting, we were describing a syndrome that I think the sense of the committees was that that was more specific to the newer generation drugs.

DR. LAUGHREN: The same kinds of behaviors are seen in SSRIs, in SNRIs. I think an argument could be made. I mean obviously, there is a lot of anecdotal data that the older drugs in some patients have the same kinds of symptoms, so I mean my inclination, in fact, some companies have already done it on their own. They have added this

new language to certain older drugs. It has already happened voluntarily by companies.

DR. RUDORFER: Just a follow-up question, semi-rhetorical. I had asked this morning about whether we know yet the impact of the label changes from March, and my understanding is we don't know yet.

Is there any rationale to giving that additional time to see the impact of that change before we make another change?

DR. LAUGHREN: You mean before we extend the language to the older drugs?

DR. RUDORFER: No, I mean before we change the warning on the newer drugs.

DR. GOODMAN: Let me try it. My opinion on that would be that now that the committee has decided that there is an association, at least within the trials, that I think the language needs to be extended to association has been established for suicidal ideation and behavior, however we want to say it. I think it has to be very careful how we say it apropos of the earlier discussion. I

think we need to define what we mean by suicidality.

I think our present discussion is whether it should be extended to the other and to the present, and I don't think our discussion is over yet, but I think probably we are leaning in the direction of yes, extending it and erring on the side of safety.

DR. LAUGHREN: Just to clarify, the current language in this warning that was implemented as of our March advisory, states as follows: "A causal role for antidepressants in inducing such behaviors has not been established."

So, the question that we have been addressing here this afternoon is whether or not we can now say that the causality has been established, and the further question of whether we should extend that beyond these nine drugs to all antidepressants.

DR. GOODMAN: Tana.

DR. GRADY-WELIKY: I just wanted to comment on the question of the warning or black box

with whatever we decide on this, and I would like to agree with Dr. Nelson that certainly having a warning, and my preference would be for all antidepressants, would be an important thing to do, but I would caution against using a black box warning because it would steer many clinicians away from using these agents, and as we heard yesterday from both patients and clinicians, that for many people, antidepressants are very useful treatment.

DR. GOODMAN: Dr. Mehta.

DR. MEHTA: Just a clarification from Dr. Laughren. If you are going to extend it to the old drugs, I guess you will also extend the same warning to all the new drugs, is that right?

DR. LAUGHREN: Yes.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I just want to remind everybody that one of the major reasons for using a black box or a box is that you think there is something that can be done to avoid the trouble that you are telling people about.

Just telling people that something

horrible has its own value, but it seems particularly important to get people's attention when there is something we want you to do.

In this case, there is something that we want you to do. We want you to pay attention, not put the people out to pasture for three weeks and never see them again.

So, we certainly are cognizant of the effect this can have on prescribing, and certainly don't want to do harm, but I just want to remind everybody that this is potentially remediable by seeing the patient, talking to them, being alert for these things, one of the main reasons for thinking that you should emphasize things by a box. I just want to be sure that is on the table.

DR. GOODMAN: How do you deal with the fact that with the exception of fluoxetine and some of the other medications in some of the anxiety disorders, these are off-label uses, how does that gibe with the general use of a black box where, in fact, you don't have an indication to start with?

DR. TEMPLE: It's a really good question

and requires great delicacy, but the box is about the warning, and we have on occasions warned people about things even though the use wasn't approved, so you have to be very careful. But if it's--what is an example--the hyperpyrexia syndrome.

DR. KATZ: One example, we have done this, as Bob says, in cases, and usually, what we say is here is a risk--specifically in pediatric patients--here is a risk in pediatric patients. We remind you that this drug is not approved for use in pediatric patients, effectiveness has not been demonstrated.

So, we tell people it is not approved, we don't know if it works, but here is a particular risk. So, there is certainly precedent for doing that, and we have done that.

DR. GOODMAN: Ms. Bronstein.

MS. BRONSTEIN: If I heard nothing from the public, it was they want to be warned. They want to hear the risk. I was thinking of big bold letters, not the black box. From what I have understood, the black box is used for really dire

situations, and while suicide is a dire situation, what we are asking is that they monitor patients closely, that they ask their families to participate in that monitoring process.

So, I see this more in the realm of informed consent, and I don't know what we have done in the past for more of an informed consent process. Have we any drugs that we require an informed consent?

DR. TEMPLE: We had a few where we did that. My own personal view is that gaining consent, after all, you have to open your mouth to take it, is a little funny. What we have moved more toward, but not entirely, is something where there is a required distribution of a piece of paper that says these things to the patient and some acknowledgment that they have read it. It's a little different concept for consent.

But we have done that in particular cases. It is very burdensome. If people are worried about discouraging the use of the drugs, they need to put that in--

DR. GOODMAN: We are talking about children. It's assent, isn't it, and it is more complicated?

DR. TEMPLE: Well, whether it is a matter of displaying what the risk is in a piece of paper that someone acknowledges having received, or you want to call it consent, it is sort of the same thing, but it's a big step.

We have done it for thalidomide and things like that, but it is a very big step. You have to balance what effect you think it has on the use of the drug.

DR. GOODMAN: Dr. Trontell.

DR. TRONTELL: Just to expand on Dr. Temple's remarks, informed consent has been used by the Agency for drugs other than ones with the extensive systems like thalidomide and clozapine. It is used for several Parkinson's disease agents, as I recall.

It is often called, some call it a patient agreement. It is some way of setting forward some kind of written system recorded often in the

patient's chart, that basically, tries to again assure that this conversation occurs between the provider and the patient.

So, again, it clearly is one area where we are again stepping into that therapeutic relationship, where some people take exception to the Agency doing that.

I had actually one additional remark, if I could make, relative to boxed warnings. In general, the Agency often uses those in context where the adverse event is associated with fatalities. Clearly, suicidal behavior can result in that.

An incidental consequence of that is that products that carry boxed warnings also have to carry that in their advertising, and quite frequently, that makes it quite difficult to explicitly advertise that product in direct-to-consumer advertising.

DR. GOODMAN: That you for that ad information. How about in sampling, would it affect detailing, sampling?

DR. TRONTELL: The requirement is if you carry a boxed warning, that boxed warning has to go on all the materials that are used for advertising. I am not aware that it would impede sampling, but effectively, the advertising that goes into popular magazines or on the television can't easily accommodate that, so you don't get specific products typically advertised that have those warnings.

DR. GOODMAN: Thank you.

Dr. Temple.

DR. TEMPLE: You can't use reminder ads either.

DR. GOODMAN: I am sorry, I missed that.

DR. TEMPLE: You can't do something called a reminder ad. That is where you just give the name and don't say much about the drug. You can't do those anymore if there is a box.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: I think those would be big pluses. As we move into the effects of the boxes and what effects that might have on prescribing, I

think we have to come back to the issue of efficacy.

We have I think very strong evidence of harm and really not very good evidence of efficacy, and although I know many practitioners are convinced that these drugs work, if you look very closely at the TADS trial, just as an example, at the Childhood Depression Rating Scale, the improvement with placebo was 19 points, and the improvement with the drug was 23.4 points.

You bring people in, you start a medication, and you see an improvement, you are very, very likely to believe that the drug is effective, and the reason why we do randomized, double-blind trials is because personal experience, however compelling, is not a reliable way to tell whether drugs work.

In the study where they worked, in the TADS, the improvement over placebo was really very, very small, and I would say not detectable by a clinician treating individual patients.

So, it would not be that bad if use of

these drugs were diminished, I think, because we don't know whether they actually help most patients when you put together all the data, and I think it is very important that this conversation about the risks take place, so I would favor some sort of informed consent process.

DR. GOODMAN: I think it was appropriate for you to remind us of the efficacy issue as we are starting to look about benefit, as well as risk, as we make recommendations and regulatory actions.

I agree and I think many of us, including myself, have said this in the room today and yesterday, that there is a dearth of data on efficacy. We do have the positive trials that were submitted, that led to the indication for fluoxetine in major depression.

We do have the TADS data, and actually, I may have misspoken yesterday when I said that there was no difference between fluoxetine and placebo on the Children's Depression Rating Scale. That is only true by one analysis, but if you look at mean

comparisons, although they are small, you are quite right, that the magnitude of the difference is small, I think they still reach statistical significance.

Where we lack the most data is on long-term benefit. I think what you are hearing, what we heard yesterday from some of the clinicians, what you are hearing from some of the people in this room who have treated children with antidepressants, sure, it is contaminated by bias and expectation. There is no question.

I have been humbled before in terms of the limitations of my own ability to discern an effect in the absence of a placebo-controlled study, I grant you that, but at the same time, we are dealing with drugs that have been out there a long time, numerous seasoned clinicians, and there is a very powerful impression among many, and from the consumers themselves, that in some cases, this has made a huge difference.

So, I worry that if we ignore that information, even though it is not good data in the

way we would like to see it, that we may risk a new increase of suicidality on the back end.

We are doing a lot here to protect it on the front end, but we haven't done the kind of studies that were recommended before, earlier by Dr. Temple, and doing a discontinuation study, and I agree we don't know the answer, but it is conceivable that there will be some patients that will be deprived of those medications that may be life-saving and may even be inclined to come off medications and have a relapse that will lead to suicidal behavior.

I welcome other comments.

Dr. Nelson.

DR. NELSON: Although I agree with you, Tom, I would be concerned that saying that alone without including drug-specific efficacy data will send the wrong message, and i think there needs to be a balance, and I would be curious how my psychiatric colleagues would react to the following suggestion, that if perhaps in fluoxetine, you included the efficacy data, which is the only drug

that, in fact, has passed that bar, would it be a bad thing if, in fact, practitioners, who are not child psychiatrists, who lack the knowledge to be able to then, if someone fails fluoxetine, to make an appropriate choice of any of the other agents.

If, in fact, what happened in general practice, family practice, general pediatrics, is fluoxetine was the first drug that would always be chosen, hopefully, under appropriate monitoring given the risk, but then if you failed that, you need help, that it is not something where you will go to multiple other drugs and start running down the list, thinking that if you just found the right one, you would be okay.

So, my question is can we custom craft the labeling where you might drive that kind of medical practice, and if we could, would that be a good thing?

DR. GOODMAN: Dr. Malone.

DR. MALONE: I think it would be a good idea to customize the labeling.

DR. GOODMAN: I am sorry, I missed your

point.

DR. MALONE: I think it would be good to customize the labeling, but in addition, fluoxetine is a positive study. As a clinician, when you look at the PDR, I think it would be very helpful to have some balanced statement regarding the number of studies that were done, say, for depression with a given agent, and the number of studies that were positive and negative, because I mean I think it has been said before, when you look at the PDR and you see a statement that it is not indicated for under 18, it is quite a different thing than to know that there were five studies done and none of them were positive.

You could add statements that negative studies don't mean it doesn't work, but it would be helpful for me, as a clinician, to be able to read that information.

DR. GOODMAN: Dr. Pine.

DR. PINE: I just have a couple of comments related to the discussions that have been going on, the first of which is, you know, we

really have not talked about the efficacy data, and I think it is very important to spend a fair amount of time talking about that.

The second thing is, for reasons that I will go into in a second, I would agree with some of the sentiments related to concern about adding a black box warning, that I would be concerned about that, and I think probably some of the most compelling data, at least to think about, is to look carefully at the efficacy data for fluoxetine.

There are a couple of things to say. The first is to remember that based on the efficacy data alone, even before we had the TADS trial, that those data were felt to be sufficiently compelling to justify an indication in pediatric depression.

Now, the second thing to say about the fluoxetine data in general is at least when I look at the magnitude of the effect in that study, relative not only to other effects in pediatric depression, but relative to other effects of psychotropic agents in many disorders, I think one would not call that to be a small effect.

In fact, I think the investigators and the journal itself called it a moderate effect, which I think is a fair summary of that effect.

The third thing to say is, if I am correct, although I would like to hear from the FDA about this, thus far the only warnings that have been given make no explicit statements about causality, number one, and then number two, make no explicit differentiation between the potential for the risk being greater in children relative to in adults.

I think just based on what I have heard, clearly those two statements could be made relatively strongly that there is something different going on in kids than adults, at least based on the level of review that we have had that hasn't been said, and it is pointing to causality.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: Well, we still believe the general warning about paying attention to people still should apply to adults and children, we don't want to change that, but as was said, it now says

causal relationships not established, and you don't think and we don't think that that is a true statement anymore about the pediatric population.

So, the thought would be to add, modify, something to convey what the new findings are.

I want to make one other comment. There are various ways of communicating with patients and their families. Some kind of form to sign is one, but there also is patient labeling that can be made to go to every patient who gets prescribed one of these drugs.

We have done that for a very large number of drugs. They are called Med Guides at present, and they can be focused on the particular concerns that one has and the risks that there are, and we would obviously have to dance around the fact that the drug isn't indicated for children, but there are still ways of doing that.

So, that is not causing a form to be handed out in the office, but it is a way of communicating. As I said before, the probability that that will be distributed, we think goes up

when it becomes part of a package, part of a unit of use package.

DR. MURPHY: But we need to make clear that the Med Guide is different than the patient package insert, that people often think about that comes with the regular label.

What might be helpful to think about, there is two things, what you want to warn about, where you want to put it or how you want to put in the label, black box, warnings, precautions, people talk about bolding versus how do you want to get the information out to others besides the learned intermediary.

That is where Dr. Temple is talking about, you know, do you want it just to be in our standard patient information in the label, which does not have to be given to a patient. A Med Guide would require that it be given to the patient.

That does not address the issue that I have heard also from you about where does the communication between the learned intermediary and the patient occur.

So, if you could think of that in three different places, there is the learned intermediary information, there is the information for the caretakers between the learned intermediary, and then there is the Med Guide where the patient gets the information whether that person has had that conversation with them or not.

DR. GOODMAN: One way of testing the confidence of this group in the efficacy, albeit unproven, of the antidepressants in the pediatric population--here I speak specifically of depression--is to go the next step, the step that the British counterpart of the FDA made.

We haven't talked about that, but it certainly has been mentioned, suggested in the public hearings, or I would like to engage this group in some discussion to see if there would be a recommendation to ban the use of all the antidepressants with the exception of fluoxetine in the pediatric population.

I am not saying I agree with that, but I think we should air a discussion.

Dr. Nelson.

DR. NELSON: A question for FDA colleagues. One of the presentations, it might have been Dr. Laughren might have mentioned that contraindication means different things to different regulatory agencies, and I would be curious if you could just be specific and say what does contraindication mean in Great Britain, what does contraindication mean in the United States to help answer that question.

DR. LAUGHREN: My understanding of what it means in the UK is that, in general, the drug cannot be used, but under specific circumstances, for example, by certain specialists it may be used, so it doesn't mean quite the same thing as it does in this country where if we put a contraindication in the labeling for a product, that means nobody under any circumstances should use that. There are no circumstances where it would be appropriate to use that drug. That is generally the way it is interpreted by clinicians.

DR. GOODMAN: Let's go with that for a

moment, a discussion of whether these drugs should be contraindicated with the exception of fluoxetine in pediatric depression.

Dr. Malone.

DR. MALONE: You just said it in pediatric depression. I was going to say that two of them are already indicated in some childhood anxiety disorders, but apart from that, I would be against banning the drugs. I think that would be a big different step.

As has been said, just because studies have not proven efficacy doesn't mean that there is not efficacy, and if you failed on Prozac in depression, you wouldn't have many other options. So, I would really be against banning them.

DR. GOODMAN: Dr. Wells.

DR. WELLS: I agree with Dr. Malone, I would not favor banning the other antidepressants other than fluoxetine, because many of these children will not respond to fluoxetine, and they certainly deserve to have access to other drugs should that occur.

However, I do believe that the labeling of Paxil should provide information consistent with the June 19th, 2003 FDA talk paper recommending that Paxil not be used in children and adolescents with MDD in light of the lack of proven efficacy and the troublesome documented signal for suicidality in that population.

I further believe that we should recommend a similar labeling change for venlafaxine.

DR. GOODMAN: Dr. Gorman.

DR. GORMAN: I think that the black box warnings in terms of labeling makes a lot of sense especially since I think there is a way to also increase transparency to the learned intermediaries, as well as the people who use the medicine.

I would strongly recommend that the Food and Drug Administration reconsider an active labeling in the pediatric section where a single sentence where it says Pediatric Usage, "After 3 randomized, controlled clinical trials including 600 patients, this medicine was not proven to be

effective."

I don't think that takes a lot of space, I don't think it's very confusing, and if you need to then reference the summary that is available for these pediatric studies at another place on your web site, I think that is perfectly appropriate.

I understand that creates some other difficulties for you, but I think that if you put it in the Pediatric Use Section, it increases the transparency.

So, then someone can say who wants to use Paxil, this drug has been used in 700 children in controlled trials, and it did not meet the bar the FDA said, but I think it has some potential benefit for my patient, then, they have the data to at least start to make a decision about that.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: Do you have a view on what we should do with a drug that had one positive and one negative study?

DR. GORMAN: I do.

DR. TEMPLE: That's not wise guy, I mean

we are going to face that problem.

DR. GORMAN: I think you will face that problem because there is one of those drugs already there.

DR. TEMPLE: That is why I asked.

DR. GORMAN: I think you should say there has been one positive and one negative, and that doesn't meet the bar the FDA sets. You can then argue. Then, people will start to argue with you whether the bar is too high or too low, but I think that if you make it transparent, which is my understanding, speaking for myself and not my academy, my understanding of the intent of the Best Pharmaceutical for Children's Act, that this should make--the public is paying for these drug trials with increased consumer prices, and therefore, they have the right to the results of that data.

I think that data should be reflected in the label even if it's troublesome to the Agency.

DR. TEMPLE: As I said, we are moving in that direction. We haven't quite gotten there yet, but we have had many of the same thoughts you have

expressed.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: I would strongly support what Dr. Gorman just said. It seems to me that what we know at this point is there is a drug for which there is moderate evidence of efficacy and a whole bunch of drugs for which there isn't, but we don't really think we have good enough data on those latter drugs, both in the sense of short-term efficacy trials, and more importantly, long-term efficacy trials, and somehow or other we need to get that information out in some useful way.

Second, I think we know that there are no trials for these drugs in things like migraine, headaches, minor acute depression, and other things that could be very, very risky.

Third, we know something about causality, but we know causality, unfortunately, only in the SSRIs, but we have no evidence that other antidepressants have any likelihood of being less causal.

DR. GOODMAN: "Causal" with regard to

suicidality?

DR. PERRIN: Suicidality.

DR. GOODMAN: It isn't just the SSRIs.

DR. PERRIN: I am sorry, the nine drugs that we are studying, my apologies. But we don't know that it covers all antidepressants. I think we can leave that out and say basically, we have no evidence that any other antidepressant is better or has less risk or whatever.

I think finally, we should say as explicitly as we can some of the comments that Jean has raised and others have raised about the explicit elements where people should be particular vigilant about risk, the timing issues, the type of patient issues, et cetera. I think we should be very clear about that.

DR. GOODMAN: Dr. Rudorfer.

DR. RUDORFER: I think what we are talking about is how to titrate the warning, if you will. One thought I had, we are clearly not going to be able to settle the efficacy issue today because we don't have the data before us. Again, as was just

mentioned, there are better efficacy data in the anxiety disorders than we have seen in major depression.

What I am thinking is the overriding issue that we had coming in, which I think remains with us, is how to discourage irresponsible use of these antidepressants in the pediatric population while--I don't want to speak for anybody else--but my sense is that we don't want to discourage appropriate responsible use of these drugs by clinicians who are in accord with the warnings as they now exist, that is, who are monitoring patients responsibly.

So, one thought I had was in terms of having a bolded section in the warning, but the bolded part would not be the adverse effect. The bolded part would be what we want clinicians to do, that is, wording to the effect that close patient monitoring is required during use of this medication especially early in treatment and at times of dosage changes.

That is just one thought off the top of my

head, again directing attention to that, and I don't know if language such as required is appropriate, but something along those lines to send that message to the clinician that a higher standard of care is required with this drug, again certainly including other warning language as we have been discussing, but my point being to find the right titration where we are not scaring off appropriate use of the drugs.

DR. GOODMAN: Ms. Griffith.

MS. GRIFFITH: We are about bouncing around a bit when you raised contraindicating, the possibility of contraindication and then going back to the best methodology for informing patients and practitioners.

I was compelled by the arguments both Dr. Nelson and Dr. Pine made with respect to the black box, and I am wondering if it is not now a knee-jerk reaction when a doctor sees a black box warning, as you suggested, Dr. Nelson, just to absolutely refuse to use that particular medication, and, if so, I think that that poses a

hazard to the ability for a doctor, a psychiatrist hopefully, in using that drug in his or her tool box.

I also, no disrespect intended to Drs. Temple and Trontell, when you said that by developing a mechanism, either informed consent or patient information letter would be burdensome, and I believe that Dr. Trontell said that the FDA does not like to get in between the patient and the provider by dictating what a provider has to do by way of informing, I think that that is wrong. I don't think burdensome is the right way to look at this.

I mean it may be burdensome, but it is absolutely necessary, and I don't think that the FDA should feel that they can't advise doctors and caregivers to be very forthcoming and very interactive with the patient, so I would recommend either a letter or--

DR. GOODMAN: Tom, you had a comment?

DR. LAUGHREN: We actually have a precedent for an informed consent in the pediatric

area in child psychiatry for Cylert. There is a consent form. The problem is that it is voluntary, and it is not clear how much it is actually used.

Maybe some of the child psychiatrists here who have used Cylert can comment on whether or not they actually use that.

DR. PINE: I can tell you that the safety issues around Cylert, when they became public, led to a dramatic decrease in the use, and I think it had more to do with the nature of the concern than the process that was used to monitor. So, I don't know that this situation is completely analogous.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: A number of us have to leave within the hour, and Dr. Temple, I believe has now raised at least two specific questions that he wants us to I think put to a vote. I am kind of concerned, I mean I would like to at least frame those two questions and see if we can at least accomplish that.

As I heard them, what I would like to do is if we go back to the text before this one, of

what we had for Question 3, and then I think you were asking us does this apply to all antidepressants, and we go around Yes/No, and then I think the second question, which is extremely important, is does some semblance of that information go into a black box. I think in that case, it might be within that black box at least for, say, fluoxetine, within that box there is some statement of the efficacy data.

I really am very, very concerned that the signal-to-noise ratio, the amount that is spent in direct-to-consumer advertising, even the patient information sheets, none of that really gets the attention it deserves.

We may not agree with this data, it may not be what we wanted to find, but what we are sitting with is no--with one exception--no evidence of efficacy, and what we have is evidence of some causal relationship.

As we were instructed, the evidence of a causal relationship for a warning that we want to really get across doesn't have to be beyond a

reasonable doubt. It may be beyond a reasonable doubt for efficacy, but for warning and drawing the appropriate attention and concern to this, I think we really need to put that.

So, I am sort of dealing with those two questions, if we could, Mr. Chairman, frame those questions and vote on them before we go ahead.

DR. GOODMAN: Unless I suffered a stroke here, I think we already voted on the first question, Question 3, that has already been voted, and I don't think we need to have that 3(b) in there, because the implication of 3(a) is that we did not exempt any of the antidepressants, at least when we were talking in terms of the trials.

I think what you are getting at is in whatever form the warnings take, should that be expanded to all the antidepressants, and although we didn't vote on that, my sense from the discussion is the answer was Yes.

So, I think we have already answered that. Partly because there isn't that much time left, and I do really want to end at 5 o'clock, is unless

there is a compelling reason, I do not want to subject these additional questions to a vote.

The only one that I think that perhaps might merit a vote at this point is the black box, but still let me remind the committee that we are not making decisions, we are making recommendations, and it will be up to the FDA whether or not to implement that recommendation.

Dr. Katz.

DR. KATZ: There is one other labeling question we either need you to take a vote on quickly or just sort of get a general sense, but that has to do with the contraindication question and whether or not the sense of the room is that they should not be or should be contraindicated.

DR. GOODMAN: I would rather start at that end. I agree with that, and I think what I would like to do is after just a few more moments of discussion, equivalent to the British ban, we are using the word contraindication, or any other discussion before we take a vote on whether this committee would support contraindication of all the

antidepressants except fluoxetine in major depression.

Dr. Nelson.

DR. NELSON: My interpretation of the meaning of the two words in the two different medical systems is that contraindication in the United Kingdom is not a ban, and is simply a way of driving the use of these drugs into the hand of appropriately qualified specialists.

If that interpretation is correct, then, contraindication in our system would not be the equivalent response, and if we think that that was the correct thing for them to do, the question is do we have another mechanism available to us here, such as adding a kind of oncology type warning about appropriately qualified specialists to accomplish that.

In my mind, saying it should be contraindicated here is a very different meaning. It would be a ban in the United Kingdom perhaps, but contraindication there was not a ban from my interpretation of what I was told.

DR. GOODMAN: In the UK, they were banned is my understanding.

Dr. Temple.

DR. TEMPLE: Well, no, there is wording that sort of suggested if you are properly trained and really need to, you can do it. But a contraindication here, and you can safely vote on that, means we think--we think you can still do it, we don't control your pen--means we think there is no circumstance in which anybody should use these drugs for that purpose.

DR. GOODMAN: But at the peril of the prescriber.

DR. TEMPLE: The prescriber doesn't have to pay attention to our labeling, and sometimes they don't, but it would reflect the view of us, and presumably the manufacturer that writes it, the rightful labeling, that you should not use these drugs for that purpose. There is no case in which the benefits outweigh the risks. That is what it means.

DR. GOODMAN: More discussion on

contraindication?

Dr. Malone.

DR. MALONE: If you contraindicate it for major depressive disorder, is it automatically contraindicated for off-label, or what happens to all these other uses?

DR. TEMPLE: Off-label use is not discussed in labeling. That is why it is called off-label use. We know perfectly well that people have been using these drugs in pediatric patients even though it is not in the label.

A contraindication actually would tend to discourage that use, because you are then reacting not to silence, but to a specific statement that says you really shouldn't do this. So, it changes the present situation, there is no doubt about it.

DR. GOODMAN: Ms. Dokken.

MS. DOKKEN: Just a quick question of clarification. What is the impact of contraindication on further research?

DR. TEMPLE: Well, further research is currently very difficult because everybody has got

its exclusivity, that is the main impediment to me, further research. I don't think a contraindication necessarily means that no one is going to bother to study it further.

I don't think we have practical experience that gives that answer, and it might discourage it some. I don't think we know.

DR. KATZ: But it doesn't legally preclude it or anything. It can be done.

DR. GOODMAN: Dr. Leslie.

DR. LESLIE: Just in the interest of time, I would like to move that we do not accept a contraindication, but we do suggest that there be wording to such that these medications should be given by people trained in their appropriate use.

I would be worried about saying subspecialist because there are a number of primary care doctors that have no access to mental health professionals in rural communities or urban Medicaid areas, and you would be doing a disservice to those populations, but if you said trained in the appropriate use, it goes back to their

professional bodies to come up with appropriate continuing medical education for the use of these medications.

DR. GOODMAN: Now, we do not have to take a vote on this. We can just continue to discuss it.

DR. TEMPLE: I just want to remind everybody that it is really hard to give instructions for use of something that isn't approved for use. I am not saying we can't figure out a way out of it, but it is a very thorny problem and we are sort of bound by our own rules, but it kind of implies that you should use it when you tell people how to get trained for using it.

DR. GOODMAN: Dr. Marangell.

DR. MARANGELL: I like the idea of the Med Scrip [ph] where the patients get information and the family gets information.

A question. Is there a way to ban direct consumer advertising without a black box?

DR. TEMPLE: The black box doesn't ban it. You just have to incorporate the black box or its

elements anyway into the label.

Our conclusion was that direct-to-consumer advertising was legal, and that is why it became allowed. There is nothing in the law against it. Therefore, under at least many interpretations of the Constitution, you are allowed to do it, and our rules. So, I don't know if there is a way to--I don't think there is an easy way to ban it.

We would not allow reminder ads. I don't know whether that is important to anybody, but those are not allowed.

DR. GOODMAN: Let me express the Chair's view on the contraindication. I would oppose it. If we took a vote, I would definitely oppose it. I am repeating myself here.

I would disagree that there is no data outside of fluoxetine. There are data supporting efficacy. They are not great data, they are not very good data, and they are very limited data. There are some negative data certainly from the clinical trials, and most of the data that we have is anecdotal experience, but it is not from one,

two, or three people. It is from a multitude of trained clinicians and patients.

Now, they could have been misled. They could have misled themselves into their being an effective drug when there was just a nonspecific effect of the therapeutic encounter or time alone.

We know that, I know that, but I can't ignore, as we can't ignore some of the public testimony about instances that seemed to implicate the medications in suicide.

We also can't ignore the possibility that there is data out there that we don't have in a form that we can analyze to our satisfaction that points to the effectiveness and the protective action of these drugs against suicide, particularly in the long-term treatment of depression.

In the absence of those data, in the absence of, say, negative studies, I would be very reluctant to deprive patients of that opportunity. So, I am not ready at this point, given what we know, to ban the antidepressants.

Other comments? Dr. Fant.

DR. FANT: In listening to the various comments, is it reasonable to emphasize the concerns with a black box and include wording in the black box that gives the serious, knowledgeable, committed caregiver license to make choices that someone less qualified or less thoughtful would make under those conditions?

I mean I think there are a number of us, when we take care of kids, institute therapies that are more risky than other situations when we are faced with limited options, but we do it thoughtfully, or at least we try to do it thoughtfully.

Is there any way to sort of strike that balance with the black box and the wording?

DR. GOODMAN: Let's ask the FDA. What kind of liberties do you have within the black box?

DR. TEMPLE: What you usually put in a black box is a warning about the adverse consequences of the use of the drug, and so you would say we know this about use in pediatric populations or whatever, and then therefore, it

says therefore, you really should monitor closely, and I guess you could stick in there, therefore, you should be particularly aware of the signs of symptoms of deterioration or something like that. We could think about that.

Those things are all possible. It is a little tricky to sort of identify responsible versus non-responsible physicians like, you know, only responsible physicians, and you know who you are, should use this drug, but you can certainly say what they should be worried about and what kind of thinking they should go through.

DR. GOODMAN: Dr. Maldonado.

DR. MALDONADO: Just a quick comment on a ban or contraindication and box warnings. There was a question about the impact in future research. I just remembered that a ban in the UK is probably not regulatorily different than a ban in the United States, is that the enforcers in the United States are lawyers, and we live in a different kind of environment. The FDA doesn't enforce that, but companies already know that with these restrictions

in the label, they are going to have tremendous liability to do any future studies.

Again, the ban in the UK is a ban in the UK, but physicians may take risks in the UK that physicians in the United States may not be willing to take.

DR. GOODMAN: Thank you.

Dr. Nelson.

DR. NELSON: One suggestion in terms of allowing the kind of information you need would be to have more of that information in the Pediatric Use Section, and just refer to that section out of the black box. You want the black box to be to the point.

The only other question I would ask the group is have we had enough discussion about the Med Quick or whatever the name is for the patient information to have formulated a view as to whether there would be a recommendation to develop that kind of a document, because that is one thing I heard is a need certainly from the public testimony.

The label is one thing, but having it in language that could be understood, maybe physicians will then read that document, would be a useful thing.

DR. GOODMAN: Dr. Fost.

DR. FOST: I wanted to get back to that patient information thing and follow up on Dr. Rudorfer's comment, that both the message to the patient and the physician has got to include this importance of monitoring, but I haven't heard any discussion yet of what monitoring means.

Does it mean seeing the patient once a week, if so, by whom? Twice a week, once every two weeks, is it phone contact monitoring? Does FDA get into that depth of defining terms? The word "monitoring," to me means nothing. I mean I have no idea what it means.

So, until somebody defines it for me, seeing it in a package insert doesn't tell me, as a physician, what it is I am supposed to be doing, but I have a sense that it is critical, that it is very important that the patients be monitored

closely.

MS. DOKKEN: Dr. Nelson just asked about the Med Guides. My question is they go directly to the patient from whom, the clinician or the pharmacist?

DR. TEMPLE: They are given out by the pharmacist, and they are required to be given out, but we don't think they necessarily always are, but they can be attached to the prescribing package, that is, to a unit of use package. In quite a number of cases, we have converted drugs to unit of use packaging in part so that they would carry the Med Guide, because then they always have it.

DR. TRONTELL: I don't know if this was your point. The patient would get the Medication Guide presumably after they have already filled the prescription.

MS. DOKKEN: So, it isn't necessarily an opportunity, sort of a planned opportunity for a conversation with the clinician.

DR. TRONTELL: If you want the patient to be informed before they actually receive the drug,

you would need to be do something in addition to the Medication Guide.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: As we are not voting on these issues, I just wanted to make a few brief comments. I would strongly support the black box, and I have to say we heard yesterday and I know we have discussed this a number of times on the Pediatric Advisory Committee, I think, for me, package inserts are a legal document between the company and the FDA, but I don't think they are read.

We heard from a physician who presented yesterday afternoon that he had not read the package insert, didn't know what was in the package insert, so I think we can put whatever we want in there, but I think if you took a poll around this table, most of us do not--that is not where we get our information.

So, I think anything other than that is important. I think the black box is important, I think the Web Guide or Med Guide, I think attached

to the box is fabulous, but we were also discussing the possibility of having a site on the FDA internet site, which is very visible, very easily navigated for the public to discuss adverse events.

Ms. Griffith and I, she was informing me about the FDA web site and how difficult it is currently to get the information on adverse events, and I think that that is another route that if you had advisories that were easily accessible, where patients could go in and get that information before or when the physician says I am going to prescribe this, but you can go back and get information.

So, I would just add those comments.

DR. GOODMAN: Ms. Bronstein.

MS. BRONSTEIN: I just want to reiterate again, I think that the family and the patient must receive something. I think having the Med Alert come with the drug itself is a good mechanism provided the information on there talks about suicidality.

I think we have to be really clear about

what the risks are that the patient has to call the physician about, even if the physician doesn't invite that half of the conversation.

I guess I vote against the black box. I want to be pretty specific about that. I think we heard very clearly from family members that drugs were helpful, we heard some that were very unhelpful, but the biggest message that I heard from the consumer is they want to be warned about what the risk is.

DR. GOODMAN: So, did you say you would vote against it?

MS. BRONSTEIN: I would vote against the black box, but I would vote for the Med Alert going directly to the patient. I think information should go to physicians on monitoring importance and frequency of visits.

DR. MURPHY: You can do both. I just want to make it clear, one does not rule out the other.

MS. BRONSTEIN: I understand.

DR. MURPHY: I think you should look at what is in the labels right now, too, because that

is the other thing. We already have bolded information in the Warning Section.

MS. BRONSTEIN: I felt the bolded information was a good beginning, but I think we need to go further.

DR. GOODMAN: Dr. Pine. I would like us to take a vote on the black box issue. I think we have had sufficient discussion. It is not clear to me what the preponderance of opinion is, and I think we won't know until we go around the table.

First, Dr. Pine.

DR. PINE: Two brief comments, one definitely relevant to the black box, the other indirectly relevant.

One thing that we haven't talked about that relates directly to the issue of restricting access or reducing access to treatments is we didn't talk about what are the data for other available treatments for children who suffer from major depression.

In some ways, some of the most disturbing or concerning findings are the data for cognitive

behavioral psychotherapy from the TADS trial, because while you can debate to some degree about the magnitude of the effect of fluoxetine, I think that there has been little debate about what the study says about cognitive behavioral psychotherapy, which currently is considered the best documented effective psychotherapeutic treatment for pediatric depression.

The data from the TADS trial were very clear. That treatment was inferior to fluoxetine alone, and it was no different from placebo. So, that is number one.

Number two, I am sympathetic to the views from the FDA that, you know, saying that this is an unusual circumstance and we are not really sure what to do, and I would, again, just speaking for myself, say that I think it calls for some very careful thought about how we are going to need to think about these kinds of issues differently relative to what the current options are, because there are a couple of highly unusual things about pediatric mental illness right now, one of which is

that the majority of treatment with psychotropic agents, at least to the extent that we have talked about it, is off-label use, which I think is a problem that we all agree that we can't ignore.

The second is that the level of knowledge in pediatric mental illness right now, in general, is not sufficient, so that we can make very strong statements.

So, I guess just in closing, to echo some of the statements from Dr. Bronstein, I, too, would not favor the black box. I am not sure what else we need to do. I think we need to do something clearly more than what has been done, and there might not be a current available thing to do.

DR. GOODMAN: Let me ask a question as we are trying to compose the question here. Is the black box warning to contain information only about risk, or does it also contain an evaluation of relative benefit and risk? If the latter is the case, then, fluoxetine would be exempt.

If what we are trying to do in the black box is convey risk, then, it should be consistent

with our earlier votes and apply to all antidepressants in the entire pediatric population.

Dr. Katz.

DR. KATZ: I think you can do both. I think you can say in a black box--first of all, black box is primarily for risk, but it's a warning, right, since it clearly is intended to convey a risk, but you can say this risk exists in pediatric patients, and this drug has not been shown to be effective in pediatric patients.

For a drug that has been shown to be effective, you can just say here is the risk, and the drug already carries the indication in the label. So, you can tailor what is in the black box depending upon what you know about the drug, both for risk and effectiveness, but it is primarily for risk, but you can handle that within the black box.

DR. GOODMAN: So, the black box for fluoxetine, you might have a statement in terms of--

DR. KATZ: I don't know, but you might not say anything about effectiveness although it is

already in the indication. In other drugs, you might say here is the risk and, by the way, we remind you that it has not been shown to be effective. We can sort of play with the language.

DR. GOODMAN: In any event, it seems like this warning should be broader. The question should apply to the pediatric population.

DR. KATZ: Right, it should not be limited to depression.

DR. GOODMAN: It is not limited to depression consistent with our earlier votes.

DR. KATZ: Right.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: Each one of us may have an opinion. Why don't we just plan then to use our 30 seconds to express it relative to what should or shouldn't be in and how to link it rather than trying to agree on that before we vote.

The box is fine, just in terms of what goes in it. We may have different views, and we could just then express that as we vote.

DR. GOODMAN: I agree with that.

Dr. Leslie.

DR. LESLIE: I just wondered if you could summarize the advantages and disadvantages of the black box, because we have kind of gone all around it.

DR. GOODMAN: I have a volunteer. Dr. Maldonado.

DR. MALDONADO: I think that it might actually be very good to know if the committee knows the criteria for precautions, one, in black box. It seems that people are all over the place. I think that the FDA has criteria. It may not be very strict, but it might be good to receive that kind of guidance before you vote.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: I wish I could remember. We put out a draft guidance document. Basically, a black box warning is for something you want everybody to pay attention to, and the reason you put it in a black box, it is more visible that way, and people pay attention to things that stand out.

You can emphasize things by using dark

print, too, but the black box is prominent, it's the first thing you see when you come to labeling. It is always at the top. Then, in relative reform, and it may be expanded on later, but it is supposed to catch everybody's eye. It shows up more or less the same way in promotion, so you see it. That is the reason.

It is used for things that matter, for things that can be fatal, and I would add it is particularly attractive where there is something you can do about it.

DR. GOODMAN: I think, in my mind, the advantages are it attracts attention, it is an attention getter. The disadvantages, which may also be the advantages, it will discourage use, and it may have some implications for the ability of the manufacturers to promote their products, market their products, at least in some forms, which again might be, depending how you are looking at it, an advantage.

We need to go to a vote. We are going to start at this end of the table.

Dr. Santana--oh, Dr. Santana is gone. Okay.

Dr. O'Fallon.

DR. O'FALLON: Because people are leaving, could you ask them to vote on both the black box and the Med Guide?

DR. GOODMAN: I don't think we are going to have time to take all those votes. We haven't finished talking about new studies.

DR. TEMPLE: We are assuming from everything that has been said that people like the idea of the Med Guide.

DR. GOODMAN: We don't need to vote for that.

Dr. O'Fallon.

DR. O'FALLON: Black box, I like the idea, yes. I vote yes. I think the idea of having the two flavors, one for those that have been shown efficacious and those that haven't is a good idea, so I like the idea.

DR. GOODMAN: Dr. Pollock.

DR. POLLOCK: Yes, I also vote for the

black box with the same comment as Dr. O'Fallon.

DR. GOODMAN: Dr. Wells.

DR. WELLS: I would vote against the black box because of my concerns that it would decrease access to many patients who need to have the medications.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: Yes, on the black box, and I guess I would like to emphasize what Ms. Bronstein said, that I think this is great for informing the physician, and the Med Guide is good for informing the patient, but it is important to have that discussion about the risks and benefits at the time the drug is being prescribed, and I don't think the black box will accomplish that.

DR. GOODMAN: Thank you.

Ms. Dokken.

MS. DOKKEN: Yes, on the black box, and if we adjourn before, I also want to say I think the Med Guide is great, but it is too late and does not involve that opportunity to have a discussion between the clinician and the family and patient.

DR. GOODMAN: Irwin has departed.

Marangell.

DR. MARANGELL: I am actually very torn on this issue. I think it is essential that we get the word out. I am very concerned about a backlash against people who really need appropriate treatment and not getting it, particularly since there is a dearth of specialists. I will vote therefore no on the black box, but support the revised bolded warning, the Med Quest, and perhaps some additional education efforts.

DR. GOODMAN: Robinson.

DR. ROBINSON: I would vote yes in the sense that if we are really saying that there is a potentially fatal side effect that might occur in 2, 3 percent of children taking these drugs, I think we have to in some way make sure that that information gets out.

I am not really as concerned in some ways of black box bolding. I just think that we need to make sure that a potentially fatal side effect with 2 or 3 percent of the population needs to get out

there.

DR. GOODMAN: Leslie.

DR. LESLIE: Yes, on the black box, yes, on the Med Guide, and then I also just come back to exactly what some of the other people have said, the importance, but I think this goes back to the professional bodies, and I don't know what the FDA can do to push this from bodies like the American Academy of Pediatrics, et cetera, but guidelines for informed consent, guidelines for follow up and monitoring, and then it really bothers me that the majority of education on these medications is done in CME that is funded by pharmaceutical companies, and I don't necessarily feel that it is always a fair perspective.

So, I also think pushing for unbiased reporting of results and in continuing medical education.

DR. GOODMAN: Griffith.

MS. GRIFFITH: I have to say I, too, am very conflicted, and I appreciate Dr. Marangell's point of view. I have anecdotal evidence from my

family background that would make me very leery of suggesting to a physician that he or she should be over the top and overly concerned to the extent that they precluded use of that drug.

But on the other hand, I am convinced by the force of some of the psychiatrists who feel that this would be beneficial, so I will vote yes.

DR. GOODMAN: Dr. Chesney.

DR. CHESNEY: Yes, this is a life-threatening complication in a severe disease, and I vote yes.

DR. GOODMAN: Dr. Goodman. My vote is yes. It will make prescribing more difficult. I anticipate there will be alarm from parents and the child, and I think that is worth that complication, because it will raise the threshold to prescribing and force an engagement of a discussion, not only about the risks, but the potential benefits and alternatives to medication.

Dr. Rudorfer.

DR. RUDORFER: I would vote no on the black box. I believe that while we are concerned

about a 2 to 3 percent increase of risk of suicidality, I think the underlying illness carries a 15 percent risk of suicide if left untreated, and I fear that the black box would impede access to treatments, and I think the appropriate warnings could be conveyed in bolded language that would be more likely to both be appreciated by prescribers without scaring off patients and families and clinicians.

DR. GOODMAN: Bronstein.

MS. BRONSTEIN: I couldn't have said it any better, just what he said.

DR. GOODMAN: You said yes then?

MS. BRONSTEIN: No, I am saying no.

DR. GOODMAN: I am sorry, you said no.

MS. BRONSTEIN: I am saying no, and the comments that Dr. Rudorfer has just said, said exactly what I wanted to say.

DR. GOODMAN: Dr. Pine.

DR. PINE: I would also vote no, and I would echo the comments of Dr. Rudorfer and then also add that I am particularly concerned about the

paucity of child psychiatrists, and I am concerned that the black box might, in particular, discourage use by primary care physicians who might have the necessary skills and might be the only physician available in certain areas, but would be dissuaded either from prescribing the agent or would force families to travel very far to try to find a child psychiatrist.

DR. GOODMAN: Gibbons.

DR. GIBBONS: I am going to vote no because I am unconvinced from the data at this point that the risk-benefit ratio is, in fact, negative.

DR. GOODMAN: Ebert.

DR. EBERT: No, on the black box warning. I also have some concerns about the nature of the warning with regards to a fine line between causality and also the cautions that would be expected to be followed.

We have talked about generalizing this to all antidepressants, and while I think that should be done as far as the warnings and the cautions, I

am not so comfortable with doing that with regards to causality.

DR. GOODMAN: It looks like a non-random distribution of opinions here.

Tana Grady.

DR. GRADY-WELIKY: I am also going to vote no on the black box and support Drs. Marangell, Rudorfer, Pine, and Gibbons' statements.

DR. GOODMAN: Dr. Perrin.

DR. PERRIN: I am going to vote yes for the black box, take my 30 seconds just to say that I hope we will get a few moments to make some recommendations to the FDA regarding special credentialing or certification or training for people being able to prescribe any of the antidepressants for children.

DR. GOODMAN: Dr. Nelson.

DR. NELSON: I am going to vote yes on the black box, but two comments. I think in this day and age, a lot of the information we get about drugs we pull from Palm-based databases. What comes up first is a black box warning. If it is

not there, you don't find it, you don't see it, you will go right to dose, you will miss it entirely. So, I think that is the only way to get it out to people.

The second is I would link that very clearly with a discussion of the risk and benefit under the pediatric-specific labeling data, which would allow, then, a very, you know, the sort of two-flavor approach and separating out fluoxetine from other drugs, and I would hope that practitioners who are not child psychiatrists would start fluoxetine and then get help if they needed it. Then, the question would be would that deal with your 15 percent. I don't know, it's an empirical question.

DR. GOODMAN: Dr. Malone.

DR. MALONE: I would vote yes on the black box, and I would also encourage that it include the efficacy data in the black box.

DR. GOODMAN: Dr. Fost.

DR. FOST: Thirty seconds, five points. Number one, high standards--

DR. GOODMAN: Your vote? What was your vote?

DR. FOST: I am coming to it. Can I start my 30 seconds now? Number one, high standards of informed consent however the FDA thinks they can best be achieved. Two, Med Guide, which is not relevant to that as we have heard. Three, yes to the black box. Four, high standards for monitoring, and I hope someone will explain to someone else what that means. And, fifth, the real black box, Dr. Temple referred to a black box that heightens attention, but the real one, as previously mentioned, is the one that conceals what is going on, which is the black box of CME, and that is at the root of the inappropriate use of these drugs, and I realize the FDA has been quite powerless to do anything about that.

DR. GOODMAN: Dr. Pfeffer.

DR. PFEFFER: I vote yes for the black box, and I am also concerned that we need more information from studies, and I am just concerned that while I am voting yes, this may inhibit that.

I think that there is such variability yet in the population studies and the methodologies that the spirit of warning and the spirit of monitoring, I highly agree with.

I would just hope that there would be an effort yet to study these drugs further.

DR. GOODMAN: Dr. Fant.

DR. FANT: I vote yes on the black box, and the comment I would like to make is that if careful attention is paid to the wording, I don't think the black box will have an adverse effect on access of potentially useful medications for kids, from knowledgeable, thoughtful providers who thought certain drugs may be of benefit. I think it may have a desired effect on wise cavalier use of drugs in an unthoughtful way.

DR. GOODMAN: We have an independent accounting firm auditing the vote at this moment.

I am prepared to read it.

This time, we have a total of 23 votes, 15 Yes, 8 No. So, more of a split decision than we had on our previous votes.

We are running nearly out of time. I think we have covered really most of what I hoped to accomplish in No. 4. We can't subject every recommendation to a question, I don't think we can come up with every possible recommendation here. I think we have made tremendous progress in giving the FDA a sense of where we stand.

The final Question 5, maybe just take two minutes. I think throughout, the meeting has been punctuated by discussion about what data is missing, what studies need to be done, and maybe people can add to what I omit.

Certainly, we need more efficacy data. We need safety data in which one of the intended endpoints is assessing suicidality, so it is being assessed appropriately and prospectively, and with sample sizes accordingly, which, of course, could represent some problems.

Nevertheless, it needs to be done. We need to have long-term data including comparison trials with fluoxetine, but also retaining a placebo-controlled group. There are things I could

mention, but I think those are some of the main clinical trials highlights.

Dr. Marangell, you want to add?

DR. MARANGELL: Any future written requests, inclusion of suicidality assessment, and consistent data dictionary.

DR. GOODMAN: Other comments on future recommendations on research?

DR. O'FALLON: Maybe even having a group that would look at suicidality events in some of these studies.

DR. GOODMAN: Dr. Newman.

DR. NEWMAN: Everyone has called for a long-term trial, and I just want to give one more reason why that is important. I agree with Dr. Nelson, who said that there should be some actual numbers in the warnings about what the risks of the increased suicidality are, but the 2 to 3 percent, that is an 8 to 12 weeks, and there doesn't seem to be evidence that it is tapering off over time.

We really need to know, you know, in a year, is it four times that, and in two years, is

it eight times that, because we don't know that. It is very important that the warning go on there, but, you know, it is going to be hard to write that accurately if someone is going to be on the medicine more than three months or two months, to know what to tell them.

DR. WELLS: I would like to recommend that it would be very beneficial, I think, if sponsors were encouraged to provide additional information with regard to benefits in order to help clinicians make the assessment of benefits versus risks.

Specifically, if they could provide, for instance, pharmacoeconomic benefits to include cost effectiveness information and cost minimization data, and also humanistic benefits, such as quality of life.

DR. GOODMAN: Other suggestions for future research?

Dr. Perrin.

DR. PERRIN: I think there is a great deal of value in doing a much better job with respect to understanding the sample selection and sample

biases, and what we know about the samples at the time of entry. I am not sure that I know exactly what the sample ought to consist of, but we ought to know something about prior history in much more detail than we currently do.

We ought to know about the issue of the likelihood of bipolar disease in these kids. We need to know how accurately, reliably, and validly to diagnose of MDD is made in these kids, and we need to know something about the social and environmental histories that might influence both response to treatment and likeliness of adherence.

I will take one other moment just to plug again, I really think that we need to find a way to make sure the people who prescribe antidepressants know what they are doing. I am a strong proponent of the fact that we shouldn't allow anyone to prescribe just by having a physician's license.

DR. GOODMAN: Dr Gorman.

DR. GORMAN: I would like to suggest that the concern about major depressive disorder in children is one of such importance to our country

that this discussion not be taking place, the study not be taken upon by a pharmaceutical company, but the National Institute of Health.

I think that it should be done in a way that allows the real world application of these medicines to be studied much closer to the TAD trial than to the constraints of randomized, controlled clinical trials.

DR. GOODMAN: Dr. Pfeffer.

DR. PFEFFER: I would agree with that, but this is something I wanted to mention for a while. It is a little bit out of the box, but given funding concerns, and given the potential for partnership, I wonder if there is a feasibility to consider that drug companies do be involved in these studies and that they be involved in a way that they might be able to help with said costs to the studies with the idea that it is totally unrestricted and that, for example, NIH can be the group leading this study, with selecting the participants, designing the studies, et cetera.

DR. GOODMAN: Dr. Fant.

DR. FANT: One of the things that I have been struck with in preparing for this meeting is really understanding how little we know about how a lot of these drugs work, and just the basic pharmacology that underlines them.

We know the primary process that they seem to perturb, you know, but reading through the inserts, they talk about either low or no affinity for this receptor or that receptor. Well, low affinity can mean anything from no affinity to 25 percent occupancy.

I think more basic research on the basic pharmacology of these drugs, the chemistry, and having a better understanding at the pharmacogenetic level of how different patients may respond to a given drug.

That involves a lot of, you know, sort of moving into the studies outside of the realm of what we have been talking about up to this point, but I think those will be important to better understand what we are seeing here and perhaps be applicable to other drugs in the future.

DR. GOODMAN: I am going to turn over the meeting now to Dr. Chesney, who, as you know, is the Chair of the Pediatric Advisory Committee. I want to ask her help in closing this meeting.

Concluding Remarks

DR. CHESNEY: Thank you. The good news is that I have a number of pages here of things to say that have a great historical and philosophic context. I am going to bypass all of that and on behalf of the Pediatric Advisory Committee, just make one comment which Dr. Nelson and Dr. Fost brought to my attention.

That is the importance of having children and families participate in research, well constructed, well designed research, because in most cases, the investigator has been well vetted, if you will, is well understood his or her credentials have to be reviewed. There is very close monitoring that goes on in very well constructed and high quality studies, and we get important results, and deaths are rare in very well constructed, high quality studies.

So, they wanted me to pass on that general comment.

My only concluding remarks are in terms of thanks. I think we would all very much like to thank the families who took so much time to come and gave us the emotional energy that it took for them to relive their tragedies.

Also, to thank the psychiatrists and the families who came and explained to us in great detail the importance of having drugs available and of the many good things that these drugs have done.

I particularly wanted to thank the members of the FDA who have come under such intense scrutiny over the last year, but have maintained their professionalism and their integrity, and that has meant a great deal to all of us.

I also want to thank all of the members of the FDA who have organized and executed this meeting over the last two days, which has taken just an awesome effort in terms of getting the materials out to us, getting the materials out to everybody else, and having us here in a very calm,

controlled, and extremely thoughtful environment.

This has been a very intense two days, and I wanted to thank all of them.

Finally, just to thank Dr. Rudorfer, who chaired the February session, and Dr. Goodman, who chaired this session, and Anuja Patel, who has brought it all together. I think they have just done a fabulous job of keeping us on track.

DR. GOODMAN: Hear, hear. I don't have much to add. I echo all the comments of my colleague. I also want to specifically thank the members of the Psychopharmacologic Advisory Committee and, once again, Anuja Patel. It would be useful if you could be at my side always, make me look as good as you did during this meeting, keeping me organized.

It has been a very challenging two days. I think we have made a tremendous amount of progress. I anticipate that there could be more meetings like this, and hopefully, the next time, if we are asked to meet, it is after the emergence of additional data, particularly on the side of

efficacy.

We didn't take a vote on the banning. I felt, in part, that I knew how it was going to turn out. We were not going to vote in favor of banning. On the other hand, I think the reason behind that was going to be based mostly on subjective experience, not so much the data at hand. So, I didn't subject it to a vote.

At some point, I would like to be in the position where, like we did on some of the other issues, is to have sufficient data before us that we could make an informed decision and make hard choices.

Right now, we are in a position where the drugs are out, they are being used. There is a widespread opinion that they not only help, but they actually save lives, but we can't really, with the data available to us, make the kind of informed decision that I think would make us all feel comfortable.

I think some of the problems that have emerged, the suicide signal and the way it

appeared, are a symptom of some disparities between our clinical practice and our clinical research knowledge, and I hope that, over time, that gap can be narrowed, so that our research keeps pace with the clinical needs and the clinical practice that is out there.

I don't know how to suggest a mechanism to do that, and I think we have done a good deal of damage control, and I think it is unfortunate that we didn't have an opportunity to intercede sooner.

With that, again, I just want to thank everybody for the participation, their attention. This has been a really outstanding meeting from my perspective, a terrific group of panel members who have grappled with very difficult decisions, and have made my job a great deal easier.

Thank you again. This meeting is adjourned.

[Whereupon, at 5:00 p.m. the proceedings concluded.]

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