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Perry Parkway
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P R O C E E D I N G S

Call to Order and Opening Remarks

DR. GOODMAN: Good morning, everybody. I am going to keep my opening remarks very short because we have a very intensive schedule today. The topic, as you know, for today's session has to do with questions about the need for long-term efficacy data along with acute trial data at the time of the submission for a new indication of a psychotropic medication. We will also be talking, not only about that question but about design considerations and how to establish--or the different ways of establishing long-term efficacy and also disorder specific considerations.

If you look at the agenda today, most of the morning is going to be taken up by formal presentations, first from the FDA by Tom Laughren, and then what I understand is a highly coherent, coordinated presentation from industry. This may be the first of its kind. There will be very limited time for questions. I am going to ask the committee members around the table to limit any

questions that come up during those presentations to clarification purposes. I hope that you will leave some time in your presentations this morning for some open questions before we go to lunch because, as I look at the schedule, most of the committee's work, if you look at Tom Laughren's series of questions, is rather complicated. It starts off easy but then it gets increasingly complex and I think for us to delve into that and give it adequate attention we need a lot of time as a committee, and currently we are only allotted three hours. So, I really hope that you will allow us to have some time for questions this morning.

Without further delay, let me go around and ask each of the committee members to introduce themselves. I will start. I am Wayne Goodman, Professor/Chair of Psychiatry at the University of Florida. My area of research interest is in obsessive-compulsive disorder and Tourette's. Why don't we start at that end of the table? Tom?

DR. LAUGHREN: Tom Laughren. I am the Director of the Division of Psychiatry Products.

DR. ANDREASON: I am Paul Andreason. I am the Deputy Director.

DR. POLLOCK: Bruce Pollock. I am Chief

of the Division of Geriatric Psychiatry at the University of Pittsburgh.

DR. ROBINSON: I am Delbert Robinson. I am from the Albert Einstein College of Medicine in New York and the Zucker Hillside Hospital, and I primarily do research in early psychosis.

DR. PINE: Danny Pine, a child and adolescent psychiatrist. I am Chief of Developmental Studies in the Mood and Anxiety Disorders Program in the NIMH Intramural Research Program.

MS. BRONSTEIN: I am Jean Bronstein. I am a retired psychiatric nurse and I am here as the consumer representative.

DR. WINOKUR: Any Winokur. I am Director of Psychopharmacology at the University of Connecticut Health Center.

DR. WANG: Phil Wang, psychiatrist/epidemiologist at Harvard Medical

School.

DR. MCGOUGH: Jim McGough, child adolescent psychiatry, UCLA. My main interest is autism and ADHD.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, advisors and consultants staff, FDA.

DR. TAMMINGA: Carol Tamminga. I am a psychiatrist at UT Southwestern and I do schizophrenia research.

MS. GRIFFITH: Gail Griffith, and an author of a book about teen depression called Will's Choice, and I live in Washington. I am a patient representative.

DR. LEON: I am Andrew Leon, Professor of Biostatistics in Psychiatry at the Cornell Medical College.

DR. MEHTA: Dilip Mehta, industry representative, retired from industry.

DR. GOODMAN: Thank you, everyone. I am going to turn the microphone over to Karen Templeton-Somers, who is our Acting Executive

Secretary today, to read some of the materials and set the stage for the rest of the meeting.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: Thank you. This is rather a long announcement because there were quite a few possible products on the list. The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 USC 208(b)(3), full waivers have been granted to the following participants. Please note that all interests are in firms that could potentially be affected by the committee's discussions: Miss Jean Bronstein owns stock in two affected firms. One is valued between

$5001 to $25,000 and the other at less than $5001. She also owns a bond in an affected firm valued between $50,001 to $100,000.

Dr. James McGough is a member of speakers bureaus for two affected firms. He receives less than $10,001 per year per firm. He is a consultant for three affected firms and receives less than $10,001 per year per firm. Finally, Dr. McGough's employer has contracts with three affected firms. Each contract is funded for less than $1000 per year.

Dr. Andrew Winokur serves on a speakers bureau for an affected firm and receives less than $10,000 per year. His employer has contracts with three affected firms. Each contract is funded for less than $100,000 per year. Dr. Winokur's employer had a contract pending with an affected firm but no funding has been received to date.

Dr. Leon is a member of data safety and monitoring boards for two affected firms. He receives less than $10,001 per year from one firm and no compensation to date from the second. Dr.

Leon is an advisory board member for an affected firm, however, he hasn't received any compensation to date. He owns stock in an affected firm worth between $5,001 and $25,000. Because the value of the stock falls below the de minimis exemption allowed under 5 CFR 2640.202(b)(2), a waiver under 18 USC 208 is not required.

Dr. Carol Tamminga's employer has a contract with an affected firm, funded at less than $100,000 per year.

Dr. Delbert Robinson's employer has a contract with a non-profit organization related to the topics to be discussed at this meeting. His employer receives less than $100,000 per year. His employer also has a federal contract for a study of affected products funded for more than $300,000 per year. The drugs under study are provided by two affected firms.

Dr. Wayne Goodman's employer has contracts with two affected firms. Each is funded at less than $100,000 per year. His employer also has contracts with two affected firms, each of which is

funded between $100,001 and $300,000 per year.

Dr. Bruce Pollock serves on speakers bureaus for two affected firms. He receives between $10,001 to $50,000 from one firm and less than $10,001 from the other. Dr. Pollock is a member of two advisory boards for an affected firm. He receives less than $10,001 for each board. He is also a member of two advisory boards for another affected firm, however, he hasn't received any compensation to date. Dr. Pollock is a facility member of a management board for a firm that is affiliated with an affected firm. He receives less than $10,001 per year. Finally, his employer has a contract with an affected firm but his employer hasn't received any compensation to date.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

In the event that the discussions involve any other products or firms, not already on the agenda, for which an FDA participant has a

financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

Lastly, we would also like to disclose that Dr. Dilip Mehta is participating in this meeting as an industry representative, acting on behalf of regulated industry. Dr. Mehta's role on this committee is to represent industry interests in general and not any one particular company. Dr. Mehta is retired from Pfizer.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you for your patience. DR. GOODMAN: Thank you, Karen. Our first presentation will be by Dr. Tom Laughren, Director of Psychiatry Products for the FDA. He is going to give us the charge for the rest of today's meeting.

Overview of Issues and Questions

DR. LAUGHREN: Good morning and I would

like to welcome everyone here this morning.

[Slide]

The topic for today is long-term efficacy for chronic psychiatric disorders. This is something that we have been thinking about for a long time, and we thought it was time to have an initial public discussion of this issue. Most of the disorders that we deal with are chronic disorders. However, we have not, up until recently, required companies to accumulate long-term data, efficacy data, for disorders at the time of the initial approval. This has generally been a post-approval commitment and, in fairness, we have generally gotten these data, probably in 75 percent of cases, but often not until several years or longer after the initial approval.

Now, most treatment guidelines for chronic psychiatric disorders recommend long-term treatment. So, the bottom line is that at the time of initial approval for most new chemical entities there is not evidence to support what is standard practice, which is to use drugs chronically. So, I

want to talk about that issue, when in the course of development companies need to generate long-term data.

The second issue is the design of the studies that are used to accumulate those data. Now, for most of the disorders that we deal with it is not possible to do a long-term placebo-controlled trial. In other words, you can't randomize patients, say, with depression to drug or placebo for a 6-month or year-long trial. You certainly couldn't do that in schizophrenia. IRBs would not allow that.

The alternative design that has been adopted generally is what is known as the randomized withdrawal design or the relapse prevention design. Typically, in this design acutely ill patients are treated on an open basis for some period of time. Those patients who respond are then randomized to either continue on drug or they are switched to placebo and one looks at time to relapse or rate of relapse as the outcome measure.

The run-in phase during which patients are treated on an open basis for most of these trials has been fairly short, often on the order of 8-12

weeks, sometimes a bit longer. The result is that patients are often in a responder status, because they don't respond right away, for a relatively short period of time, sometimes a matter of just a few weeks.

Now, why is that a problem? These trials are supposed to inform us about long-term efficacy. In fact, in the literature these trials are often characterized in terms of the randomized phase, the double-blind randomized phase where you are looking for relapse rather than in terms of the open run-in. Often, however, when you look at the results of these trials you find that many of the relapses occur relatively early so there are often relatively few patients still in the trial at the end of that often fairly long observation period.

So, in recent years we have begun to shift our focus to the run-in phase because we think that focusing on that phase really answers the question

that I think the clinician is interested in answering, which is if I have a patient who has responded and who has remained stable for some period of time, say 6 months, what is the probability of getting worse if I take the patient off that drug? That is the question that the patient would want to know and that is the question that the clinician would want to know. For that reason, we felt that the run-in phase, the period of time during which the patient is actually in a responder status, is the most important.

In fact, in clinical practice most clinicians would not stop treatment after a patient has been a responder for, say, a month. It would not happen for most of these disorders. So, from a clinical standpoint and even perhaps from an ethical standpoint one wonders about doing these trials where patients are stopped after such a short period of time.

Before I go on, I want to say a word about this distinction in the literature that is made between continuation of therapy and maintenance

therapy. As you know, the term continuation therapy is generally used to refer to continuing drug after the initial response for up to a period of, say, 6 months. The thinking is that by continuing therapy during that period one is preventing what is known as relapse which is viewed as the return of the symptoms of the same episode that was treated. Whereas, maintenance therapy is used to refer to continued treatment beyond 6 months, and the view is that what one is doing during that phase is preventing what is called recurrence, which is viewed as the emergence of a new episode of that illness.

Now, that 6-month period for depression, say, is based on a belief in what is the average duration of an episode of depression. Of course, in an instant case for any given patient one can't possibly know whether returning symptoms represent a reemergence of the same symptoms that were treated initially or a new episode. So, from a clinical standpoint and from a regulatory standpoint we have not felt that to be a useful

distinction. But I just wanted to acknowledge that that is a distinction that is made in the literature.

As you know, over the past 6 months or so the division has begun to not only encourage companies to do these trials early, but we have added it as a requirement. We have told companies, several companies, at the end of Phase 2 meetings when they come in with an application, that they will have to have not only acute data but would also have to have long-term data for the initial filing. So, this was a shift in policy.

In addition to that, we have told companies that the trial to support long-term efficacy has to be of adequate design. By that, we have meant patients have had to be in responder status for some reasonable period of time, and the period of time that we have arbitrarily picked is 6 months because that seemed like a reasonable period.

As you are aware, this policy shift has generated a lot of discussion. In effect it wasn't

intended as a straw man but in effect it has served as a straw man. That is fine because I think we do need to have a lot of discussion of this issue, and that is really why we are here today.

Now, as you can see from the materials that you have, we have a list of questions, a series of 12 questions that we would like you to address. The first eight questions focus on major depression. After that I want the committee to broaden the questions to consider a range of psychiatric disorders beyond depression. We are only asking for a vote on the first two questions. For most of these questions we are happy just to get some discussion.

Finally, I want to assure you that we have an open mind on this issue. We are interested in your feedback and we would like your help in going forward with developing a policy in this area.

[Slide]

So, the first question is an important one. Is it a reasonable expectation that a sponsor would have accumulated data for both acute and

longer-term efficacy trials at the time of filing an application for major depression? So, is it reasonable to expect that you would have had both at the time of an initial filing?

[Slide]

The second question, if you agree that it is reasonable to ask for both at the time of an initial filing, is it then also reasonable to expect that the sponsor would have demonstrated both acute efficacy and longer-term efficacy? In other words, you not only have to do the trial but you have to show that not only does it work acutely but it also has longer-term efficacy at the time of filing.

[Slide]

Question two has several parts. If you don't agree that it is reasonable to expect that a company would have demonstrated both acute and longer-term efficacy at the time of filing, would it be acceptable in a situation where a company does have acute studies that support an acute claim but the longer-term trial fails to demonstrate an

effect? Would it be reasonable to approve that drug for acute use, with a mention of the negative longer-term trial in labeling? That is question 2(a).

2(b) deals with the opposite, where you have done both acute studies and chronic studies but it is only the chronic studies that succeed. In that instance, would it be reasonable to approve the drug for maintenance therapy but not for acute therapy? In this case we have actually set a precedent. As you know, Lamictal is approved for maintenance treatment in bipolar but not for acute treatment because the acute trials failed so we have already set a precedent there but we would still like your discussion of that.

[Slide]

Again, questions one and two and their various parts are the only ones that we are actually asking for a vote on. Question three, if you answered yes to number one, in other words, you think it is reasonable to ask for both acute and longer-term data, at what point in a development

program should that policy be implemented?

If you look across the spectrum of drug companies and their development programs, obviously they are in various phases. Some companies are just getting started; some companies are just about ready to file an application. You know, we don't think it is reasonable to implement that policy for a company that is already in Phase 3. But we have thought that Phase 2, if one were going to implement that policy, would probably be the right time because a company is in the process of designing its Phase 3 programs so we think that would be reasonable but we would like some discussion of that.

[Slide]

Now I want to shift focus to design issues for these trials. The first question has to do again with this issue of how long a patient should be in a responder status before the patient is randomized. So, the question is what is the minimum period of time that patients with major depression should remain in a responder status

before being randomized in a randomized withdrawal study? An extension of that question is the question of whether or not one is dealing with monotherapy or add-on therapy and if that should be a factor in how long that run-in should be.

The thinking is that if a patient is on monotherapy one might argue for a longer period of stabilization before randomizing the patient. Whereas, on the other hand, if a patient is getting add-on therapy to enhance a suboptimal response to the initial drug one might argue that it could be a shorter of period of time before one randomizes. In any case, we would like some discussion of that.

[Slide]

The next two questions focus on the definitions of responder and the definitions of relapse. They are similar questions. Really, the issue here is how rigid or how flexible should one be in defining either a responder or relapse. The problem is this, ordinarily responder is defined in terms of meeting some criteria on some rating instrument and staying below that persistently. In

fact, in clinical practice clinicians know that patients have fluctuations in their symptoms.

So, with regard to responder, the question is can you still consider a patient a responder if that patient has had some fluctuation, say, above that threshold level for a brief period of time during that open run-in? Or, if that patient, you know, may have required some adjustment of dose during that period, is it still reasonable to consider that patient a responder? So, that is the responder question.

[Slide]

Question six is a similar question with regard to relapse. In other words, should we be flexible or rigid in defining relapse? In other words, during that randomized observation phase for relapse, if a patient temporarily goes above some threshold level but then immediately comes back down or requires some minor adjustment in dose is it reasonable to still consider that patient to be a responder during that phase and not count that as a relapse?

These questions get to the point of the efficient conduct of these trials so they are important questions in the conduct of these trials.

[Slide]

The next question--this is getting, I know, a little technical but these are all questions that companies bring to us. You know, we have our thoughts about them but we want to get the committee's thoughts as well. So, question seven deals with the issue of where you get patients for the randomized phase. As I said, ordinarily for most of these trials you have an open run-in period so patients are treated on an open basis. Those patients who respond on drug are the ones who are randomized.

There is an alternative source of patients for these trials. Those are patients in a randomized acute trial. Some of those patients get drug; some get placebo. You get responders in both groups. The problem is that you don't know until that trial is completed and the blind is broken what the status of those patients is. So, you have

responders. You don't know what they are taking. At the end of that trial they are either continued on drug or they are put on drug if they had been a placebo responder, and after some period of stabilization they could be randomized. The question is should we be thinking of those patients who are placebo responders, who then are switched to drug during the stabilization phase, in the same way that we think about the patients who respond on drug and then are continued? So, that is a question that several companies have asked us to address at this meeting.

[Slide]

The next question, again, is another practical question dealing with the conduct and the interpretation of these trials. It deals with the issue of whether or not these randomized withdrawal studies should be flexible dose studies or fixed dose studies.

The issue is this, patients respond on a particular dose in an open run-in phase. Then one wants to ask the question whether or not there is

any benefit in continuing that patient on treatment. It is possible that the dose that is required to maintain a patient who has responded is not the same as the dose that was needed to get the response initially? And, we think that a fixed dose randomized withdrawal study is the way to get at that issue. We think it is an important question because, obviously, one wants to use the lowest dose that is needed to maintain a patient who has responded and we think that a fixed dose study is the way to get that. We have seen a few of these but most of the randomized withdrawal trials that we have looked at are flexible dose studies. So, the question for the committee is should we be strongly encouraging or even requiring companies who are doing these randomized withdrawal studies to do fixed dose studies?

[Slide]

At this point we are going to be asking the committee to focus the questions more broadly across a range of chronic psychiatric disorders. The question is would the answers to any of these

questions change in considering other chronic psychiatric disorders, other than depression?

Now, obviously, we are not going to be able to discuss every disorder here--this is a one-day meeting, but what we would like to get is a sense from the committee of whether or not in general this is an important issue to try and address for any chronic psychiatric disorders, and what the issues are in terms of extrapolating a policy from depression to other psychiatric disorders, and whether one can easily do that or whether it is something that one has to think about very carefully for each disorder.

In addition to that, we would like you to think about the course of the chronic disorder as a factor in determining the policy about the requirement for a longer-term trial and the design of that trial. Obviously, different chronic psychiatric disorders have different courses. Depression and schizophrenia tend to have episodes; they tend to be episodic. Patients get worse; they get better. The same with bipolar. Other

disorders, for example, panic disorders, social anxiety disorder or obsessive-compulsive disorder tend to be rather chronic and persistent. So, should that factor be something that one thinks about in designing a longer-term trial?

[Slide]

This is just a list. It is not a comprehensive list but this is a list of many of the disorders that we are looking at that are having drugs developed for.

[Slide]

Question ten deals with the issue of alternative designs. We have been talking mostly about this randomized withdrawal design. The question is are there other ways of approaching this? I am going to give you a couple of examples that we have seen in development programs to think about. One an example is the drug Effexor in generalized anxiety disorder. They actually did a 6-month trial. In other words, patients were assigned to drug or placebo and they were treated for 6 months, as an approach to getting longer-term

efficacy. As I say, one can't do that trial for many disorders, but the question is, is that an acceptable design for some of these disorders?

A second design that we have seen--actually, this was a study done with aripiprazole in schizophrenia, and instead of beginning with patients who were acutely ill, they started off with patients who were stable on another drug but were not optimally controlled. They switched those patients to either aripiprazole or placebo and again looked at time to relapse. So, this is sort of a variation of the typical randomized withdrawal study.

A third example that we have seen, and this was with risperidone in schizophrenia, involved a comparison with an active control. In this case it was haloperidol. In that study they actually beat haloperidol. So, from our standpoint that was fine. We view that as evidence of efficacy. Of course, the problem is that you wouldn't always expect to be able to beat an active control with a new drug.

The fourth alternative design, that you are going to hear about from one of the companies today and this deals with schizophrenia, is the

possibility of a non-inferiority trial. In other words, comparing a new antipsychotic drug with a standard drug, not with the expectation that you are beating it but showing that you are as good as so it is a non-inferiority trial.

The question is whether or not we are at a point in the evolution of this field, and the trials, and the data to date that we can consider a non-inferiority design. We have argued against that for years for disorders like depression where the placebo response rate is so variable. But one of the questions that maybe we will have some time to talk about is whether or not a non-inferiority design is a reasonable idea to consider for an entity like schizophrenia.

[Slide]

The next issue I want to deal with is assuming that a company has done a randomized withdrawal study, how do we characterize the

results of that trial in labeling? As I have told you, in recent years we have focused on the open run-in phase as being the important part of that trial. I am not picking on Zyprexa. I want to use this as an illustration of how we have characterized the results of a Zyprexa trial in bipolar, a long-term trial, in labeling.

Again, as I pointed out, we focused on the open run-in period. The findings from these trials are characterized in the clinical trial section and indications and use and then in dosage and administration.

[Slide]

This is obviously too small for you to see but you have this in your handout. The point I want to make here is that this is from the clinical trial section. In characterizing this trial, as I say, we have focused on the run-in phase and what we have said here is that during an initial open-label treatment phase patients who were responders on average for about 2 weeks--so, that was the period of time that patients on average met

response criteria, those were the patients who were randomized to either continuation on drug or placebo.

It also points out that about 50 percent of the patients in the drug group had discontinued by 2 months. I forget how long but I think the observation period was up to a year. I may be wrong but it was a long period of time. But the point is that by 2 months you had lost half of the drug patients and you had lost half of the placebo patients by day 23. Then it just goes on to give the rest of the results. But the point here is that we have been focusing on the open run-in phase so clinicians know basically what you are dealing with here in these patients who were randomized.

[Slide]

Then in the indications and use section, again we have focused in this case on the average duration of 2 weeks being responders before they were randomized.

[Slide]

Similarly, in the dosage and

administration. Basically, it again covers the same information very briefly but focusing on the 2-week duration and saying that the drug showed a continuation benefit or maintenance benefit in those patients.

[Slide]

So, the question for the committee with regard to that issue is whether or not the way we have been translating those findings into labeling is reasonable or whether you have some other advice about that.

Finally, question 12 deals with the issue of whether or not one can extrapolate these findings to a pediatric population. These days, companies are often doing pediatric trials so the situation is this, a company has done an adult program. They have shown acute efficacy in adults. They have done a long-term adult trial and they have shown efficacy. They do an acute pediatric study. Is it reasonable to extrapolate then from the adult long-term data to pediatrics, or should they have to do another long-term trial in

pediatrics? We have taken the position that one can extrapolate but it is an issue that has come up so, if we get to question 12, we would like to have some discussion of that.

I am going to stop there. Thank you.

Questions from the Committee

DR. GOODMAN: Thank you, Tom. Before you step down, I think it is only fair to give the committee an opportunity to ask you some questions.

DR. LAUGHREN: Okay.

DR. GOODMAN: We have about 20 minutes before we get to the next part of the presentation. I would like to start off by asking you two questions, each of which has eight parts!

[Laughter]

The first question has to do with the impetus for this topic. When I first heard that we were going to be looking at the question of the need for long-term efficacy trials I thought it might have been because of the recent series of issues that had to do with safety, issues of safety that emerged post-marketing not only of psychiatric

drugs but others. But I have the impression that that is really not the issue here and I wonder if you could clarify because I assume that when a new entity is being considered for an indication and you have the acute efficacy trial you also have long-term safety data. So, if you could just clarify that question for me.

DR. LAUGHREN: Yes, as I said, this is an issue that we have been thinking about for a very long time. These are chronic disorders. Clinicians, we think, need to have some evidence bearing on the question of whether or not they work long term. But it is also true that the issues over the last couple of years of concerns about safety of drugs, either short term or long term, have factored into this.

Just to think back to last year and all the discussions about antidepressants and pediatric suicidality, it seemed to us in that context that having some longer-term trials in pediatric depression might have been very helpful. I think clinicians view the benefits of many of these drugs

really more for long term than for short term. You know, the long-term trials have a much higher success rate, and it would have been good I think to have some longer-term data as part of that discussion.

But on the safety issue, yes, absolutely long-term safety. And, we generally do have some long-term safety data even if we don't have long-term efficacy. That is really a requirement.

DR. GOODMAN: My second question has to do with precedent. Maybe you could tell us briefly in other therapeutic areas what currently are the FDA policies or requirements--pick cardiovascular--in terms of need in that area for both acute and long-term efficacy data.

DR. LAUGHREN: There are very few precedents, it is true if you look across the spectrum of drugs and indications. For the most part, FDA does tend to rely on relatively short-term data. Now, in some areas, in neurology for example for some conditions like MS or Alzheimer's disease the acute trials are relatively

long-term trials. They are 6-month or a year trials. You can do that because, at least until recently, you haven't had effective treatments so it is possible to do a long-term placebo-controlled trial. The problem that we have had in psychiatry is that for many of our conditions, as I pointed out, like schizophrenia you couldn't do a 6-month or year-long placebo-controlled trial that was done, you know from day one.

DR. GOODMAN: Other committee members have questions for Dr. Laughren? Gail?

MS. GRIFFITH: Tom, when you talk about the minimum period of time that patients should remain in responder status as 6 months, what data did you look at when you formulated the 6 months?

DR. LAUGHREN: You know, there is not a lot of data. I mean, that is part of the problem. This was based in part on looking at treatment guidelines for various conditions where generally the recommendation is that a clinician would continue the drug for at least 6 months. So, you know, we thought it was reasonable to link that to

the design of these studies. In other words, it might be reasonable, for example, in a patient who is having a first episode of depression who has responded acutely. It might be reasonable for a clinician to begin to think at 6 months about whether or not it is reasonable to stop that medication. Whereas, no clinician, even with a first episode of depression, would ever think of stopping it after a month. It just wouldn't happen. So, both from a scientific standpoint and a practical/ethical standpoint, it seemed to make more sense.

But, obviously, there needs to be more discussion of this. It was arbitrary, I will admit that. There isn't a lot of data to back that up, although in preparation for this meeting, there has been some data that has been discovered that may bear on that issue of whether or not you need to have 6 months, whether there is any benefit in randomizing after 6 months compared to randomizing after a couple of months. That will probably come out in the discussion.

DR. GOODMAN: Dr. Pine?

DR. PINE: Could you talk a little bit about, in your mind, the difference between

requiring, which has a fairly obvious meaning, versus strongly recommending? If you require the companies to do something, obviously they have to do it. On the other hand, if you strongly recommend what kind of weight does that have and how would that be implemented? What does that mean, to strongly recommend or strongly encourage?

DR. LAUGHREN: It has very little weight.

DR. GOODMAN: Dr. Tamminga?

DR. TAMMINGA: Dr. Laughren, does the agency now, or would it consider, giving staged indications within a single disease indication so that you could give one indication for the acute treatment and then let some time pass and then give another indication for chronic or maintenance treatment?

DR. LAUGHREN: Well, that is basically the way it is now. As I say, we haven't required until very recently long-term data so the typical

situation is that a company gets an acute claim with their initial application. If they then do a randomized withdrawal study, that trial is added to labeling and it is added to the indication section as well. So, the indication section for the initial filing would focus on the acute data and it would say that we don't know about longer term. In fairness, for certain conditions like depression the dosage and administration section, even if you don't have long-term data, will probably say it is generally recommended in practice that patients be continued but it would emphasize that there are no data to address that.

DR. TAMMINGA: What I was actually meaning was something like a two-year conditional permission so that the whole indication would be removed if they didn't come through with the chronic data.

DR. LAUGHREN: Oh, I see. That would require, I believe, some legislative change. I don't think it is, you know, within our current authority to do that.

DR. GOODMAN: Other questions among the committee members? Dr. Rudorfer?

DR. RUDORFER: Tom, just as a matter of

nomenclature, when you refer to various psychiatric disorders is it fair to say that the agency typically thinks in DSM-IV type terms?

DR. LAUGHREN: Generally, yes.

DR. RUDORFER: And just as a related question, you used the example for the patient with depression that the agency feels 6 months might be a reasonable time to randomize. Has there been any consideration of issues of individual patient history? That is, should patients with a history of recurrences, for instance, be considered differently from people who might be experiencing their first episode or their second episode in decades? In other words, should the individual perceived risk of recurrence in the near term be a consideration?

DR. LAUGHREN: Well, we haven't considered that but it certainly is something that as a committee you can introduce into the discussion

later on.

DR. GOODMAN: Other questions from the committee? If not, let's proceed with the series of presentations on behalf of industry. This will include employees of industry as well as some of their distinguished consultants. As I mentioned, we are going to allow committee members to ask questions for clarification purposes only, and we are going to strive to have some time left at the end of this block of presentations before lunch in order to have an opportunity for more in-depth questioning. Dr. Mark Ammann is our first presenter and he will kick off the series.

While he is getting ready, let me just suggest to fellow committee members that as you listen to these presentations you keep in mind those first two questions that you should have a copy of. The first two are the ones that require a vote. So, we have to get through those two. I am not confident that we are going to make it all the way to the end of Dr. Laughren's questions but at least we have to get through those, and I am sure

we will get further. So, read through those and keep them in mind as you listen.

Presentation from Industry

Introductory Remarks and Review of Agenda

DR. AMMANN: Thank you, Dr. Goodman. I am Mark Ammann, as you said, from Pfizer Global Research and Development. I work in regulatory affairs. What I would like to do is take just a moment to introduce the industry portion of the agenda.

[Slide]

Before describing the agenda I thought it would actually be useful to explain the approach that we have taken in terms of preparing the presentation for this morning. As Dr. Goodman has already alluded to, we actually have a composite presentation this morning.

With the encouragement of the FDA, the ten companies listed on this slide have worked in partnership to prepare an integrated presentation for the meeting. During our initial discussion we recognized that there was remarkable overlap in the

issues that we intended to address. As a result, it was clear that it wouldn't be optimal for each of us to present the same messages repeatedly. I don't think you would want to hear it eight times over and over again. Instead, we elected to work colaboratively, dividing the topics and covering them sequentially in one combined agenda.

In the past couple of months we have also discussed the proposed FDA policy with a number of academic and clinical experts in psychiatry, and have learned that they too share the concerns that we have about how this policy change would impact our ability to bring important new medications to patients in need. For this reason, we have invited a number of them to join us today on the agenda.

Overall, this is a critical issue to industry. Our mission is to develop novel agents to fill unmet medical needs. Collectively, we feel the proposed policy will create an undue barrier to access for patients with psychiatric conditions and is not in their interest, nor in the interest of the physicians treating them.

[Slide]

The agenda for this morning that we have planned is as follows: Dr. Goodwin will begin by

providing an overview of the issues we intend to address in the discussion today. This will be followed by two presentations addressing some general issues in the long-term treatment of psychiatric disorders. Then we move to the disease focused portion of the agenda covering depression, bipolar disorder, as well as schizophrenia. This is followed by some remarks regarding the statistical considerations in the use of active controls for long-term efficacy trials. Next, we provide some perspective on the timing and duration of clinical trials to evaluate relapse prevention. Finally, Dr. Goodwin will return to make some concluding remarks.

We do intend to have a break after Dr. Sachs' presentation, as is stipulated in the agenda. As Dr. Goodman has already mentioned, we will provide a couple of minutes for clarifying questions after each of the presentations, however,

the presentations do build on one another so many of the questions may be better addressed at the end.

I would like to now introduce Dr. Goodwin. Dr. Goodwin is a research professor of psychiatry at the George Washington University, and Director of the University Psychopharmacology Research Center. Prior to that, Dr. Goodwin was the Director of the National Institutes of Mental Health, and prior to that held a presidential appointment as the head of the Alcohol, Drug Abuse and Mental Health Administration. He joined NIMH in 1965. So, I would like to turn it over to Dr. Goodwin.

Introduction/Overview

DR. GOODWIN: Thank you, Mark and thank you, Dr. Goodman. It is nice to be here.

[Slide]

I would like to start by saying that I am here representing basically myself and a group of academic colleagues that I met with about this issue, including Joe Calabrese, Bob Hirshfeld and

Charlie Bowden, all of who, like I do, do our work mostly in affect disorders. I have also been authorized to inform the committee that the views of the Depressive and Bipolar Support Alliance, which is the largest patient-directed advocacy group in the country, are reflected in what I will say this morning. As a charter member of the scientific advisory board of the DBSA, I have had extensive discussions with them about this issue and have gone over my presentation and they have, in effect, signed off on it as reflecting their views as well.

[Slide]

I think we need to start at the beginning which, of course, is the public health implications of what we are doing. We can't forget throughout the whole morning that these disorders are highly prevalent. They cause untold suffering; have substantial morbidity and mortality; and they impose substantial cost not just broadly over society but in healthcare.

As one example in my field of bipolar

disorder that is under-treated or untreated generates twice the medical care costs compared to age-matched controls, and medical care costs represent 94 percent of the total mental health costs or 6 percent. So, anything that we don't do successfully in our arenas has an enormous impact on overall healthcare costs.

Even among the most successfully treated illnesses that we have approximately one-fourth of patients don't respond to existing medications or even the combinations of existing medications. Of course, if you look at the controlled trials and subtract out the placebo rates you are talking about true responder groups somewhere in the range of 25-35 percent, which leaves lots of room for the critical development of new agents.

That is the next bullet. It is not only important to have new agents for various patients in the non-responsive groups but also just simply to broaden the range of available agents.

This bullet I think is my most important point, and that is that I was in the government

virtually all my career and I am very familiar with what we are all taught and what our responsibility in government is and public health agencies, like FDA, like NIMH, along with all of us in academia now with the professional organizations like APA and the industry, we all share one thing which is an ethical obligation to facilitate the timely availability of safe and effective new agents for the treatment of these devastating illnesses. There might be some areas of medicine where what they have available is fairly satisfactory. That is certainly not the case in the major mental illnesses. And, this ethical obligation is especially compelling when we are talking about new treatments that involve novel mechanisms of action which, of course, are what you want with the non-responsive group of patients.

[Slide]

This overview reflecta some of the major points you will be hearing this morning. First, both acute and long-term efficacy data is needed. Everyone agrees with that, as Dr. Laughren said.

But some acute agents are not appropriate for long-term use, as he pointed out, and some maintenance agents may not be effective acutely. He mentioned the example of lamotrigine. So, clearly, making these two very different types of indications interdependent has serious problems, and we will go through some of the details with the speakers who follow me.

Requiring long-term efficacy data for an acute indication has to reduce and delay the availability of new treatments. The cost of trials alone, which are already putting a limit on what companies are willing to invest in--the cost of these trials is going to go up because maintenance trials are more expensive and expecting to invest in a maintenance trial before you have a clear signal from an acute trial is presenting, I think, a major disincentive for the development of new agents. I am, in fact, aware in one company's case that I talked to about a novel agent that I was interested in that under these conditions they wouldn't even go there. The people in the

neuropharm. component of the company would be happy to do it but the top people are saying no, we already were questioning whether we should go there.

There are also real interesting safety and efficacy issues, which other speakers will address, in asking for long-term efficacy before you have the experience, the dosing, the side effect experience and the efficacy signal of an acute trial.

[Slide]

So, the type, the extent, the timing of clinical studies differs by indication, and Dr. Laughren said this or implied this in one of his comments. The type of medication is very different, and the nature of existing data for for medications and class. Hence, there cannot be one size that fits all and the regulatory requirements have to be flexible. This I think was, to my ears, the most important question that Dr. Laughren addressed to the committee.

Stabilization time for discontinuations

will vary by indication. It is one thing to continue with a depressed patient for 6 months on an antidepressant; it is quite another to continue a bipolar depressed patient with an antidepressant for 6 months. That is not, in fact, recommended in the guidelines.

I happen to believe that the way the long-term safety data is currently obtained, which is by open-label extension of the acute trial, is actually closer to the real-world conditions we face as clinicians and, in a funny way, kind of overstates the adverse effects because you don't have a placebo to subtract out.

[Slide]

Now, industry does, of course, provide long-term safety data, as Dr. Laughren noted, at the time of the initial filing as the current regulatory ICH guidelines say. That is by the method I just mentioned. Again, to go to a point I made earlier with a few examples, acute use can be valuable for patients even if long-term efficacy has not been proven or hasn't even been attempted

to be evaluated for certain reasons.

Going back a little bit in history, if you take the typical antipsychotics like haloperidol, there are very effective drugs for bipolar mania but they are not recommended for long-term use because they may trigger or exacerbate subsequent depressive episodes, if you take valproate in mania, a very effective anti-manic drug but it didn't yet achieve its goal in terms of proving to FDA's satisfaction maintenance. Would this mean that under these new guidelines we wouldn't have the market leader in the treatment of mania now, and we wouldn't have that drug because it hadn't passed maintenance before it got its acute indication?

An area that I have been interested in, way back in the early '80s, antidepressants in bipolar depression were not recommended for maintenance use. Indeed, you would get into some safety concerns really about behavioral toxicity in long-term use associated with cycling. Then we have examples, of course, like acute use of

benzodiazepines in anxiety, not recommended for chronic use. Of course, with the exception of one agent, treatments for insomnia are clearly not recommended for long-term use.

[Slide]

The advantages of a sequential approach that I think we will all be speaking to today are that the ethical and safety concerns are not there. When you commit a patient to a long-term trial you already have some acute safety and efficacy data and you feel better about telling your patient in informed consent here is what we see acutely; here is the safety that we have uncovered including with the open-label extension, and it makes it a lot easier to design an informed consent document.

I think this is a very important point about the way the real world works. If you have a drug that is out there acutely and clinicians begin to pick up experience with it, and academic scientists begin to study it more and more and begin to try to extend the use of it, you then get a signal which becomes the basis and the incentive

to do the extremely expensive and difficult task of the long-term trial.

Patients then have earlier access to new options. That is clearly obvious, and you will hear from others estimates, I think rather thoughtful estimates of this new 8policy, if it went into effect, would do in delaying the availability of new agents, not just delaying but, of course, disincentivizing companies to develop them in the first place. But the delay is more easy to establish because we know what time it takes to achieve a maintenance trial and that time has to be spent before the acute indications are given. We can actually estimate how long patients might be denied treatments.

The companies are more likely to invest in novel agents, particularly those that are so important for the treatment of resistant patients, if they can obtain an acute signal before committing to a long-term study. Then, of course, long-term data for recently introduced compounds has been submitted. I think if you look at the

drugs in the depression area in particular, there is a fairly good body of evidence that, indeed, the industry is not going badly in that area. There are a couple of exceptions but, by and large, it is not doing badly in the timeliness of its submissions.

I am going to stop here and I forgot whom I am introducing--Earl. I would like to now introduce Earl Giller, from Pfizer. I am sorry, I forgot my sheet of paper, but Dr. Giller has been an expert in clinical trial design and we have turned to him over the years for his sage advice, and he is an expert in his field. Dr. Giller?

Rationale for Long-Term Treatment

DR. GILLER: Thank you, Dr. Goodwin.

[Slide]

My objective in this presentation is to provide an overview for the rational for duration of treatment across psychiatric disorders, with an emphasis on long-term treatment. I am not going to cover all the areas. The speakers to follow will be doing a fair amount of that.

[Slide]

Just to point out that treatment duration beyond the acute episode really depends on multiple

factors, including diagnosis, illness, the chronicity and course of the disorder, severity, treatment resistance, concomitant therapy. That is the clinical reality. Our focus is primarily going to be more simplistic than that, on the guideline recommendations for duration of treatment beyond the acute episode, which varies from months, for example first episode of major depressive disorder, to several years in schizophrenia, to a lifetime for may patients with recurrent episodes or chronic symptoms.

the clinically relevant stabilization times, as you have heard and you will hear, differ by disorder. Most patients--and this is a critical factor I think that Dr. Laughren was alluding to in terms of looking for data--most patients actually discontinue or switch medications well before guideline recommended durations, and I will show you some information about that.

So, given this variability in the rational for long-term treatment, long-term clinical trials will be different by disorder, indication and the type of medication.

[Slide]

Just briefly to review, most psychiatric

disorders require acute, continuation and long-term treatment, as Dr. Laughren mentioned. New medications are still urgently needed, as Dr. Goodwin has said and you will hear also from other speakers. And, we really need more information about acute treatment before you can go into continuation or maintenance treatment. This phase of treatment prevents the immediate return of symptoms but for many disorders long-term treatment is required to prevent new episodes but, I would also point out, to control chronic symptoms not necessarily associated with an acute episode. So, the disorders differ. Some have episodic nature; some do not. However, the majority of patients do require long-term treatment so that the terminology of maintenance treatment to prevent relapse for

most psychiatric disorders is certainly reasonable.

[Slide]

There is a different course of illness by disorder if you think about it from DSM-IV which supports different trials. So, I think in mood disorders where the episode is maybe 4-6 months--it is hard to know because we don't know what the pathophysiology is and we simply follow symptoms--again, the relapse and recurrence notion is that you have to recover--in other words, after full remission to get to recovery that remission has to last for 2-6 months. So, there is some variability there. However, symptom worsening without full inter-episode recovery is not well defined. So, again, long-term treatment is important even though you think about it sometimes in terms of phases.

In schizophrenia it can be episodic but the episode length is really undefined and you can only really get full remission after a single episode. Most of the time you have inter-episode residual symptoms.

Finally, in anxiety disorders, again as Dr. Laughren mentioned, episode is really not necessarily considered. It is more of a chronic

fluctuating course. So, again, it emphasizes that long-term efficacy studies should differ because of disorder-specific courses of illness and treatment.

[Slide]

This is sort of the classic multiphase treatment approach in major depressive disorder, written about by Frank et al. initially and summarized really by Frank et al. initially, and the diagram from an article by Kupfer et al., where you have the acute treatment phase to get people out of their episode and into remission; the continuation to kind of consolidate that; and any time in here that they have a return of symptoms it is a relapse. Once they have recovered, then it is recurrence. Now, that is a very heuristically helpful way of thinking about a mutliphasic approach to a number of different disorders but, as you can see from the Frank et al. study, we still have this multiphasic approach in thinking of

initial treatment--

[Slide]

--this is an example of patients who start with mania and go to euthymia. Some patients actually go to depression and stay in depression. The yellow indicates people who start in a hypomanic phase and the variable course they can have, and similar for depression. So, this multiphase approach is important but it is much more complex in bipolar disorders than a simple model that you would get from major depressive disorder.

[Slide]

The guidelines for duration of long-term treatment start anywhere from 4-5 months after remission from major depressive disorder. To Dr. Rudorfer's point, maintenance or much longer-term treatment than continuation really depends on the risk of relapse and the severity. So, you might not have long-term maintenance for first episode of major depressive disorder but you would for recurrent or severe. As you can see, the range is

from 4-5 months to years, and for some patients chronic maintenance treatment.

[Slide]

However, do patients usually last in treatment, the same treatment for the length of time the guidelines suggest? Very rarely. Here are some prescription data discontinuation curves. If you start here with a first prescription and follow patients continuing to refill a prescription that get treated with the same medication, these are discontinuation curves on SSRIs--fairly similar here. The median treatment is 4-6.5 months but that also includes acute treatment.

Similarly, in discontinuations of antipsychotic treatment in schizophrenia and bipolar disorder, by the time you get out to 6 months you are talking about a minority of patients who are sort of super stable. They are not really representative of the initial population of patients who were treated. The median here is 3-4.5 months. So a clinically relevant stabilization period of about 2-3 months, given

these curves, is certainly reasonable. The patients remaining after 6 months are a small minority.

[Slide]

We can also see similar information from clinical trials. Here are the discontinuation curves from the CATIE study. At 6 months 40 or 50 percent of patients are left. I think sometimes in clinical trials, because there is an emphasis on holding onto patients, the recruitment rate is a little bit better but, even so, it is fairly steep.

[Slide]

So, in conclusion, clinically relevant stabilization time is about 2-4 months across a number of disorders because of discontinuation rates in clinical practice and trials. So, long-term treatment is actually a series of short-term treatments.

The regulatory requirements for long-term treatment should be flexible because the type, extent and timing of long-term clinical studies differs by indication, the type of medication and

existing data for the medication and class.

One suggestion, and you will hear more about this as we go along, is that expert consensus workgroups should be convened to develop guidelines for appropriate study designs for long-term efficacy data for each indication. Thank you. Questions?

[No response]

I would like to introduce Dr. Robert Leadbetter, who is Group Director within the Neurosciences Medicines Development Center at GSK and is based in North Carolina. He is a psychiatrist and specialized in clinical research in severe schizophrenia prior to joining industry. He currently leads the clinical development programs for bipolar and schizophrenia at GSK.

Disease and Compound Specific Approaches to the Development of Psychotherapeutic Agents

DR. LEADBETTER: Thank you, Earl.

[Slide]

Basically, as has been outlined already, the issues facing the committee today center around

the issues of will a delay in filing to obtain long-term data be in the patient's best interest, i.e., weighing the benefits of obtaining that data versus delaying the availability of medications to patients in need. In addition, obviously, there is a lot of discussion that will follow around what the designs should be for long-term trials and how they should be influenced in terms of the designs based on the illness in study.

So, as has obviously been stated already, currently the policy is to submit data for acute efficacy at the time of NDA and provisional longer-term data subsequently. Our position is that when and how long-term efficacy data are provided should be determined on a case-by-case basis.

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There are factors that influence the decision. Basically, some psychiatric diseases require long-term treatment. Clearly, that is the case in the majority of times. However, some only need acute therapy, and that has been alluded to

already, whereas some, again, require long-term targeting. Obviously, psychotropic drugs differ in their pharmacokinetic and pharmacodynamic properties and those should influence study design.

So, our stance is really that the differences in treatment goals and product characteristics should influence when and how long-term data should be provided. The study designs, obviously, should be adjusted accordingly. So, the idea of one size does not fit all is a theme you will hear through the subsequent presentations.

[Slide]

To give some specific examples, and Fred already has alluded to some of these, basically, there are situations in which patients only need acute symptomatic treatment and then treatment is withdrawn, i.e., acute bipolar depression with antidepressants, and typically the short-term use of hypnotics for insomnia. In addition, there are some psychiatric disorders that do not require long-term treatment such as delirium, brief

reactive psychosis and adjustment disorders.

[Slide]

Again, some illnesses clearly are targeted for long-term treatment, i.e., to prevent or delay future episodes. The example of lamotrigine has been mentioned a couple of times already and will be mentioned again. This is a situation where acute efficacy has not been established to meet the regulatory requirements, and the FDA took it upon themselves to take a novel approach to approve lamotrigine for long-term use despite the lack of sufficient evidence of acute efficacy.

Other examples include anticonvulsants and beta-blockers as other ways of thinking about long-term treatment targets. Finally, there are examples of chronic persistent or deteriorating symptoms where the probability of spontaneous remission is very low. Clearly, these are situations where long-term therapy is necessary.

[Slide]

In addition, compound characteristics need to be considered when considering study designs and

studying products specifically for various psychiatric disorders. Examples include the use of benzodiazepines for anxiety. Clearly, they are not used long term or should not be used long term but SSRIs can be used longer term fairly safely.

We would also note that in the development of novel therapies it may be that these novel therapies require different approaches to establishing long-term efficacy, and the pharmacokinetic factors, such as long half-lives, also need to be considered when putting together study designs.

[Slide]

Study designs to generate long-term efficacy data should be determined on a disease target and compound sort of specific basis. There are issues, a number of which will be raised in subsequent presentations, around randomized withdrawal studies as a specific type of study design to obtain this information. There needs to be taken into account the known consequences of treatment interruption. In some cases the risk to

the patient actually may outweigh the knowledge gained. There are other limitations such as generalizability which, again, will be discussed in subsequent presentations.

[Slide]

So, to require long-term data at the time of filing will obviously delay availability of new treatments to patients. There are certain things that we feel you need to have established prior to launching long-term efficacy trials. Clearly, some evidence of acute efficacy is typically needed. An understanding of the dose response relationship is important before exposing patients to long-term therapy. Typically, there is some longer-term open-label safety data prior to launching long-term efficacy trials and, clearly, all this data needs to be sufficient to obtain IRB approval before long-term efficacy trials, which might include placebo, would be considered.

So, our position again is that the additional information gained with inclusion of longer-term efficacy data at time of filing needs

to be weighed against the potential delay incurred in making new medications available to patients.

[Slide]

In summary, the differences in psychiatric disorders, treatment objectives and compound characteristics necessitate an individualized approach for long-term efficacy requirements. Providing long-term efficacy data at the time of filing will incur a delay in the submission of NDAs and this time loss must be weighed against the potential benefit to patients.

Questions? If not, it is my job to introduce Dr. Potter. Dr. Potter is currently with Merck Research Laboratories and runs the CNS clinical development. Prior to that, he was at Lilly for approximately six, seven years, and prior to that was at the NIMH for over 25 years.

Informative Studies of New Therapeutic Agents in Major Depression, GAD and Panic

DR. POTTER: Thanks very much.

[Slide]

Good morning to everyone.

[Slide]

Just a quick overview of the points I would like to cover, and to get to some of Dr.

Laughren's comments, for depression the current approach is actually "have delivered" the data necessary to use in a broad population. Second, as Dr. Goodwin and others have already emphasized, the greatest need right now is for us to find novel antidepressants that either have greater efficacy, better onset or a better risk/benefit ratio. As a field, we have been worrying about that and our research to achieve the optimal yields with the current designs should be applied to this medical need. This is where we have done our research, how do we use the current designs to get better signal detection and introduce new drugs? We haven't been studying proposed new designs for which there is very little data, as Dr. Laughren admits. Alternate studies supporting registration is a matter of research, and we will come back to GAD and panic.

[Slide]

Now, the goals of treatment studies everybody has already reviewed so I will skip by this.

[Slide]

I will make the argument that if you look at the current requirements, what we have found out

historically is that these are delivering remarkably well for major depression. The real point here is why are these not still a reasonable standard for novel agents since, again, we have been trying to understand the sources of variability to picking up effects of antidepressants using the designs we have been using over the last twenty years? Okay? So, that is what we studied. That is what we understand.

[Slide]

Even understanding those, how effective have we as a field--I don't mean the pharmaceutical industry; I mean as a clinical research field to try to apply the rules of molecular pharmacology to novel antidepressants--been?

[Slide]

This is a slide that, when I was at Lilly, we put together about a few drugs out there being tried for depression. Not a single one of these, as far as my knowledge, is going to reach the market, except for a couple of these. This is an enantimer of fluoxetine and in Europe that is available. But all the rest of these are novel mechanisms, some big PhARMA, some small PhARMA. So, what is wrong? Are these just terrible

targets? Are we looking at the wrong things? Or, is it so hard to really pick out what is a new and different drug with new mechanisms, in the current environment, that we have a lot of failed studies?

[Slide]

Well, we know we have a lot of failed studies because this very nice review, by Dr. Khan that came out a few years ago, taking the FDA summary basis of approvable data sets shows you that for those antidepressants we call new antidepressants we are basically talking about SSRIs so they are not even that new. I mean, this is fluoxetine data so most of these are not even

new by scientific criteria. Of those, in the original trials 52 percent of trials failed, and these trials included doses later known and proved to be effective. Okay? Even standard antidepressants which have been around for very long, which have a very large effect size, side effects, and all the old tricyclics and whatever comparators they used, even there we are seeing a fairly high failure rate of trials.

[Slide]

So, clearly, those of us interested in coming up with novel drugs, we have tried to understand and study what we call signal detection. Obviously, this would be a matter of hours of going over data sets but, suffice it to say, the variables that go into that high rate of failed studies have been an immense focus of research for us, both in academia and industry, over the last eight years or so.

[Slide]

I am just going to highlight again that GAD is a similar analogy, and then show you some of

the high level findings. This is another phenomenon independent of failed studies. You notice that even with benzodiazepines which back here, around 1980, were showing a difference of about 6 points on the HAM-A, in other words, a large effect size, over time--same designs; same drugs--go out and study GAD and, as you get out to 2000, you are lucky if you show a 3-4 point difference. So, our ability with what we call secular trans-emerging populations to pick up new drugs is not as sensitive as it used, you know, just trying to get patients in studies.

[Slide]

Actually, in the venlafaxine FDA summary basis of approval--now, this is not all separate studies and some of these doses are across studies, but you see that only three times was it possible to show that venlafaxine separated from placebo, and you notice that here the differences are barely reaching the three points that you get with benzodiazepines but, nonetheless--and I believe we believe this--this is an effective drug for GAD.

[Slide]

So, just to highlight very quickly some of the factors we research which contribute to all

this variance and signal detection with our current designs, there are very marked differences both in efficacy measures sometimes and side effect measures depending on what country you go to. This is quite systematic in terms of reporting. So, this is a phenomenon we need to understand better. So, the way we run our studies you see something different in terms of effect size and safety profiles.

There is what we call a ski slope phenomenon. In the traditional single-blind lead-in period everybody after randomization shows a big decrease and now this has been shown systematically to be of no value whatsoever, and we are moving as a field to tests of double-blind alternatives, at least for depression and we believe this might have been useful in certain studies, when I was still at Lilly, around duloxotone where rates of signal detection were

greater.

We find great evidence of systematic bias. Without going into details, the way in which we constrict entry criteria cluster severity rates. This has a huge effect on what you see in terms of efficacy, and the rating scales themselves need a great deal of attention. The items on rating scales that carry the information--for instance on the Hamilton only 7 items carry all of the information driving the registration of antidepressant drugs. So, we are learning a lot. Why not apply what we are learning and use the studies which we understand better to enhance our new drug detection?

Moreover, there are these secular trends, these issues such as why do people even enter studies? Probably a lot of them do because they were partial or noon-responders to existing drugs like the SSRIs. This might be good if you are picking up a novel drug but, gee, if you can show efficacy in these patients with a novel drug don't you want to have that drug available as soon as

possible? I mean, isn't that what we are about?

Of course, the lack of novel agents, as Dr. Goodwin has already said, biases the way in which we invest and the wish for a novel drug is so huge, for instance in places like Merck which invested literally--well, without going into numbers, a great deal--

[Laughter]

--in pursuing an idea that people believed in very much and wanted very badly. So, you did very large late-phase studies based on really rather limited early clinical efficacy data, failed studies. This has not only happened there; it has happened to others. This does not help the field. It doesn't help industry. It doesn't help academia. It doesn't help the public. And this is the way the world works when you use our current systems to drive drug development.

[Slide]

So, what is the value of the current study design? Well, it is something we are understanding better. So, given this heterogeneous disease,

there is a shifting population of people to study. Shouldn't we be thrilled if we can actually establish sub-acute efficacy that is, you know, for a few months with a really novel drug and bring that forward and then deliver the next stage?

On a more technical point, in fact, the large drug effect size that you see in the discontinuation studies actually only confirms and predicts the long-term efficacy. I mean, that is just what the data says in depression. It is possible it won't always happen but why assume now that it won't? What is the risk of working on this and bringing in the long-term studies next?

Finally, as we have already seen, 6 months on drugs obviously means more dropouts. There is hard data on that. It is going to have restrictive effects on patient populations. I can show you what we mean in terms of bias. And, it is going to be less informative because you have this bias population; you have a very different population and it is going to be less informative at this point of development if what we are interested in

is getting at least one novel antidepressant out there. Finally, I am going to show you that a 2-3-month design captures both those who truly require drug and those who are out of episode by 6 months.

[Slide]

This would be a point I guess for extended discussion. I have taken this slide directly from the Pittsburgh study maintenance therapies in recurrent depression. This is a classic study, 12 weeks followed by discontinuation. The top two lines are either imipramine with clinic visits or imipramine with some therapy. The bottom line is pure placebo.

The point I want to make here is that whatever design you choose, whether you include psychotherapy or not, ultimately people stabilize pretty well. Now we are out to 120, 144 weeks. This curve is remaining flat over time. The only curve that continues to fall asymptotically out here at 132 weeks as it asymptotes out is the placebo curve. So, there is nothing in here to

suggest that the signal that you are getting between, say, drug and placebo early on using the current discontinuation designs, isn't representative of your drug effect and, if anything, underestimates your long-term drug effect. So, what is the risk, what is the danger in using the current design is the question we would pose.

[Slide]

For GAD and panic it has already been acknowledged that these are chronic conditions, particularly GAD, and the big thing with benzodiazepines, of course, for discontinuation is a rebound effect. It is interesting when you look at GAD as a secondary indication, because that is what it has been recently for some of the SSRIs or SSRIs plus venlafaxine at higher doses. The pattern that you see is remarkably similar to that in depression. Now, maybe it just happens to answer coincidence but that is the way it is working.

[Slide]

I just want to take one example from the Stocchi et al. paper, showing with paroxetine a lead-in period of only 8 weeks and, again, you see

the deterioration over time, which takes a few weeks out to almost 6 months to plateau out and the drug [sic] stays stable and improved. Again, the curve that is shifting is the placebo curve, not your drug curve.

So, I am really not clear on what is driving the idea about specifying a particular stabilization period at this point of how we understand our data. Here 8 weeks is doing remarkably well in terms of signal detection. To get to Dr. Laughren's point about effects of parallel study design for 6 months, in fact, you see the same effect size with that even without the stabilization. So, again, what is the evidence for different signals with these different designs?

[Slide]

Finally in conclusion, we would argue that for depression the current approaches do deliver the data necessary for drug use in a broad

population are particularly compelling and appropriate for getting to this greatest need for finding novel antidepressants since we understand better how to use the current designs than we used to. Our research in achieving the optimal yields should be applied to this need for new antidepressants. Whether alternate studies supporting registration would yield benefit is a very interesting question but should be researched. Give us a chance to generate data. Give us a chance to do some of the research on that that we have done with the current designs. Finally, GAD and panic might benefit actually from a formal consensus discussion among experts as to best studies to support registration.

Thank you for your attention. While the slide is being brought up, the next speaker will be Dr. Joseph Camardo and he is the Vice President of Global Medical Affairs at Wyeth. Thank you.

Key Questions Engendered by Proposal to Change Long-Term Efficacy Requirements

DR. CAMARDO: Good morning. I appreciate

the opportunity to speak today.

[Slide]

I want to start by making two points. The first--I think we could agree on this, that the current development paradigm under which drugs for psychiatry have been approved is actually very scientifically rigorous; it is very practical; it is very rational. We have studies of 8 weeks or so. Those are considered for approval. We have post-approval commitments to answer the questions of longer-term effectiveness.

The second point is that the randomized withdrawal study is a very powerful design. But the 2- or 3-month average baseline is a very tried and true method that has told us a lot of what we have learned in the last several years. A 6-month period might be appropriate in some specific circumstances but it shouldn't be applied as a new standard for all drugs all the time for all psychiatric illnesses.

In his memo, Dr. Laughren wrote that the relevant clinical question is what is the

probability of relapse after stopping a treatment in a patient who has responded. Dr. Laughren noted also that most clinicians would not discontinue treatment in a responding patient after only a few weeks, and this is absolutely true. The randomized design is not clinical practice. It is a clinical trial tool and it repeatedly confirms what we have learned about all these illnesses, which is that they are episodic; they are chronic; and in general patients have fared better with continued medication.

I prefer to ask the question in this way, what is the probability of staying well if you continue on the drug? In this regard we do have a lot of studies and you will hear data that show that a drug that reduces the symptoms, for example of depression, over the short term has an excellent chance to keep the patient free of depression symptoms.

I want to make a third point. Truly better drugs for psychiatry will not be developed simply by changing the protocol designs or by

requiring long-term data earlier. It is a problem that can only be solved by a better understanding of mental illness and more work in the laboratory.

[Slide]

You have some questions to vote on today and I would like to pose three additional questions for your consideration. They are questions we asked ourselves. What are the strengths and weaknesses of the proposed changes? Will the proposed requirements improve the programs? Does the current process need to be fixed?

[Slide]

Let's go to the first question. What are the strengths and weakness of the proposal? I think everyone would agree that the longer run-in period for stabilization will enrich even further the trial population with patients for whom early relapse, over the first 6 months, is less likely. This is a strength in terms of clinical trial design if you want to study these particular patients.

But you have seen, and you will see more

data today showing that the weaknesses of the design and the lack of practicality of execution are drawbacks that may outweigh the strengths. The reasons I conclude this are as follows:

The 6-month period is not consistent with current treatment guidelines for all illnesses. Those are based on evidence and practice. And, 2-3 months is generally designed as a reasonable stabilization period. The longer period--I repeat this--will enrich the study population but not with the average kind of patient, rather, with a subset of patients not broadly representative of a condition. This may make the trial less attractive to investigators and to patients because the results cannot be easily generalized, and I would suggest that the somewhat limited results of a trial like this might actually be less attractive to the regulatory agencies.

But regardless of the study design, the request for longer-term data prior to approval presents a feasibility problem. A critical aspect for long-term studies is the need to determine the

effective dose, as well as to know quite a lot about the efficacy and the tolerability of the drug and we often don't know that until the end of Phase 3. We could not easily do short- and long-term studies in parallel without a very high risk of non-informative results and, as you know, we generally do many short-term studies because in psychiatry the rate of non-informative results is pretty high.

That is the reason why we find the current process rational. It allows us to do the controlled short-term efficacy studies, prepare and submit the NDA and concurrently complete the next phase of post-approval development with good knowledge of how the drug is acting. This helps us avoid doing studies that are non-informative due to, to take a very obvious example, that the dosing was not optimal.

[Slide]

I want to pose a second question. Will these new requirements improve the development and availability of new psychiatric drugs? Let's

consider first that there are good treatments available but everyone agrees that the response and remission rates are way too low. We should have better drugs.

I want to suggest that this is not a result of development programs lacking rigor and scientific validity but it is, rather, the result of the complexity of psychiatric illness. So, I submit that changing the development programs alone will not solve the problem which is basically the need for new molecular entities. Furthermore, at the current time we can be confident for at least three reasons I can think of that short-term efficacy generally predicts long-term effectiveness.

First, we do not have many late failures, that is, drugs that work for 6 weeks but fail routinely in 6-month withdrawal studies. We have some but not many. Most drugs approved based on 8-week studies, especially in depression, demonstrate longer-term benefit.

The second, we do leave some decisions up

to the judgment of practicing expert physicians treating individual patients. Practice confirms the benefit of continued treatment for most patients.

The third, the APA's clinical practice guidelines, to take an example for treating major depression and this is based on literature review evidence, recommend continued treatment.

Now, one thing we do know and others have mentioned this and this is unfortunate, many patients do not continue medication and this is a critically important problem. But, like with more research to find new molecules, this isn't the result of faulty development and it won't be improved with earlier or different kinds of long-term data.

Others have proposed, and will propose later that the development paradigms need to link the design of the trials and the approval requirements with the specific condition and the specific drug. For example, longer-term effectiveness will be an absolute requirement for a

drug that maintains remission but is not good at inducing remission.

The proposal that is on the table today does not seem really to be consistent with the drive we have to find new ways to improve clinical development, being very specific and targeted, and make new drugs available more rapidly. I think we all would have to be convinced that any change from what we currently have, which is rational and practical, would lead to better drugs and that is really the goal.

[Slide]

Finally, the third question, should the current process be changed? Let me make it very clear that long-term effectiveness data is a benefit for patients. We all agree on that. Up to now, the data have been submitted by all of the companies using a randomized withdrawal design, or some variant of that, and it has always merely confirmed what we might have predicted.

[Slide]

However, I would suggest that the

scientific incentives and the current post-approval process for generating the long-term data has actually been working. It may not be perfect but it should be improved and not abandoned. The current process selects out for an accurate determination of the dose; good definition of the efficacy and tolerability; and safety of the drug; and it allows treatments to be approved and made available while longer-term outcomes are being defined.

As long as we have sufficient safety information and good post-marketing surveillance for safety, approval on this basis is a low risk situation. It is low risk because in practice physicians will use their judgment to decide in individual patients how to continue the drug, and they will only do this if the drug is working and if it is tolerated.

Finally, we suggest, and others have as well, that the new approach may delay access to novel drugs. This is not just by more than the additional time of the run-in period. That is only

the new follow-up. It would not account for the need we would have to recruit larger studies, have more sites, analyze more data and then, finally, we would have to wait until the long-term studies are done before we could submit the NDA. As I said, we can't always do the long- and short-term studies in parallel. We estimate that the change could add at least, in the best case, one year and possibly more to the average NDA program for promising new drugs for patients with psychiatric conditions. This would be especially problematic for novel drugs with untested mechanisms of action. In this situation delay is ultimately a disadvantage for patients because in these areas--we have all said this--they are still not enough optimal treatments.

I can't say this enough, we support the need for long-term effectiveness data. We have conducted and will continue to conduct long-term trials. That is not really the issue. But this is best accomplished with a more flexible approach to determine the actual study design that is required and to allow for this as a post-approval

commitment.

I want to thank you for your attention, and I am pleased to turn the program over to Dr. Gary Sachs, Associate Professor of Psychiatry at Harvard, who is an expert in bipolar disorder. I see there is a question though.

DR. LAUGHREN: Yes, I just have one question. You know, one fact that has not been entered into the discussion as yet is the fact that the EMEA guidelines for major depression for filing do require long-term data at the time of initial filing. Could you comment on that since you are obviously directly involved in that, and whether or not you think that is a wrong policy?

DR. CAMARDO: Actually, Dr. Sachs is going to comment a little bit on that. I can't say that is a wrong policy. It is a policy that we live with and we hold up our submissions in the European Union partly because of that policy. I can only say that we think it makes more sense to have the kind of policy we have in the U.S. which is to do things in this step-wise fashion. But we have our

NDAs ready and they sit on the shelf until we get the rest of the long-term data. Routinely, what we do--and I can ask my colleagues to elaborate if you want--is we are just waiting for data and it usually doesn't change what we would have done in the first place, but we are waiting for it. So, I can't say that is a bad policy; I just say it is a different policy and we prefer the one we have in the United States.

Issues with Long-Term Trials in Bipolar Disorder

DR. SACHS: Good morning.

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I am Gary Sachs and I direct the bipolar clinic and research program at Massachusetts General Hospital where our staff treats more than 800 bipolar patients.

I really want to express my appreciation to Wyeth, Solvay and Astra Zeneca for allowing me to use the time that is allotted so that I can bring the perspective of a clinical researcher to this question. I have lots of consulting relationships with the companies here, but I

thought it was important that I come today on my own dime. So, I may have to run out to the airport to catch a cheaper plane at the end of this--you will understand!

[Slide]

Many of the other speakers have addressed the issues before you quite broadly. I am going to have the luxury of focusing in on bipolar disorder. There are some principles that I think we can use to frame the discussion. The principles that are helpful to me are that we want the standards, of course, to reflect the interest of patients; that research design should be informed by the clinical epidemiology to the degree to which we know it. I think we would all also agree that the best design methodology is that which optimizes the validity as well as the feasibility of studies. I think we all really agree about these principles. They are not controversial.

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Now, in understanding bipolar disorder in particular you cannot escape the fact that this is

a very cruel disease. What I hope you can see from this data from Jules Angst is that the standardized mortality ratios are telling us one thing very clearly, and that is that good treatments save lives. We need more good treatments for our patients, no question about it. We would like to have these ratios collapse all the way down to one.

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When I heard FDA was going to look at the approval policies, I thought what a great idea. A lot more could be done; a lot more could be done better. The question is whether the policy of requiring approval at the time of acute indication, requiring that we have long-term efficacy, is that really a good idea? I would argue that the public interest is really not served by this requirement; that this requirement could be causing a lot more harm and confusion than benefit.

Why would I think this way? Well, I really think that if you were to say we are going to hold up acute approval until we have long-term efficacy, that would be like telling somebody with

a heart attack that we have a drug that could work for your heart attack but we are not going to give it to you because it hasn't yet been proven to prevent subsequent heart attacks. I don't think that would be a very good policy.

[Slide]

What would be a well considered policy in this area? Let's think about this carefully. Is there really a need to protect our patients who get treatments that have been only proven to work based on short-term efficacy? We know they work there but we don't yet know that there is long-term efficacy. Well, if you think this through I think you see that there are relatively small numbers of patients who could benefit from this and large numbers who could potentially be harmed. We know that when treatments don't work patients stay on them very briefly; that effective medications are discontinued over relatively short periods of time; and that most patients who use medications long term are using them for a reason, either because they have responded acutely and they perceive a

continued benefit, or because they actually suffered when they tried to discontinue them.

I am going to go into this data in a little bit more detail but this thin slice, the green slice is the slice that people who would continue long term. We will see from some of the studies that have been done that this probably constitutes less than 10 percent of the patients who start a medication.

[Slide]

Now, when we recommend a medication be used long term, that is all well and good but our patients sometimes have different ideas. This is data on continued use of lithium in cases where patients have been diagnosed with bipolar and it has been prescribed. What you see is a kind of fall off at the edge of the earth sort of curve. We may recommend staying on it but you can see that for the majority of patients, they have other ideas and, for whatever reason, almost as soon as they walk out of the hospital they are stopping their treatment. You can see that only 8 percent of

patients stayed on lithium for 90 percent of the time it was prescribed, and the median duration of use turns out to be less than 3 months. Well, that is a treatment we all say is good for life-long use.

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Bipolar disorder is certainly a life-long condition, but the organizing principle for treating bipolar disorder is around the episodic nature that we understand bipolar disorder to consist of. This is the principle for us because we are going to use it to direct our treatment against the acute episodes or to prevent the recurrence of those acute episodes. So, we do use this idea of a multiphase treatment strategy which you have heard before. We separate treatment into acute, continuation and maintenance.

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Here is a little schematic like the one you saw before. If we think through the case of how we would be treating a patient for whom we had a treatment that had acute efficacy but had not

been shown to work in the long term, let's take the worst case and apply this. We have a patient and we are going to be beginning treatment when they are acutely ill. They would respond to treatment and we would continue on it.

The point of this strategy is not so I can determine what to call a relapse or a recurrence. It is so I know how to direct my strategy acutely because when the patient is doing well I want to consolidate that recovery and I want to get beyond the natural course of that episode before I would consider making a change, before I would consider myself to be in the maintenance phase. This is the way we would direct treatment.

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Now, the basic paradigm that I use at the critical decision point, let's say for bipolar depression, is that I am going to look at the evidence of what works and I am going to choose this drug that has been shown to work acutely. Now, it would be great to know that something had also been shown to work long term, but let's take

the example that we only know it works acutely. I am going to be offering that treatment and perhaps some others to patients. They choose it. I measure the result. This integration of measurement into management is a key clinical concept. If the patient is doing well with that treatment, each time I go through their evaluation I need to decide whether they are going to stay with it or not.

[Slide]

Now, the way we talk to patients about these decision points is along the lines of a grid like this where we are constantly looking at the ratio of benefit to adverse effects. So, it is quite easy as I do my assessments. If there is no benefit, that is the end of that trial. Right? Patients are not going to stick with treatments that don't work. It is also a very simple decision when we have treatments that do work because that favorable ratio means that we continue. Of course, the big grey area--patients really get to make this decision. I do not tell patients whether the risk

to benefit ratio is positive; they tell that to me. As a clinician, I have learned to listen to that.

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Now, this idea of continuing what works is not just clinical tradition. It is actually based on some data. You have heard a little bit about Ellen Frank's operation at University of Pittsburgh. This is a study that was done there that actually backs up this idea of staying with what works beyond the acute treatment phase.

In this study patients came in with an acute episode of depression. These bipolar patients were randomized to receive initial acute treatment with a fancy form of psychotherapy called interpersonal social rhythm therapy plus medication, or, in the black box, just structured medication management alone. Interestingly enough, the response to those two treatments acutely did not differ. There was an equal percentage of patients who recovered with each of those treatments.

We then move on to the next phase. For

those recovered patients, they are re-randomized to either stay on what they had been getting or move to the opposite treatment. Now, the idea here was to show the benefit of this enhanced psychosocial intervention but the results did not show the benefit of a treatment.

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What the results actually showed, the top two purplish lines, is that the people continued to get whatever had worked for them before. The two yellow lines are people who changed their treatment. Even adding psychosocial intervention was destabilizing. I really fear that many of our paradigms for research, particularly maintenance research, are treatment disruption paradigms and I think they give misleading results and I think we have to bear this in mind as we look at the studies that are put forth.

[Slide]

How well do our currently available treatments work for bipolar disorder? Well, for bipolar depression there is no single agent that

has FDA approval. Data from STEP-BD and the Stanley network really, as I will show you later on, has under-scored the need for more acute treatments. There are 8 FDA approved medications for acute mania. But look at the data from all the 3- and 4-week studies that have been used to establish the efficacy of these agents and you will see that, without exception, every one of those trials has ended with the patients having an average severity score that would still qualify them to enter the study anew. So, we have 8 treatments better than placebo but we are nowhere near good enough on that score.

When we look at preventative treatments, there are four approved agents. You heard that one of them doesn't have an acute indication. Now, if I was to require long-term data proving efficacy, I would reduce my entire pharmacopeia, the agents I have available for my patients, to three or less. That would be a devastating impact. We clearly need more treatments. There is no surplus of treatments.

[Slide]

Let me take you through those agents that have been shown to work for bipolar depression. We

have three positive monotherapies, lamotrigine, olanzapine and quetiapine, and the one FDA approved combination of olanzapine and fluoxetine. As I said, these agents have been proven to work.

[Slide]

Here are the efficacy trials. I am not going to burden you with understanding these. All of these, from a statistical point of view, were strongly positive. However, it plays out a little bit differently in my clinic.

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What I would want you to understand is why there is such great need. So, we have a little metric we have developed for clinical effectiveness. This is sort of a rough metric of how you might expect the data from those trials to transfer in our clinic, and I think it gives you a much more realistic picture.

In the first column we have who did the

study; then the response rates. But if we take those response rates we get a very rosy picture. We need to combine them with the completion rates. So, this clinical effectiveness index is simply taking the product of response times completion and that is what that "CE" column stands for. When you start to look at the clinical effectiveness you can also look at the clinical effectiveness of placebo in each of those trials.

So, I have taken one of the principles from evidence-based medicine to give you a sense of how robust these treatments are and computed a so-called number needed to treat. That is, how many people would be required to get this treatment before one more got the benefit of the treatment compared to placebo. Okay?

What you can see here if you look at those numbers is that we need between 5 and 17 people to get that treatment. If you are not familiar with number needed to treat, think of it as going to the store and buying cereal. If you are getting 25 percent more in this deal buying the cereal

package, you have to buy 4 before you get a free box of cereal. If I need to treat 17 patients before I get a benefit, that is not a very robust treatment. Even needing to treat 4 or 5, I think we could do better. Our treatments are nowhere near as good as we would like them to be.

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In terms of how long people use these treatments, you can see here median duration of use. For lithium, it is really nice to know that we get our patients using lithium almost 6 months. Valproate and lamotrigine is the same. But for atypical antipsychotics and antidepressants you can see median durations of about 3 months. So, that is where we are in terms of how long our patients take them even in a specialty clinic.

[Slide]

I want to quickly tell you about acute phase and maintenance phase results from that Stanley study that I mentioned before. If we were to look at the acute phase, we have over 1000 patients in the Stanley Foundation Research

Network. Half of them or so got an antidepressant but only 186 stayed on them for 60 days or more, and only 84 remit. That means with the clinical intent to treat bipolar depression we get a whopping 15 percent. Well, that is who moves on to the maintenance phase.

[Slide]

In this quasi experimental report that Altschuler published you can see the rate at which patients suffer recurrences over time. What we really get from this is only 15 percent ever better. Over 4 months, whatever group they are in, we lose a quarter of them so we are down to 11 percent, and then whether you stay on an antidepressant or not the benefit through a year is somewhere between 4 and 9 percent--hardly an impressive result.

[Slide]

From STEP-BD we get a little different picture when we view the data. I show you acute phase treatment involving 2000 bipolar patients for 377 clinician indicated intent to treat an acute

bipolar depressive episode. At 90 days, if they got an antidepressant added we had 21.5 percent recovered but if they didn't get an antidepressant it was 27 percent recovered--no evidence that our treatments are working very well and. As we go through the maintenance phase, by the time we get out to 3 months we have lost half of those patients who have recovered--not indicating great efficacy.

[Slide]

So, we clearly need better acute treatments for our patients. There is no compelling need I think--no more compelling need than to have better treatments for bipolar depression and I don't see that it is as yet reasonable to raise the bar for approval.

[Slide]

We have seen that less than 10 percent will benefit and I don't think that there is any compelling benefit even for those patients who stay on treatment long term.

[Slide]

I think to sum up this part of the talk,

the thing that I would say is, yes, I would like to know about the long-term benefits of treatment. I think our patients would like to know it. But I don't think it would be reasonable to ask patients to sacrifice what it would take to have that data at the time of submission for an acute indication.

[Slide]

I want to move on from there and focus on the question of designing trials. When you are designing a maintenance trial, I think what Tom said is that there really is no great substitution for the current randomized study that we use. But we apply the same principles to thinking about treatment and we would want to think long and hard about the stabilization period. I think we should emphasize that when we say stabilization we are talking about what Tom referred to as the time of being in the responder status because this really is a critical determinant of outcome in these studies, as we will see.

In terms of the validity and feasibility, I just want to emphasize a couple of points before

I get into this. The DSM-IV actually gives us a definition for what it means to be recovered from a mood episode. It is 8 consecutive weeks of being well. The new proposal calls for 6 months for all chronic conditions, and Tom has acknowledged that that is arbitrary.

We will see that the EU gives rather different recommendations and I am not sure that it makes sense for us to use one for all various clinical entities. I am going to talk a little bit about the idea of enrichment because all of the successful maintenance studies have used enriched designs. I think we want to be careful about this because it can be misleading.

[Slide]

Now, for different disorders our colleagues in Europe actually do recognize the differences in clinical epidemiology and, therefore, have different recommendations about stabilization period. We may or may not agree with them but certainly they take an approach that is different for each illness, and I think that is

what makes sense.

[Slide]

Focusing in on this idea of the stabilization phase, the time in the responder status, I want to share with you a little data from STEP because our definition is 8 weeks. We use the DSM definition. There are two curves that we generate looking at the data from STEP. The orange line is showing us the time to having a full episode but, as you are probably aware, maintenance studies don't allow patients to slip into full episodes. We consider that to be unethical. Instead, we wait for what we call in STEP roughening. We are talking about new sub-syndromal symptomatology developing that requires an intervention. You can see that the curves for both of these are actually rather steady, gradual curves. I have been told to be careful referring to this as radioactive decay in Washington, but this is kind of what a radioactive decay curve would look like.

[Slide]

Now, when we get to the studies, I think Dr. Laughren also mentioned this study. This is a Lilly study. What you can see in the placebo group

in particular, the dotted line here, is not a radioactive decay curve. It is a falling off the edge of the earth curve. Of course, the point I want to make to you is that the duration of time in responder status is something that can allow us to judge whether we have accomplished what we want to in the stabilization period, whether we have gotten a gradual curve or a very sharp immediate steep slope. That lets us know have we gone long enough to have patients who are truly in remission. He mentioned that half the patients were done with the study I think in 23 days in the placebo group.

[Slide]

This is with adjunctive treatment, another Lilly study. It turns out in this study that in 15 days 25 percent of the patients were gone with relapses. Again, immediate steep slope. These studies used very brief periods of being in the responder status, sometimes one assessment based on

rating scale scores and patients were randomized. I think we would all agree this is a treatment disruption study that did not randomize well patients.

[Slide]

This is a GSK-sponsored study, just so I can be an equal opportunity critic. You can again see in the white line, which is the placebo, an immediate steep slope. This study randomized patients who were well on monotherapy for just one week. No surprise in this.

[Slide]

We can look and we can see this data from Stanley again. The Stanley study, you may recall, is a quasi experimental comparison and patients were well 6 weeks. Whether they stay on an antidepressant or not, there is a gradual radioactive decay type slope. And, some clinical trials that have been submitted to FDA actually used these more reasonable lengths of being in a responder status in their pivotal studies.

[Slide]

This is a BMS-sponsored study and it compared aripiprazole, in the gold line, to placebo, in the dotted line. Here, again we have

restored that steady, gradual slope. But pay attention to this. What intrigues me in this very successful study is that the curves don't separate until we get out to 3 months. You might say that those curves look pretty much the same for the first 3 months. So, what has happened in the study is that perhaps we have randomized a number of patients who you might refer to as pseudo responders. I will come back to this idea because enrichment really is key to having a successful study.

[Slide]

In the grey bar you are seeing an Abbott-sponsored trial where we can get a handle on enrichment by taking the proportion of patients who were randomized and divide it by the total number who entered the study. So, 65 percent of the people who entered this trial actually got randomized. That low rate of enrichment resulted

in a failure to detect a benefit not only of valproate but of lithium as well. So, low enrichment, low chances for success.

The other studies we have seen were enriched by only randomizing less than half or about a quarter in the Stanley study and only 15 percent of the patients made it into the comparison. Well, that is very interesting. The key idea of enrichment is that we have true responders.

[Slide]

But let me take you through a little experiment so you can see how inherently difficult maintenance studies really are. Let's make some conservative assumptions and see what our obstacles are to feasibility. Let's imagine that our eligibility criteria for randomization are that we have a responder. That is what all the studies have done. But a true responder and an operationally defined responder are not the same. We know from acute efficacy studies that let's say we have for whatever our active compound was a 50

percent response rate and for placebo 25 percent. That means that in calling somebody a responder there is a 50/50 chance that they are a true responder and a 50/50 chance that they are what we refer to as a pseudo responder. Well, if that is the case, let's assume that what we saw in the BMS study with aripiprazole is true and that the response rate of pseudo responders would be the same whether they would be in the placebo group or the active group. I think that is a reasonable model, maybe not a complete model.

[Slide]

If we did that, and we were to do a study where we are looking for the difference between placebo and active, we could power the study based on the idea that the placebo group would have a 60 percent relapse and our active treatment group would have a 40 percent relapse. Well, in that case our enriched sample, the group that is going to get randomized, would be half true responders and half pseudo responders. Our placebo cell would have 100 patients, again half pseudo and half true

responders but they would have 60 people who would relapse. If we look in our active cell we would still have 50 pseudo responders, and if that group responded the same as they had in the placebo group they would contribute 30 relapses. That would mean that to make our 40 we could have no more than 10 relapses among the true responders. That means there would be a pretty stiff challenge for treatment. It would have to work 80 percent of the time in maintaining benefit in true responders.

[Slide]

Well, that is a challenge but if we were to cut down the group that gets randomized to cut out the people with the shortest cycle lengths, because we are going to require a much longer period in the responder status, we would be cutting the relapse rates for both groups. So, let's say we were going to do the study now and we are looking for a 40 percent relapse rate in the placebo group and 20 in active, well, you can follow the exact same math and say, okay, we are going to have 40 relapses in the placebo group but

now the pseudo responders would account for 20, and that would mean that to succeed in this study active treatment would have to be 100 percent effective. You can imagine going to the management in any company and saying we can succeed if we are 100 percent effective, and they would say what other drug could we study? I don't know that we are going to do this research. That means my patient doesn't get that treatment.

DR. GOODMAN: Excuse me a second, Gary. I probably just missed this but could you go back and clarify what the definition is of a pseudo responder?

DR. SACHS: Yes, what I was referring to is based on this idea, so we are looking here at this BMS trial and notice that over the first 3 months of the study the curves are essentially the same. So, we randomized these patients based on them all meeting response criteria. Okay? So, obviously, since those curves are the same you have to get the idea that they are not all the same responders. Even though they are in the active

group, they are having a relapse rate the same as in the placebo group over the first 3 months.

So, what I have suggested here is based on the idea of the predictive value of calling somebody a responder. What are the chances that they are a true responder? Well, if the placebo response was half of what the active response was I am assuming it would be about 50 percent. Okay?

[Slide]

So, if we use a 6-month stabilization period, this is the distribution of cycle lengths in step, if you will. What we would be doing is truncating this. We would be only randomizing people with long cycle lengths. This would definitely be an unrepresentative sample.

[Slide]

I don't want you to just rely on this calculation to say, gee, that is kind of nice on paper. Let's look at what the implications of this would be for some of the studies we have already looked at. We looked at this study from the Stanley Foundation. If I were to limit it to just

those people who were well 6 months or more, here is what the data would look like. All of a sudden, this big gap has been greatly reduced and I don't have a finding anymore. My strongest finding has gone.

[Slide]

What about the data from Ellen Frank's group? Here is the original finding, on the right. Look at what it would be conditional on having a 6-month response. We have lost the separation between those groups. So, this is more than just theoretical.

[Slide]

That brings me to the conclusion. In terms of validity, one size definitely does not fit all. The data does suggest on the whole that we got you well; we keep you well, but it looks to me like we could all agree 1 week and 2 weeks are insufficient, but with 6 weeks and, clearly, if we went with the DSM definition of 8 weeks, we would be having a sufficient duration of being in that responder status to get valid results, to have that

steady slope down in our placebo-treated groups. So, a 6-month stabilization period, I think you would agree, would greatly increase the challenge to showing that any new entity would work for maintenance.

[Slide]

I also think that we have to consider the feasibility. Six months would require a much larger sample and we would have to be treating lots of patients, and these larger samples will increase the time for there to be rater drifts and all the kinds of problems that actually Dr. Potter alluded to that plague our current designs. It would be that much worse. We would increase the enrollment time and that would not only necessarily delay but could also prevent the introduction of new therapeutic entities. So, let me stop by saying that this proposal to have a 6-month stabilization phase is clearly against the interests of patients. Thank you very much.

DR. LAUGHREN: Just one question, just to clarify your recommendation for an 8-week

stabilization phase. That means that the open run-in would have to be longer than 8 weeks.

DR. SACHS: Absolutely.

DR. LAUGHREN: It would have to be perhaps 12 weeks, or long enough to get a sufficient number of patients who have been actually stable for 8 weeks.

DR. SACHS: Absolutely, that is the idea.

DR. GOODMAN: We are scheduled to take a break at 10:30 but I would like to take that break now.

DR. AMMANN: Could I just make one comment?

DR. GOODMAN: Sure, go ahead.

DR. AMMANN: Dr. Laughren, you had raised the issue with regard to the European guidelines and I think we would acknowledge that they are guidelines in Europe of a regulatory nature that do require long-term data at the time of the original approval.

I think a couple of points need to be made though. I think the development programs that we

have in place, just to reiterate what Dr. Camardo said, have anticipated in them a substantial delay in introduction of those products. Moreover, I think it is important to note that the guidelines that exist in Europe have differing requirements by indication. There is not one size fits all applied across that, and in no case are the guidelines stipulating the design that is under discussion today in terms of a 6-month prospective stabilization followed by randomized withdrawal. So, I think it is important to point out that there are some substantial differences in what they have in place there versus what we are talking about today.

DR. GOODMAN: As I said, I would like to take our 15-minute break now. Before we do, I want to remind you about the rules of engagement, so to speak. In the spirit of the Federal Advisory Committee Act and Sunshine Amendment, we ask that the committee limit their conversations about these issues to the public forum of the meeting. To help the committee with this, we ask that industry,

press and other members of the audience not discuss today's topic with committee members during breaks and lunch. The weather is always an acceptable topic and so is the World Series! Let's reconvene in 15 minutes.

[Brief recess]

Long-Term Anti-Psychotic Trials:

Challenges and Opportunities

DR. POLYMEROPOULOS: Good morning. First of all, I would like to thank the agency and PDAC for allowing us to express our thoughts and opinions today on this very interesting subject.

[Slide]

I am Mihael Polymeropoulos. Along with my position at Vanda Pharmaceuticals, I am a physician and have practiced psychiatry for many years in the Washington, D.C. area so the issues in front of the committee today are very dear to me.

Vanda's mission is to use genetic and genomic technologies to optimize therapeutics to treat diseases that are in front of us today. On this very issue of examining the long-term efficacy

of compounds in psychiatric disorders, Vanda believes that it is very useful to accumulate and have long-term data for both depression, schizophrenia and other chronic psychiatric diseases. However, as many on the panel have discussed and Dr. Laughren addressed as well, one size does not fit all. These are different diseases. They have different disease burdens. They have different treatments and different courses.

So, we believe that in order for one to examine and answer the questions in front of the panel today we need to examine one disease at a time. We have focused at Vanda on understanding schizophrenia and we will describe our thoughts in schizophrenia for the purposes of this discussion. In fact, that brings you to questions nine and ten later in your list which address does the discussion apply to schizophrenia and other diseases. Question ten is are alternative designs possible?

So, we have concentrated on discussing an

alternative design that in a way counters a lot of the issues that many of the speakers, including Dr. Sachs, addressed before, that is, the role of active control designs in the treatment of schizophrenia. In fact, just to point to the EMEA dialogue and discussion, on this matter EMEA has accepted active control designs as a standard for long-term efficacy examination of schizophrenia studies.

We think, however, we would like to set forward a method by which one would understand whether active control designs are valid in the case of schizophrenia or any other disease. We have done our independent work and talked to a lot of experts in the field, and we believe there are two domains that one needs to examine before answering this question.

The first domain is the statistical domain, and we will talk quite a bit about that. The second one, a very large one, is the ethical domain. What are the ethics for conducting these trials? On the statistical domain, Vanda has done

its own analysis and research, and has consulted with experts in the field, and concluded that in order to determine validity of active control designs two assumptions need to be understood and met before these designs are valid.

The first one has to do with a historical separation of active versus placebo. What does this mean? It means that patients on active control do better and patients on placebo fail to address the symptoms of their disease. We know that historically in schizophrenia studies that separation has held in short-term and in the few long-term studies that we have. As you heard from previous speakers and Dr. Potter, this is not true in the case of major depression where it is a lot tougher to separate active from placebo. So, assumption number one most probably is met in schizophrenia.

The second assumption has to do with the margin of separation between active and control. This difference has to be identifiable and has to be consistent in order for this design to be valid.

We have asked Dr. Gene Laska to discuss his own analysis of historical aspects and how these assumptions are being met in the case of schizophrenia trial designs. After our own analysis, however, and explorations with experts in the field, we have concluded that both these two assumptions for validity of active control, non-inferiority designs in schizophrenia are being met.

On the second aspect of ethics, Dr. Nina Schooler will discuss the historical perspective over her 30 years of experience thinking about placebo-controlled studies and what it means in identifying effective treatments, but also what it means for patients and their lives and the impact that these trial designs actually may have.

Finally, while our mission is to optimize therapeutics and bring them forward with these advanced technologies, we have a long ways to go and until we get there we need to use a thorough scientific and ethical objective approach to understand trial designs.

Dr. Nina Schooler, from Georgetown University, will address the ethical aspects and she will be followed by Dr. Laska, from the Nathan

Kline Institute. Thank you very much for allowing me the time to express our thoughts.

Long-Term Anti-Psychotic Treatment in Schizophrenia: 30 Years of Data and Experience

DR. SCHOOLER: Thank you so much.

[Slide]

I want to thank Vanda Pharmaceuticals for inviting me and I want to thank the committee for giving me this opportunity. As I say in this title slide, I have been doing this for a long time and what I would like to do is, rather than review mountains of data with you, I would like to give you the perspective of some of the studies that I have been involved with or that I have observed closely, and give you a sense of how I feel about these things.

[Slide]

First of all, what I am going to talk about is the issue of prevention or, to be more

precise in schizophrenia, delay of relapse because one of the things that you will see is that there are always relapses in the active groups. So, we do need long-term trials that target symptomatically stable patients. We know that placebo produces high relapse and rehospitalization for patients that are treated in the community and that, even for hospitalized patients where there is more protection, we see symptom exacerbation.

Then, last what I would like to address is the question of whether we can conduct placebo-controlled trials without these consequences. My judgment is that rescue medications are largely ineffective in this context but I will show you some data and I would like your reaction to that as well.

[Slide]

So, first we have what is probably one of the classic trials in schizophrenia which was a relapse prevention trial conducted by Gerry Hogarty. I was part of the group that was involved in this study. These were patients with a

schizophrenia diagnosis who were community dwelling and stabilized. They had been identified in hospital but discharged to the community and were stable for at least 12 weeks. We had a 2-year treatment period and a 2 X 2 design comparing chlorpromazine, a drug I am sure you have all heard of, to placebo with the addition of a psychosocial treatment versus treatment as usual.

The definition of relapse was a stringent one, requiring return of psychotic symptoms. Indeed, we say in the paper that we validate our definition of relapse by the statement that a substantial proportion of patients were actually rehospitalized. It was supported by the NIMH and conducted at three hospitals in Maryland, where we are today.

[Slide]

Here are the cumulative relapse rates for the 4 groups. The top 2 lines are the placebo and, as you see, this reaches 80 percent at 2 years. The bottom 2 lines are for the drug treatments. I will also call your attention to the 6-month point,

which is a point that will be considered further by Dr. Laska. You see that already at 6 months there is very substantial separation between the two. There is a sense of asymptote here at 80 percent. There were over 300 patients in the study so the Ns are about 75 in each of the 4 groups.

[Slide]

What we conclude here is first, obviously without statistical test, the placebo relapse rate is significantly higher than active medication. Finally, you have 80 percent of the patients relapse and what you see even further that is important is that 75 percent of those relapses went on to rehospitalization. This is, of course, in an early era. The placebo rate was relatively consistent over time. We estimated approximately 3 percent. The psychosocial treatment might reduce relapse rates in the second year. There is some hint of that, not statistically significant, but only in patients receiving medication.

[Slide]

This is 1990s placebo-controlled relapse

prevention trial, the study that is known as the Zeus trial. This was conducted in Central Europe. Patients with schizophrenia were hospitalized but stable; a one-year treatment period; three doses of ziprasidone versus placebo. It was a definition of impending relapse that depended on daily observation over a 3-day period. This was sponsored by Pfizer.

[Slide]

Here are the survival curves for the 3 drug treatments, active and the placebo. Again, here you see a very, very steady decline in those who were relapse-free in the placebo group. If you look at the 16- or 26-week period, again here you see substantial separation.

[Slide]

So, the risk of rehospitalization can't be estimated here because it is a moot point given the fact that patients were already in hospital. But the medication-placebo differences do increase over time.

[Slide]

In summary--and these are just two exemplary studies from a host of studies that have been conducted over the last 45

years--antipsychotic medications are effective in delaying relapse, and I would emphasize the point that they do not prevent it. What you see is a delay because all the studies show relapse on medication. Among patients who are stable on medication, placebo differences may be difficult to detect in the first few weeks of placebo substitution.

Now, Dr. Sachs addressed this question of whether those people were actually in the bipolar disorder situation, whether they were true responders, or were people who had not really responded. That is one possible interpretation of the high relapse rates during that initial period. An alternate interpretation is actually methodological and suggests that when people are doing a trial with placebo they are very quick to consider a change as representing a relapse because the operative assumption has to be that patients

are receiving placebo.

[Slide]

Then the question becomes can we design long-term controlled trials in a manner that will actually prevent undue harm to patients? The phrase "undue harm" is a difficult one as well and something that I think the committee should consider when they think about this issue. What is the level that rises to undue?

[Slide]

There has been a strategy that has been developed in schizophrenia which is based on the fact that for many patients prodromal signs and symptoms often precede relapse. The idea is that the monitoring of these early signs could allow early intervention before a full relapse occurs. The strategy has several names and any time you see any of them, it is the same thing. It has been called early intervention, targeted treatment or intermittent treatment. What is important about this strategy is that it depends on relatively frequent observation of the patient.

[Slide]

We designed a study. You see this says over 1980s to 1990s. It took us ten years to do it

and we didn't start until the middle of the decade. This was called the treatment strategies in schizophrenia study. They were patients with schizophrenia and schizoaffective disorder. They were community dwelling, stabilized patients with families, and the families were there for two reasons, one because we were also interested in a family-based intervention but, secondly, because we wanted patients to be in situations where there were people available to observe prodromal signs.

We looked at 3 doses of fluphenazine decanoate, a moderate dose, a low dose and essentially the administration of the vehicle only which was actually a placebo. Then in interaction we also had a high and low intensity family intervention. Early intervention with oral or additional decanoate was provided at prodromal signs. Now, this was in all groups so it is not that you had a condition where the early

intervention was only for those receiving placebo.

Our definition of relapse is not precisely relapse. Since we were looking at strategic intervention, our question was whether we needed more than 140 days of additional medication. If that was the case, we concluded that the strategy, whichever one of these 3 was, did not work. It was multicenter in the U.S. We had five sites and it was sponsored by the NIMH.

[Slide]

Here are our results. What I would like to suggest is I recommend squinting for looking at these lines. Here you see the survival curves for the 2 groups that received the moderate dose closely intertwined, in the sort of greenish lines for the low dose, and in the red lines for the placebo with early intervention. Early intervention in all groups, and the study numbers here were in the 60-65 per group range.

What you see again is an issue that is important I think, that if this study had been a short study we would have seen no difference

between the treatments if we had only done it for 6 months. We would have concluded from this study that, indeed, the early intervention strategy was a very good one. By 12 months you can separate the moderate dose from the low and the placebo, and it takes you up until about the second year before you see the difference between only early intervention versus the 2 groups that received rescue medication, building on a platform of medication.

[Slide]

Essentially, the conclusions from this are that in terms of this outcome measure early intervention alone looks like placebo. The relapse rates were the lowest in the moderate dose, intermediate in the low dose and, of course, highest in that group. Equally important, with the early intervention treatment we were unable to forestall relapse in these patients so that 48 percent of the early intervention group experienced a rehospitalization in the 2 years compared to only 25 percent in the moderate and low dose, suggesting that the notion of rescue is not easily feasible.

[Slide]

So, our conclusion is that early intervention does not effectively prevent relapse;

that the relapse rates look much like those with placebo; and use of impending relapse will not prevent rehospitalization. The suggestion, of course, from this is that withdrawal of medication in stable patients may have substantial social and economic effects on patients even if they are monitored closely and restarted on medication. For example, people may lose jobs. They may lose housing. They are destabilized in the community.

[Slide]

Here is a brief summary--75 percent rehospitalization in a community sample with placebo; 48 percent hospitalization even with early medication and I would say that the use of placebo leads to unacceptable risks.

I want to take the last minute or so to present you with a scenario that I am in very often as a researcher studying patients with treatment, that is, sitting across the table from a person and

presenting a clinical trial as an option to this person. For the placebo controlled withdrawal study in schizophrenia my presentation would go something like this, what I would like you to do is to start treatment with a new medicine, and we would like to offer you this new medicine because you have not done well on the medicines you have received before. If you do well with the new medicine, length of time to be determined, then what we will do is ask you to stop taking that medicine by chance. We will toss a coin and some of you will get to continue; some of you will stop. Then we will follow you until you relapse or up to X period of time. I must tell you that in my prior experience this happens for people who are taken off medication in approximately 80 percent of the time. Would you be willing to participate in this trial? For me, that particular presentation is an unacceptable scenario and if I were offered the opportunity to conduct that trial I would have to respectfully decline.

Thank you very much for your attention. I

should do my next course of action, which is to introduce Dr. Gene Laska, from NYU and the Nathan Kline Institute, a more than distinguished biostatistician and an old friend. Gene?

Some Statistical Issues Regarding the Use of Active Versus Placebo Controls in Longer-Term Efficacy Trials

[Slide]

DR. LASKA: Let me thank Vanda also for allowing me this opportunity in supporting the work that went into preparing this talk, and the committee and the FDA as well.

[Slide]

It is clearly not required to go over the findings of Montero who reported that something like 42 percent of patients with schizophrenia will relapse in a year, and for those who discontinue medication it is almost certain at one year, a finding by Widen and Olfson.

[Slide]

So, the issue that is before the house at the moment is whether or not we can do the clinical

trial in another way, that is, we must acknowledge up front that comparisons to placebo in a randomized trial are clearly the gold standard. That is the way to find the best evidence possible. But in circumstances where it may be unethical to use placebo when alternative treatments exist, is an active control trial using a non-inferiority design an alternative that will convey some validity?

[Slide]

The logic of the approach goes like this, if a standard is consistently superior to placebo and I am trying to show that T is superior to placebo, it should suffice to show that the test is as good as or not as good as the standard. That is the logic without the statistics.

[Slide]

To put it into a framework where we can do some scientific testing, we need to set a value, which we commonly denote by delta, to be the non-inferiority margin, the degree to which one treatment is equivalent to another if the two don't

differ by more than that margin. That is again clear from a great big placebo response but these two treatments are pretty close to each other.

[Slide]

How do you do it statistically? Well, in the simple form you test the difference between test and control, the two treatments in the trial, and form a confidence interval around that difference. If the confidence interval lies completely in the non-inferiority margins the two are equivalent. If the confidence interval covers the outside line but fails to cover this one, then you can declare non-inferiority in one direction, and here is non-inferiority in the other direction and, not an uncommon finding, although not in this area, a confidence interval that spans those two limits is essentially uninformative.

[Slide]

The question that is somewhat knotty is how to determine a non-inferiority margin. If one sets it too large it is entirely possible that an inferior treatment will be called non-inferior.

That is a mistake or a type 1 error. If it is too small, then huge sample sizes are required and it becomes impractical. So, statisticians and others in lots of fields usually have selected to use some fraction of the historical control difference between control and placebo.

[Slide]

The ability of a randomized trial to detect something that ought to be detected is called assay sensitivity. If there is a true difference, then we would like to find it. This assay sensitivity is the property of one trial, to clarify the language, where sensitivity is often talked about as being the property of a class of designs. So, the question is are the class of designs-- placebo-controlled, non-inferiority--are they sensitive enough to do the job required? This last piece is called by statisticians power, a concept you have all looked at.

[Slide]

Now, a 3-armed trial allows the detection of assay sensitivity if the trial results and

comparisons are statistically different between placebo and the active or the standard and the active--sorry, I said that wrong, between the test and placebo or the standard and placebo. But if the trial shows no difference among the treatments what can you conclude? Well, you conclude the trial has no assay sensitivity because the standard wasn't better than placebo, but you can't really draw any inference about the equivalence of S and T because there was no sensitivity in this trial.

[Slide]

A 2-armed trial has a different set of properties. If you find a difference then ipso facto the trial has sensitivity but if the two are not found to be different, then what can you conclude? You can't tell whether the trial failed or whether the trial found no difference properly. So, how do you make some judgments about whether the trial we are considering today is useful?

[Slide]

Well, we have to go to the record. We can only conclude that the approach is valid if we have

a placebo in the trial or if we can go to the historical record and reach the conclusion that if we see that it happens all the time in prior studies, then we might be able to believe it there too.

[Slide]

So, I did that. I went to the literature and found one major source, published in 2003, which was a kind of meta-analysis that included many studies, and two subsequent studies were published after the 2003 data and I used those trials. I didn't include any studies that failed to use the Kaplan-Meier approach because those trials are providing estimates that are no very reliable.

[Slide]

This is the result of that review. There were 5 trials. These are trials in which placebo was compared to atypical. This column represents the relapse rate at 6 months and the next column is the placebo rate. The lines connect the 2 points which are from the same trial. Rather

interestingly, you see that the placebo rates were always in the 50 to low 60s range. This had a bigger spread. The slopes of these lines look remarkably the same. These trials are different, with different criteria, different run-in periods. One has to take a deep breath when one puts them all on the same slide. Nevertheless, the results look remarkably consistent.

[Slide]

These are the trials in which an atypical was compared to a conventional. The lines, again, remarkably roughly have the same slopes, with a certain notable exception and a couple of slopes that are different. But in every case, except one, the conventional treatment had a higher relapse rate than the atypical.

[Slide]

Putting them together on one slide, one sees how the influence of the drug that is used together influences the outcome. So, the atypicals are somewhat higher but not very different than those in the conventional and the

placebo-controlled trial.

[Slide]

The numbers break out like this. The range of atypicals relapse rates in 6 months were 3-39; conventionals, 3-47; placebo, 53-63. You see no overlap between the actives and placebo. The mean relapse rates are shown in this column and, again, there is very large separation of placebo from both the conventionals and the atypicals. The mean value for the atypicals will depend on what the other trial drug was. Apparently physicians behave differently in knowing what the alternative treatment is, maybe patients too. Here are the mean differences. They are very small relative to the sizes we are talking about.

So, one sees a relatively consistent pattern across these trials. To do a full, fair and complete analysis one would have to do a meta-analysis of all these trials in a formal way, possibly using Bayesian priors. There is a lot of work yet to be done.

So, the next remark is, in art form,

post-impressionism maybe, maybe even abstract impressionism I am not sure. But it might be reasonable to suspect that what we will get out of such a trial is a non-inferiority rate between 10-15 percent if a new drug were tested against a conventional, and maybe 15-20 percent which is kind of generous, if it were tested against an atypical.

[Slide]

Just to give one illustration, if the rates of relapse are assumed to be about 35 percent for the control and the test, which is a little high, and the delta, the non-inferiority margin was set to be 15 percent and the 2 groups had equal sample sizes, then it would take about 183 patients per group to have power of 0.8 to be able to declare non-inferiority when, in fact, it was true that there was non-inferiority. So, these will not be easy trials to conduct. It doesn't take into account how many patients you need to put into the trial to get to the point where you can do the relapse prevention study.

[Slide]

Now, the regulatory concern is the same in this trial as it is in an acute trial. It is important to know what the probability of a type 1

error is. That is, what is the chance of concluding that an ineffective drug is effective in long-term use? But the historical record that I have described to you looks to me to be pretty consistent in will give one I think some confidence that such a strategy is valid and, given the considerations of the ethical points, may be worth being very serious about. Thank you very much.

Our next speaker is Dr. Michelson, who is from Lilly. He is the head of the early clinical CNS drug development program.

DR. GOODMAN: Dr. Laughren has a question.

DR. LAUGHREN: Gene, I just have a couple of questions. I wasn't entirely clear how you arrived at that margin. I mean, I looked at the Vanda materials and, as I understand it, there are 6 studies that you are looking at here.

DR. LASKA: Vanda produced its own materials. I had nothing to do with it.

DR. LAUGHREN: Okay.

DR. LASKA: These are a different set of studies. I did it totally independently of them. But your question is technically right on target. One needs to get a proper estimate of what the treatment differences are. Mine were

impressionistic; they were not based on a formal analysis.

DR. LAUGHREN: Because I was looking at their chart and I picked the smallest difference as a place to start. That is one way of doing this.

DR. LASKA: Yes, it is.

DR. LAUGHREN: Then if you take half that as the margin I get to 10 percent.

DR. LASKA: Yes, I wouldn't disagree but if you did it against atypicals--well, the table shows you. The atypicals are 39 versus 53 so you are not far off. This is still subject to work.

DR. LAUGHREN: Okay. I guess the other general question is, is this enough of an experience to feel comfortable that you have thoroughly explored the question of consistency of

the placebo response?

DR. LASKA: Right, that is a very tough question. My subjective view, not done with a formal analysis, is that the placebo data was what is the most comforting. That is always in this range. The atypicals certainly bring it down tremendous amounts and there are no failures. This was in all the trials. So, 10 out of the 11, something like that, showed a large difference independent of so many factors which you know affect the outcome. It leads me to be somewhat confident. I would be happy to have more formal work done to finalize that story.

DR. GOODMAN: We are going to have at least 20 minutes for discussion.

Timing and Duration of Relapse Prevention Trials in Psychiatric New Drug Development

DR. MICHELSON: Thank you.

[Slide]

I am David Michelson. I am responsible for early phase clinical development at Lilly in neurosciences. What I want to do is go back, sort

of as the last presentation before Dr. Goodwin comes back and summarizes, to speak to a couple of the sort of earlier questions that you were asked and to provide some perspective on them, really from the perspective of someone who is struggling with both doing the studies and thinking about them as part of sort of an integrated drug development program.

[Slide]

In particular what I want to touch on is the questions the FDA has asked around what evidence or when evidence should be provided around long-term efficacy, and whether it should be provided earlier than is typically the current practice and, secondly, whether the 3-month lead-in adequately assesses efficacy.

I think we all agree this is not a discussion about whether you should have long-term efficacy data. I think we all agree we clearly should and it is in everybody's interest. It is in the patient's interest; it is in the physician's interest; and is also in PhARMA's interest to have

long-term data.

Given that, the question is really how much data, researched how, at what point. I would argue that the process of establishing that is really one of figuring out what is the balance between facilitating new treatments coming forward, making new drugs available to patients--I think we have had a lot of discussion today about the need for treatment--balanced against providing optimal information.

Around these two questions, I think what you have to ask is, first of all, is it really established that current practice provides insufficient data? That is, do we really feel like there is a risk of approving inefficacious treatments doing it the way that it is typically done today?

The second piece is given the changes that are being proposed, given particularly for example the change around duration, are you actually going to get clearer, more interpretable data? So, are you going to do this extra work and end up with a

more informative data package? Because, if you think of it in terms of this balancing of facilitating versus providing information, the flip side of it is that there is no question that the changes are going to make the conduct of studies more difficult. They are going to make bringing forward a new NDA more difficult. I am going to show you some data to suggest that it may be considerably more difficult.

So, in that context, I think what I would like to do is to show you a few analyses from some of the studies that have been done, basically to look at some historical data and to try and understand what might be the effect of some of the changes that are being proposed.

[Slide]

So, I have gone back and looked across several indications of some of the relapse prevention studies that have been done with various drugs at Lilly. So, we have depression, panic disorder, ADHD, bipolar, mania. Schizophrenia is not up there but I am going to touch on that in a

moment.

Basically, you have a chart here looking at the typical 8-12 week, mostly 12-week, initial periods. What does attrition look like? Then, you obviously continue in the trial in the blinded phase and look at what would attrition be had you carry that period forward to 26 weeks. What you see is that typically attrition is around 50 percent at 3 months so basically you have lost about half the people who started the trial. If you carry it out to 6 months you are going to lose typically around 70 percent. That is a little bit different in ADHD where you have better retention rates but basically you are looking at 3 months and 50 percent across most disorders; 70 percent loss across most disorders at 6 months.

I think that is important because basically what you are talking about is generalizability and you are talking about interpretability. That is, how applicable are data that come from a very small set of the universe that you originally randomized which is in itself

already a smaller set because it is a clinical trial, not usual clinical practice? So, how informative is it going to be in terms of potential for selection bias; in terms of generalizability of the sample to pull that out?

[Slide]

Does it apply to schizophrenia? Well, I couldn't go back and do this with olanzapine studies because they are conducted slightly differently. Basically, patients were stabilized at the outset. But if you look at the bottom bullet point there, in 12-weeks studies the typical attrition rates or all-cause discontinuation rates in olanzapine studies run about 50 percent. So, I think the likelihood is that in schizophrenia the numbers are going to look very similar, at least based on the Lilly experience and based across a number of different disorders.

[Slide]

There is another aspect to duration of initial treatment that I want to touch on. One of the other issues, actually, that I didn't say but

is important around attrition is that it is going to increase sample size. Right? The more people that drop out prior to randomization, the more people you are going to need to have at the outset in order to get an adequate sample at the time of randomization. In the previous talk you saw that the randomization samples need to be fairly large.

Well, what I have done here, there were actually 2 studies in which we did more than one randomization. That is, a randomization at 3 months and then a randomization at a later point. One of them was an older study that Charles Beasley did with Prozac and one of them is a more recent study in ADHD with atomoxetine that I was involved in.

What you can see in both of them if you look at the chart is that you have 12 weeks, 26 weeks and 52 weeks. In the Prozac study, where there were randomizations after 12 weeks and after 26 weeks, I have shown you the relapse rates for the relative treatments. What you see is that the treatment effect difference, that is, the relative

risk for relapse on drug, doesn't really change but the event rates go down considerably. The effect of that is that your sample size requirement goes up markedly. So, if you want to do a randomization at 6 months you are going to have a considerably larger sample size based on the fact that the event rate goes down and based on the fact that you have higher attrition before you get to the point of randomization. So, these become very big studies, in this case almost 800 people.

It is probably going to differ a little bit from disorder to disorder but the take-home message is that it is going to be big. Even in ADHD where you have relatively less attrition, the sample sizes are still quite large and increase significantly as you push out.

So, is this just sort of an industry bias against wanting to do larger trials? I guess what I would say, with a little bit of chagrin, is that we wrote up the ADHD data at the 1-year relapse and the push back we have gotten from reviewers, that is, from the field, is that it is not

generalizable. The concern is essentially that we are not convinced that these data apply broadly to ADHD. That is essentially what we were being asked to respond to in writing it up. So, I don't think this is a parochial concern.

[Slide]

I think there are some other issues around duration of treatment that are worth thinking about. We just talked about the treatment effect sizes. They don't really decrease markedly with longer run-ins. I think what that suggests is that the drug is working in the same way. There is something going on in terms of the disorder that changes but the treatment effect sizes don't change.

We have looked at attrition. We have looked at event rates. We don't know--we really don't know whether there is another issue around selection bias, which is whether longer stabilization time just makes patients more stable or whether you simply selected for those patients with a more stable course of illness.

In terms of sample size, you have another problem which goes to the issue of positive controls. If you require these for approval, if

you require them to be able to be interpretable at the time of approval, what are you going to do with a negative study? And, if you put a positive control in there the study is that much larger, that much more impractical.

To one of the other questions that has been asked, you can certainly increase stringency around what you want in terms of excursion; in terms of what you want in terms of response rates; but you are going to have marked effects again on sample size. In terms of practicality in doing the studies, you create a variety of issues.

[Slide]

Let's switch a little bit to the study timing and when you do them. It ought to be intuitively obvious. These studies are bigger and longer in duration than acute studies or sub-acute studies. They take significantly longer to conduct than do acute efficacy studies. If you ask for

them at the time of NDA approval you will delay approval and you will delay patient access. I think it is fair to say that you are going to delay that significantly. I will show you a little bit of data around that.

Why is that important? Well, it is important if you believe that there is a critical need for new treatments and there is a critical need to get new treatments available to people who aren't doing well on what is currently available.

[Slide]

This is from the atomoxetine database and it shows you two of the pivotal trials and then the long-term relapse prevention study. There is a little bit about the study description but, basically, if you look in the last column what you have is how long did it take to do these trials. So, you can see they actually went pretty quickly for the pivotal acute trials and it took two and a half years, more than two and a half years to do the relapse prevention study. We can argue about is it going to be exactly the same in every

disorder. It will probably be a little bit different in depression, somewhat different in schizophrenia relatively, but it is almost always going to be the case that the relapse prevention trial is significantly longer.

There is another piece to that, and that piece is that you typically do not want to start a relapse prevention study at the outset of Phase 3 for a variety of reasons that have to do with dosing, that have to do with what you know about the drug. So, it is not 31.3 minus 8.1 in terms of the extra difference, and there is also long-term data safety collected so it is a little more complicated than that. But, in fact, you have to take the end of this dose-response study and then start your relapse prevention study and add that time on at the end. So, the potential for delay is really considerable, certainly more than a year in many cases.

[Slide]

A couple of other issues about what happens if you require the completion of these

studies at the time of the NDA filing. We have talked about dosing. You typically--not typically but you often don't know your dose coming into Phase 3. So, you don't want to do these studies without being reasonably confident about your dose. What are you going to get otherwise? Well, what you are probably going to get is a study which uses a suboptimal dose or an excessive dose. Ultimately what you are providing to clinicians is not optimally informative data and may, in fact, be misinformative data.

There are issues around attribution of safety that have been spoken to and I won't dwell on them but, basically, the earlier you do these without a control the more difficulty you have in terms of attribution and interpreting adverse events. You are going to be putting large numbers of patients on drug for extended periods prior to having a definitive demonstration of acute efficacy. Now, if you are going for a primary relapse prevention or long-term maintenance indication that may be a reasonable thing to do.

But if your thought is that you have an acutely efficacious drug and that is sort of where you are starting from, that doesn't seem so reasonable. So, I do believe you really have the potential to really delay patient access to these treatments if you require the relapse prevention study.

[Slide]

The flip side of all this is that I think you do have to ask what is the risk of a chronically inefficacious drug being approved and being used under current practice. Bill Potter has touched on this; I think Gary Sachs has touched on this. I am not going to spend a lot of time on it. Basically, I think what is worth thinking about, you know, the question you have to ask is what is the predictive value of a 3-month lead-in or longer efficacy as we do it typically currently, at least in depression, at least in schizophrenia?

The available data are limited but the studies that we do have, the Pittsburgh study that Bill showed and the 2 studies that I showed, at least do suggest that 3-month data predicts 6-month

data.

conversely, we are not aware of good, strong evidence in the opposite direction suggesting that you would have a different effect or essentially a loss of effect at 6 months that you saw at 3 months. There is anecdotal data around Prozac poop-out but that has not, in fact, held up when you look in a controlled fashion.

The other piece of it is that there is a predictive value to the sub-acute data in terms of longer efficacy, which is that it is basically unlikely that a novel compound could induce an acute symptom response but not maintain it and still fare well in an 8-12-week trial. That is, a compound that had marked early therapeutic tachyphylaxis, if you will, would almost certainly have a difficult time sustaining superiority to placebo to a trial's endpoint if it went out 8-12 weeks.

[Slide]

I want to conclude on a slightly different note which is from the perspective of someone who

basically--I mean, one of the things I have to do at Lilly is to essentially advocate the larger company to be an advocate for new neuroscience targets for new neuroscience drugs. If you require longer relapse prevention studies, if you make them a condition of initial filing you will delay patient access to new drugs. I don't believe you will provide a clear offsetting benefit over current practice and that delay will be considerable.

What is the issue around that? Well, the issue is that we all know that neuroscience drug development, psychiatric drug development particularly, is challenging. It is challenging in a lot of ways. There have been a number of events over the past couple of years. It is a hard place to work and it is seen as a hard place to work. The proposed changes, many of them, could significantly increase the barriers to approval and they have the potential for discouraging sponsors from undertaking some psychiatric drug development programs.

I guess my concern about that is that the programs that are likely to be most affected are those drugs with highly novel, highly unprecedented

mechanisms, which are also the most likely to provide breakthroughs for patients but which have the highest likelihood of failure and are viewed most skeptically in terms of whether or not they can compete with an oncology project or with a cardiology project.

So, I think at this point I am going to stop and turn it over to Dr. Goodwin to summarize.

Concluding Remarks

DR. GOODWIN: Well, it has been a long morning and I am not going to, obviously, reiterate everything that everybody has said. Again, my summary is really speaking for myself. It is my own impression of the morning. I am not representing anybody here in that regard.

I would just start again at the beginning where I started this morning, which is that the public health implications are the ball we really have to keep our eye on. For very serious, very

costly, devastating illnesses for which existing treatments are sadly lacking, our first obligation is to make sure that new agents have no unnecessary obstacles to rapid deployment, rapid investigation. So, there is no way to separate the public health nature of these illnesses and their severity from the issue of the urgency of new treatment development.

Now, the other ball we must keep our eye on very clearly is to address what the FDA asked us to in the first place. While it is very interesting to have discussions of what is the best method for long-term efficacy evaluation, the main point is not that. The main point is our concern about requiring long-term efficacy demonstrations as a precondition to acute approval.

We do not feel--and I think there is unanimity of the presenters this morning and my colleagues that I have consulted with on the outside--we do not feel that that is in the best interest of the field or our patients, to require that. We think, as you have heard, that this will

definitely delay the availability of new agents. The estimate conservatively, in the best case, is about a year. And, because of the increased sample sizes that are required with this 6-month requirement, and all kinds of new statistical data analyses requirements, the cost of this would go up to the point, as Dr. Michelson just said, that CEOs of companies might say let's stay away from this messy mental health area.

We have heard a lot about how different acute efficacy is from long-term efficacy, and we have heard Dr. Sachs' example describing the way in which long-term efficacy in a clinical and research setting is often a series of acute interventions.

While I am mentioning Dr. Sachs, I want to take one minute out of my own presentation to ask him to explain your response to the question that Tom asked. I think there was some confusion about what you meant when you responded to that. This is the issue about the 8-week run-in period and whether that would actually involve a longer period. You had a response which I think not

everyone understood.

DR. SACHS: I am not sure if there is a lot of confusion about this, but what I was imagining when I was saying that there would be an 8-week period in the responder status is, let's say, we have a lead-in phase that would be no more than 24 weeks and if a patient were started in that, they might begin their 8 weeks the second week in that treatment so they would end up getting randomized at week 10 of the lead-in. And, no patient would stay in it beyond, let's say, week 16 if they weren't doing well. That way, you would have a relatively straightforward opportunity to randomize people who were, in fact, true responders.

DR. GOODWIN: So, the key issue is to have them stable and keep them stable on the 8 weeks of the drug being studied.

One of the other concerns, besides the issue of delay and disincentivizing industry, as has been mentioned by Dr. Michelson, tis hat to move into a long-term trial without having the

dosing information, the efficacy information and the safety information from an acute trial really raises all kinds of concerns that I think would be not only concerns to IRBs but concerns to patients that we are trying to sign up for these trials.

I think we feel that the current procedures are working reasonably well, and we know a lot about the problems of them and there are a lot of people working on those problems. What we are being asked to consider is taking a system, with all its frustrations that we know and are learning more about, and go really into unchartered waters, not based on real-world conditions of how long patients stay but sort of idealized conditions of what guidelines say they should stay. That does not seem to me to be a sufficient base for a real fundamental change that has a number of risks that are not explored. Some of them are obvious ones that we have stated.

Of most concern to me, thinking as a researcher and a clinician, is this issue that Dr. Michelson raised at the end which is that not only

will this clearly drive up the sample sizes and, therefore, the costs of these trials, but it will make the samples increasingly non-representative. That has a lot of implications for how the field interprets data. There are already problems with how randomized, controlled trials represent the real world. This would exacerbate that problem considerably. Thank you.

Questions from the Committee

DR. GOODMAN: First, I would like to thank all the speakers this morning for providing informative and cogent presentations and for keeping us on time.

Now I would like to take advantage of the next 25 minutes for the committee members to ask questions of the presenters or Dr. Laughren. I would like to start that off myself first with a comment. I had asked Dr. Laughren earlier if part of the impetus for this meeting had to do with safety considerations that emerged. He said in part that was true and cited the example of our deliberations on use of antidepressants in

pediatric patients and the question of suicidality. He pointed out that we all had wanted and would have liked to have had available to us long-term efficacy data. That is, indeed, true.

However, I would point out that probably the bigger deficit in our database at that point in the discussions was the acute data. Really, that was the most striking deficit, that we only had 3 out of 15 submitted trials that were positive so only 20 percent of the acute trials were positive. So, it wasn't just the absence of long term, I think it was the promise with the acute trial data.

Now, for a question, Dr. Goodwin mentioned that, by and large, industry has been adhering to its post-approval commitments to conduct the long-term trials after initial approval. I wanted to ask Dr. Laughren or whoever else would like to respond if, indeed, that is the case or if there have been concerns about adhering to those commitments.

DR. LAUGHREN: Yes, I don't have exact numbers on that but I agree that, by and large,

probably 70, 80 percent of these Phase 4 commitments to do a long-term trial get done within a period of 4-5 years. I could probably get the exact numbers. But it is a matter of years. It is a matter of years after the drug becomes available so that is the question, whether or not that is acceptable.

DR. GOODMAN: Dr. Pine?

DR. PINE: I want to go back to the impetus issue that you raised, again, thinking back to some of the discussions on the pediatric issue. I remember that both Dr. Laughren and Dr. Temple felt very strongly that one of the things they really needed, both for a safety issue but also for an efficacy issue, was the discontinuation designs, particularly in pediatric studies.

I have the sense, even though it wasn't explicitly stated, that that might be behind a little bit of your thinking for today's meeting, that there weren't enough of those studies done even to deal with the issue of efficacy in kids. Is that right or not?

DR. LAUGHREN: Well, there were none of those studies done in kids. I agree with Wayne's point that the main concern was the substantial

failure of the acute studies, and 2 of the 15 being studies with one drug was of concern. It would have been helpful to balance that. And, I don't know why; I don't really have a good explanation for why there was such a high failure rate in those studies. It would have been helpful to have something to balance that longer term. These trials, as you have heard, have a much higher success rate and, as I said before, I think clinicians clearly, you know, value these drugs for the short-term effects but in some cases probably value them even more for their long-term benefits in keeping people stable. It would have been helpful to balance off that failure to have those kinds of data, and we didn't.

DR. GOODMAN: Carol?

DR. TAMMINGA: One of the things that I didn't hear anything about this morning from all of you guys was anything about what the European

studies do to inhibit drug development. So, you all said--I mean, nobody would like new regulations, for sure--but that the studies delay the drug to market. The cost discourages development. People are going to be reluctant to get into these long-term trials. I don't know a lot of the long-term data in other areas than schizophrenia but I must say that, for as long as these trials have been going on in Europe, I haven't really seen such a delay happen and I wonder if anybody has any data. Has anybody gone over the data about the drugs approved in Europe and the drugs approved over here and really demonstrated that the issue of all of the things that Fred ended with are really true?

DR. AMMANN: I don't think we have any firm data that would substantiate that. The problem is that each individual component is confounded and there are all sorts of extenuating circumstances and it is not always so simple to tease out whether there would be, you know, an imperative delay. I am looking more forward at

this point in time to programs that we are designing now and our introduction dates for Europe in many cases for psychiatric drugs are substantially later than our anticipated introduction dates here, in the United States. I know that there probably are examples and maybe some of you have some specific examples you can cite.

DR. TAMMINGA: Can you give us a quantity--significantly later?

DR. AMMANN: Well, the other thing that is important to point out is that the type of trials that we are doing here have different requirements across different disorders. But the types of trials that we are being asked to do in terms of providing long-term data in Europe are not as lengthy as the designs that we are talking about here. So, the delays you may hear about are probably not reflective of the delays that we are talking about in terms of the U.S. Bill looks like he wants to comment, and David as well.

DR. POTTER: I don't think I am sharing

anything that shouldn't be obvious to everybody, but if you look at the financials--and we as a society have decided that we are going to introduce drugs through the public sector and a for-profit approach--the driver is that there is some hope of profit. For any antidepressant drugs the U.S. market is guarantied large enough to go to that alone, and your added value of going to Europe is a business decision. If you are going with essentially a "me too" or a "me better" drug which you already know works, then it makes financial sense to do it more or less in parallel in Europe because you are going to hit the numbers and you are going to make more money. It is as simple as that.

However, with novel targets you don't know where you are, and we want new drugs and better drugs. I didn't look at the Merck that way, but Merck did not have all these long-term studies for worldwide launch because Merck had a new drug and it was a different approach. So, that would have been much, much later, Carol, had that been going

forward. So, that is the thing with novel targets. You don't know the value of your drug so with the novel things, in many cases, you are going to extend this much further out because you are not going to make that European investment until you are darned well sure that you have nailed your acute efficacy here.

DR. MICHELSON: To echo Bill's point, there are two things. One is that there is an issue about when you decide to commit to doing a drug development program and considering what you need to do for it. As Bill said, Europe usually comes along with the U.S. for the ride, as it were. That is an unfortunate way of putting it but to some extent that is often true.

In terms of actual data, I can give you two examples. With atomoxetine we actually started the relapse prevention study during Phase 3 following the completion of the dose-response studies. It ended, as I recall, 6 or 8 months after the U.S. approval. U.S. approval was in November, 2002 and, if memory serves, it ended--the

last patient visit was, like, in June of 2003 and by the time the data locked you were well into the fall so you were pushing something like 8 months or a year later. Then it had to be incorporated into a common technical document for Europe. So, you have at least a year delay there.

Duloxotone would also have been delayed significantly. You actually don't show a delay when you look at the numbers, and the reason for that is, because of the manufacturing issues around duloxotone around the U.S. NDA, the approval was held up for a considerable period of time. But the relapse prevention study for that would also push out.

The only way you don't push it out is if something delays the U.S. approval process because typically we do at this point plan for a relapse prevention study. Once you are reasonably confident your drug is going to go forward--at least I can speak to our own experience, we do plan for a relapse prevention study and get going on it. So, if something then happens to delay the approval

process following the submission of the NDA it doesn't necessarily show as a delay. But when things go smoothly it has the potential to delay significantly.

DR. GOODMAN: Dr. Wang and then Dr. Pollock.

DR. WANG: This is a question for Tom. Is the agency's goal here to try to leverage the sponsors in a more timely fashion to generate long-term data? If the answer to that is yes, would initiating these long-term trials at the time of approval, as opposed to requiring completion, maybe be a less drastic way of trying to do this, and it would also allow the sponsors the chance to, you know, use their acute phase data in terms of dosing and actually would not remove their incentive because presumably they would only have to initiate long-term trials for products that have shown some signal of acute efficacy.

DR. LAUGHREN: Yes, that would be one option but, again, there are several issues here. One is the timing, but the other one is the design

of these studies. We really want to have a lot of discussion of what is the optimal design.

DR. POLLOCK: Just to a point I want to see or make sure I have clearly, Dr. Laska conveyed that for at least schizophrenia non-inferiority active control trials may be a solution, or at least a reasonable solution for longer-term efficacy trials. I think that was your message. My sense though, and this is where maybe Dr. Goodwin or Dr. Potter could comment, is that in depression, major depression, the placebo response rates are escalating and are so enormous and have changed, as we know, over the last few decades that we are really not in a position to say that an active controlled, non-inferiority study would be valid at this point for antidepressants, that we are simply not at the same strength that we are in the differences with schizophrenia. So, I gather that I have that?

DR. GOODWIN: [Not at microphone; inaudible].

DR. POLLOCK: Then, could I also just ask

Dr. Sachs' feeling about that with regard to treatments for bipolar?

DR. GOODMAN: Please use the microphones.

DR. SACHS: I do think we all agree that some of these points are good illustrations of why we need to think illness specific. Since I am here, I also wanted to, if you don't mind, respond to Carol. Wellbutrin would be an excellent example. Here we have the most frequently prescribed antidepressant for bipolar depression in the U.S. and not available for treatment of depression in Europe, not approved. Decanoate, which is the most frequently prescribed drug I think overall for bipolar disorder, does not have EMEA approval. So, I think there really are dramatic differences between here and Europe at least in the bipolar field.

DR. GOODMAN: When were those changes in the EU regulations instituted? Does anyone have the answer to that? I know we are belaboring this point a little bit but I think it is very critical to the one Carol raised. It offers a kind of

comparison group and if we at least knew, for example, when it was instituted we could see what has happened to drug approval in Europe comparing before and after the regulations were instituted.

DR. LAUGHREN: I think obviously industry would have a much better sense of the international regulations than we would.

DR. TAMMINGA: My guess would be something like 8 years, but I wouldn't know it as well as you guys.

DR. GILLER: I really don't have the answer either but I think it was long enough ago so that some of the comparisons may be difficult because a lot of other regulatory things have changed at the same time.

Just one comment on non-inferiority studies, sticking my neck out a bit, I think non-inferiority studies certainly in acute indications are problematic. There is the potential I think--and this is something that might be explored--for when you are looking at long-term therapy even in mood disorders whether

non-inferiority studies might be of more value.

DR. GOODMAN: Dr. Leon and then Dr. Winokur.

DR. LEON: I have two questions. First, how many antidepressants currently have an indication for relapse prevention for major depression? Are there any?

DR. LAUGHREN: There are a number of antidepressants that have a long-term claim based on relapse prevention trials. I don't have the exact proportion but, you know, more than half of the current drugs.

DR. LEON: My other question is regarding the long-term extension studies. I didn't hear the details of the design. Are these extensions of subjects who were in acute trials, and who was extended? Is it just those on active who don't relapse? Maybe someone behind me could answer. And, do they have a comparator is my final question? I believe the last speaker, Dr. Michelson or it might have been someone else, referred to a long-term extension, I believe, of an

acute antidepressant trial or of acute trials. Can you just be more specific about the design? These are acute trials? Is that correct?

DR. MICHELSON: There are two things that typically happen. I am not sure I can speak to your specific question but there are a couple of things that typically happen during drug development. The first is that--and I think this was sort of stated at the outset--in addition to providing acute efficacy data you have to provide long-term safety data. One of the ways of doing that is to continue patients who are in an acute study for some period of time, with the idea that you will obtain long-term safety data. Those typically, not always but typically are open-label studies in which the placebo group is offered the opportunity to get active compound at the end of the acute period.

The other purpose they serve is, frankly, two things. One is that people who benefit, presumably benefit although it is not proven at that point but presumably benefit from the test

drug get the opportunity to continue on the drug for an extended period of time and people who are on placebo get an opportunity to have a putative active treatment.

But those are typically done as open-label trials. So, in Prozac with panic disorder one of the studies actually took the blinded portion and then re-randomized patients from the active arm into the relapse prevention design. I think that was discussed. That is one way of doing these studies.

I have done one study where we actually maintained the blind but without placebo following the end of the acute period, with the idea that it was a dose-response study and could you, under blinded conditions, look at patients who hadn't responded to a lower dose being randomized to continue on the same dose or go up to the higher dose and show some evidence around the higher dose. But extensions are typically open-label extensions that typically aim at safety and/or providing drug to those who got it acutely.

DR. GOODMAN: I think it is fair to say that there is a limited menu of designs for showing long-term efficacy but the gold standard would be

the relapse prevention study. I think we can discuss some more specific design alternatives after lunch. That is one of the questions that is raised by the FDA. You had a follow-up, Dr. Leon?

DR. LEON: My question is I heard some of the speakers this morning refer to, yes, we have had long-term extensions or long-term follow-up that demonstrated--I thought they implied that these studies demonstrated efficacy. But in a trial with no comparator or an open-label trial, I don't see how that is demonstrating efficacy of relapse prevention.

DR. MICHELSON: I didn't hear that this morning. There were sort of questions as people were looking at the presentations. We tried to be very careful not to suggest that open-label studies provide a basis for efficacy. I think there is unanimity among the group. Nobody is claiming that you can make an efficacy claim off an open-label

study.

DR. GOODMAN: Dr. Winokur?

DR. WINOKUR: This is also for Dr. Michelson. I just wanted to follow up on this exact same area. You made a comment towards the end of your presentation about good consistency between short-term efficacy in depression studies and studies that did look under double-blind, placebo-controlled and extension. What we didn't get is really a review of how extensive the literature is in this regard; how robust is the data set; and are there demonstrated exceptions to that. I would also be interested, from Dr. Laughren's perspective, if there are any signals of concern about the relationship between demonstration of short-term efficacy and under controlled conditions maintenance or prevention of relapse.

DR. MICHELSON: So, I think there are a number of issues in answering that question. Around the relapse prevention studies, if you take 3-month, 6-month and whatever, there are relatively

few instances and in the instances where they have been done it is consistent.

I think what you are asking, and correct me if I am wrong but I think what you are asking is if you look at a short-term trial or an 8-10-week trial, which really isn't quite so short term, are there drugs which have done well in those which fail in relapse prevention studies? The answer I think would be that there are failed relapse prevention studies but I am not sure that you can interpret them as saying the drug doesn't work. So, if you do one study and it doesn't work--you know, that is the comment I was making about the positive control and it gets to this sort of broader issue of could you approve a drug in acute without long term, and what would you do with a negative study, what does it mean.

So, I think the answer is there aren't a lot because the relapse prevention study design is actually pretty robust, but I do believe there are some instances, and I am sure that Tom is more familiar than I, in which the relapse prevention

study was, at best, not informative. Is that fair?

DR. LAUGHREN: Yes, there have been very few. I mean, I don't have the number off the top of my head but the overall success rate of the randomized withdrawal studies is extremely high. You saw in the example of schizophrenia that there have been no recent examples of failures of that design. There have been a handful in other areas that haven't made it for one reason or another. But, unlike the acute studies in depression for example where you see that the failure rate for studies that, in fact, look like they should work is about 50 percent. They almost don't happen with the randomized withdrawal design.

DR. GOODMAN: Other questions from the committee? I have one more question, this one for Dr. Potter. Bill, you showed a slide of a double-blind discontinuation study for SSRI in GAD. This really is a question directed at the need for stabilization or not. It may be too hard to put that slide back up there again but it is in our handout. These patients were assigned to either

placebo or ongoing paroxetine at 8 weeks after a single-blind run-in. Do you think that the results would have been any different if the single-blind run-in phase had been continued longer, like, say, another 2 months? Would those results have looked any different or not?

DR. POTTER: Of course, that is the question for which we don't have systematic data. What I commented on was the effect size. The difference ultimately at the end of that that you observed between drug and placebo during the randomization phase begins to reach that which you used to see with the classic studies in GAD. So, you appear to be reaching sort of what I think a lot of us believe is a true population difference there. So, I know of no evidence that a longer-term period before going to the randomized withdrawal would have yielded a different signal.

What is interesting, as Dr. Laughren referred to with the drug venlafaxine, is that there was a different design in which they simply put people on drug or placebo and followed them

prospectively over 6 months. But, again, if you look at that data--and I have that paper with me if you are curious--if you look at that paper, there too at about the same time that you look in the Stocchi et al. paper on paroxetine you begin to see essentially the same sort of difference. Now, they reported their data in a different way so it is a little hard to infer.

So, what I would say is if we had all our meta-data sets and put all the data sets together and worked with some individuals--we really haven't, you know, sat down and done this as a field and modeled all the possible trajectories and all the differences in signal detection you would get by making cuts at certain points--we might learn something and that could be an extremely interesting thing to do and I think we would all be strongly supportive of it. One of the things some of us have been arguing for is that we should find ways of sharing data sets for data mining to look at just these sorts of prospective things. I am not speaking for industry at this point but as

myself as a researcher and individual.

So, I think there are immense opportunities here to learn more but we do not have the data to answer these specific questions about 8 weeks, 12 weeks, 16 weeks, 20 weeks or whatever. What we have data about is the classic designs which we have done and studied and we are beginning to learn something about how those behave.

DR. GOODMAN: Thank you very much. Once again, thanks to everyone who participated in this morning's session. Before we break, just for the committee members to let you know that we have a room reserved in the restaurant and to remind you of my admonishment earlier, and that also holds for discussions among committee members. So, we will be talking about the weather some more!

[Whereupon, at 12:05 p.m., the proceedings were recessed for lunch, to reconvene 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

Open Public Hearing

DR. GOODMAN: We will resume this afternoon with the open public hearing portion. It is my understanding that we have three presenters. Our first one is Dr. Darrel Regier from the APA. Each speaker will be allowed a maximum of ten minutes.

DR. REGIER: Good afternoon. I am Darrel Regier, representing the American Psychiatric Association where I am the Deputy Medical Director and Executive Director of the American Psychiatric Institute for Research and Education.

APA is a national medical specialty society with 36,000 physician members who specialize in the diagnosis, treatment and prevention of mental illness, including substance use disorders.

For the record, I would note that I am speaking on behalf of the APA, with no pharmaceutical or outside funds used in conjunction with my testimony to this committee.

Mental disorders affect and often severely disable some 48 million Americans across their life span. Oftentimes the illness is persistent and

recurrent and, not uncommonly, disorders that first manifest in childhood and adolescence persist throughout adulthood. For these reasons, it is critical for us to assure the short- and long-term safety and efficacy of medications that we typically use as a key element of comprehensive treatment programs.

In the lengthy process of drug development, which extends from basic preclinical animal research to Phase 4 post-marketing research, we can identify several points at which we might focus efforts to better ensure long-term safety and efficacy. In the handout that I provided to the committee that is much longer than this presentation I outline ten different leverage points within this system.

We recently have seen attention focused on Phase 3 testing wherein safety and efficacy are examined in large clinical populations with pure

conditions for acute and subsequently chronic or maintenance indications. It has become evident that this process is seriously impaired when clinical trial data needed to make possible assessments of true effect size and side effect risks are not available on public registries, or when spontaneous report endpoints of measures such as suicidal ideation are given precedence over systematic assessment endpoints. These, however, are correctable shortcomings.

We also have seen concerns about shortcomings in the Phase 4 post-marketing stage of monitoring both acute and long-term use of medications for adverse events and drug interactions. A review of FDA MedWatch data suggests problems at this point of the process with minimal spontaneous or systematic reporting of adverse events. Just as open registries and meaningful endpoints can contribute significantly in Phase 3, we would suggest that expanded clinical research can do much to resolve the difficulties we see at Phase 4. I am referring to clinical studies

of approved medications in large populations with pure indicated conditions that entail head-to-head efficacy comparisons with multiple treatments. An example of this type of study is the NIMH-sponsored treatment of depression collaborative study of imipramine, placebo, IPT and CBT in the 1980s. Unfortunately, these kinds of studies are all too rare.

Also needed are studies that test approved medications in head-to-head effectiveness comparisons of multiple treatments administered to complex, often co-morbid cases typically seen in clinical practice. Examples are the NIMH TADS and CATIE studies which respectively examine the effectiveness of medication and psychosocial treatments for adolescent depression and effectiveness of various antipsychotic medications.

The question has been raised as to whether such trials should be combined with Phase 3 testing. Because they do not fall under FDA's purview and are subject to funding constraints at NIH, we should be keenly aware that their absence

would significantly impede efforts to ensure safety and efficacy. Let me return to this point in a moment.

But given the persistent nature of many mental disorders, there is the question about medications that may be used for long-term treatment of patients should be withheld from the market until complete information is available on long-term safety and efficacy, information that clearly would have direct bearing on clinical practice. Yet, if the answer to the question about this is yes, how much information then would be considered enough? We do have a concern about the delay that could attend over-interpreting the need for that information.

The APA attaches high priority to the immediate challenges to front-line clinicians who are struggling to help patients with intractable conditions. Physicians who are not adequately informed by data available from classical short-term Phase 3 clinical trials need better information on long-term safety and efficacy. As

we work together to examine additional solutions to those, I have suggested here we must be aware that failure to understand the most appropriate cost effective and clinically useful roles of the FDA, the NIH, the pharmaceutical industry, patient groups and clinicians in large and smaller practices--failure to recognize the role of each of these could compound today's problems.

With appropriate collaboration, what more can we do to ensure a rational process that will continue to bring new medications forward in a timely manner, while fully attending to long-term safety and efficacy questions? It is not clear to us that combining short-term and long-term efficacy studies will be in the best interest for patients given the potential impact such a policy would have on the timely availability of new medications. It is interesting that this very same question was raised yesterday at the annual Institute of Medicine meeting which was addressing exactly the same issue.

If this proposal is further explored, we

would want to understand that greater FDA emphasis on long-term safety and efficacy studies, conducted with diagnostically pure samples, should not lessen the need for NIH to continue supporting informative but very expensive clinical effectiveness trials such as TADS and CATIE. In the hydraulic world of Washington, oftentimes the thought that the FDA is doing this can very well lead to the Congress deciding, well, we don't need to fund NIH studies in this area because that is being done at FDA.

It would seem more useful to bolster our capacity to utilize existing sources of long-term safety and efficacy data before undertaking a fundamental restructuring of the drug clearance process. We would suggest that one possible innovative and cost effective strategy for addressing this need may be to create partnerships with large managed healthcare plans that maintain extensive databases on prescribing patterns and patient outcomes. Mining these data would offer invaluable information and feedback to the FDA. And, the recent agreement that the FDA apparently

has with several large health maintenance organizations to systematically monitor the safety of medications used in their very large populations could be a major improvement over the MedWatch post-marketing surveillance.

It will be important too for multiple parties, including the NIH clinical trials.gov program, the FDA and industry to intensify their collective efforts to improve the transparency of the safety and efficacy data emerging from industry, government and academic clinical trials.

Another opportunity for improvement became evident in the recent FDA-sponsored review of suicidality associated with SSRIs. APA, along with numerous professional, scientific and consumer groups, believe that a focus in the meta-analyses on spontaneous reports from study participants was at the expense of attention to the considerably more informative data available from studies in which systematic reporting of suicidal thoughts and behaviors were available. These data demonstrated no increased risk attributable to medication use.

My point today is that legitimate differences may exist within the field regarding what constitutes good and bad data endpoints in

assessing safety and efficacy. That being so, it is critical for FDA to follow-up on its policy decisions looking at the impact of access to treatment and changes in health indicators impacted by policies, including the ones that you are discussing today.

In closing, I would note a special challenge confronting research on psychiatric illnesses that is often not experienced in research and other general medical/surgical disorders. The FDA is under substantial pressure from individuals and organizations which deny the existence of mental illness. If mental disorders did not exist, certainly many of the issues addressed by this committee would be moot.

Yet, mental disorders are real, and only through the combined expertise of all parties involved in this discussion have we realized the scientific revolution in treatment of mental

disorders. The decisions facing the FDA are profound and have the potential to greatly improve our ability to accurately assess and understand both the risks and benefits of long-term use of potentially life-saving medications. We commend the exploration of scientific questions raised in this hearing, with the hope that better and safer treatments will emerge as a result. Thank you.

DR. GOODMAN: Thank you, Dr. Regier. Our next speaker is Dr. Awad, and I will let him introduce himself.

DR. AWAD: Thank you, Mr. Chairman. My name is George Awad. I am the current President of the newly developed International Society for CNS Clinical Trials and Methodology. I am quite grateful for the opportunity that we have been given and, before I get to discuss the issue at hand today, I would like to familiarize you, for those who have not heard about us.

Our organization is an independent organization in its second year. We are delighted that we have among our members clinical

methodologists who come from academia, from industry and regulatory agencies and, certainly, we are quite pleased with the progress so far.

The society conducts two meetings, scientific meetings a year. The first meeting this year has been in Montreal and actually addressed the issue that you are discussing today. There was a large session, a half-day session, which discussed aspects of long-term treatment or maintenance of long-term treatment and which actually constitutes the background of what I am presenting to you today.

I think in the handout there is the mission which is quite an ambitious mission statement. I think in reviewing CNS efficacy data, the FDA requirement for the acute phase in terms of the requirement and approved indication where the objective is demonstrating control of symptoms over a short period of time, the usual 4-6 weeks, is quite satisfactory. Where we have questions is about the proposed FDA requirements and label for continuation or maintenance treatment based on

preventing relapse of the index episode or recurrence of new episodes.

I think there are three key issues here in study design. The first one is the disease characteristics; the stakeholder needs; and, actually, the question which is asked. I think the need for longer-term data varies by disease course. Generally speaking, in depression a broadly similar course for most persons can be observed and frequently it returns to the baseline. While, say, in schizophrenia there are prodromes which are present. Usually it does not return to baseline and the course and response to acute exacerbations are unique and variable for each individual. What that means actually is that different study designs are needed to address differences in disease and treatment needs.

I think we need a new vocabulary or a revised vocabulary of long-term efficacy. While there is an adequate vocabulary for depression, similar terminology is required for other CNS disorders. For example, schizophrenia is chronic

and may not return to baseline with irregular exacerbations.

I think also we have to consider what are the needs of the stakeholders. From the patient perspective, the question is will I continue to do well if I take this medication, or do I need to continue to take this medication?

From the clinician's perspective it is will the drug that effectively treated symptoms in my patient continue to have an adequate effect long term and will it be safe?

From the societal perspective, the question is different, does the drug improve functioning, quality of life and outcome during long-term treatment in a population of persons with the index disease in treatment trials?

The regulators will ask the question, is the drug which demonstrated an acute effect still providing risk/benefit when its use is continued for long periods?

The developers will ask whether the drug which demonstrated an acute effect is still

providing risk and benefit when its use is continued for a long time?

I think the clinical question should be the primary driver of clinical trial designs. There are many alternative designs which are available, and just to cite two of them which are the most frequently talked about, the randomized withdrawal designs--and we believe really that its value is limited based on some questionable scientific principles, and ethically questionable.

The double-blind, long-term treatment studies are an alternative approach which differs from typical extension, and this is a difference that has to be understood. This model is actually not an extension. It differs from extension studies. It assesses long-term effectiveness. The analysis is based on all randomized patients.

There are possible questions in design and label for long-term efficacy. One question, for example, is during continued treatment with medication, will time to relapse or incidence of relapse be reduced?

Well, in a randomized withdrawal study the possible indication will be compound X has been demonstrated to increase the time to relapse or

increase incidence of relapse in patients who had previously responded to treatment as compared to a control during 26 weeks of continuation treatment.

Another question could be if a patient has responded to medication, will continued long-term treatment result in persistence of the initial response? In a double-blind long-term study, the possible indication would be that compound X has been demonstrated to be effective in maintaining an initial treatment response compared to a control for up to 52 weeks. The difference here is not just semantics. I think there is a difference between the two. One really is more or less relapse prevention and the other one is maintenance of effects.

I think there are points on which we have consensus in our society. Recent changes in guidance requiring extended stabilization followed by randomization with treatment discontinuation

paradigm risks. They are ethically questionable trials; scientifically questionable outcomes; and logistically prohibitive protocols. I think proof of long-term efficacy requires specific definitions, outcomes and protocols for each disorder.

Definitions of long term are specific to each disorder and treatment. They differ greatly whether they are antipsychotics, mood stabilizers or short treatment of acute panic attacks. Stakeholders still need to clarify definitions of long-term efficacy. I can add another point here which has been touched upon during the day, which is the issue of the length of stabilization. There are actually a number of studies now. I think I am quite familiar with Ross Balzarine's study in which he reviewed 27--it was actually a meta-analysis of 27 studies in depression and he came to the conclusion that the length has no impact on the relapse rate.

Also the appropriate timing of approval of new agents for short, intermediate and long-term

applications. What data are required, at initial regulatory submission versus post-marketing; whether the current process of acute followed by long-term indication is sufficient.

Finally what is the way forward? We believe that we need to reevaluate current concepts of long-term efficacy of psychotropic drugs; prioritize needs by specific disorders; redefine objectives and designs of clinical trials adequate to assess long-term effects. I think for the FDA to sponsor workshops can prove very helpful by having expert consensus workgroups to develop guidelines for appropriate designs for long-term effectiveness trials for specific indications and include representative key stakeholders from regulatory, academic, clinical, industrial and statistical expertise. Thank you.

DR. GOODMAN: Thank you, Dr. Awad. Our next speaker is Dr. Vogel-Scibilia. I believe she is representing NAMI.

DR. VOGEL-SCIBILIA: Good afternoon. My name is Dr. Suzanne Vogel-Scibilia and I am the

President of the National Alliance on Mental Illness, also known as NAMI. I speak to you today from a number of perspectives, as NAMI's president of the board of directors, as a practicing psychiatrist, as a person living with bipolar disorder who has had significant major depressions and manias, and as the parent of a child and a daughter of a father who suffers also from severe mental illness.

Throughout its 25-year history, NAMI has been a staunch advocate for increased and improved research because our members understand that research is the best hope we have for finding treatments to alleviate the devastating and debilitating symptoms of brain disorders such as schizophrenia, bipolar disorder and major depression.

When NAMI was founded there was little thought that a cure for schizophrenia might one day be discovered. Today, many of our members feel that a cure for schizophrenia may one day be the case. Today, many of our members view this as a

distinct possibility and are encouraged by the progress that has been made in discovering new treatments, and the emergence of evidence-based services helping many people achieve levels of recovery and independence that 25 years ago did not seem possible.

At the same time, we know that progress has been very slow in discovering effective treatments and the road ahead is still very long. The landmark CATIE study recently released by NIMH provides an illustration of how far we still have to go. The study, above all else, shows that none of the existing medications for the treatment of schizophrenia, first generation or second generation, are a panacea. While people derive therapeutic benefits from medications, they appear to be limited and the side effects of these medications are for some people quite profound.

Clearly, the discovery of new and more effective pharmacologic treatments is desperately needed. This is true for bipolar disorder, major depression and other serious mental illnesses.

NAMI, therefore, strongly believes that a research environment that encourages discovery and innovation must be fostered and maintained.

Recently legitimate concerns have been raised that consumers do not have full access to information about medications that they are taking, particularly negative information about risks associated with the medications. NAMI firmly supports the need for greater transparency in research. Consumers and their families must have complete access to all information, positive and negative, about research on psychiatric medications. Without this information informed decisions cannot be made about what medications to take and the concept of informed consent then becomes meaningless.

At the same time, in my experience and that of our members, far more people have been helped than hurt by psychiatric medications that are available today. Lack of treatment frequently is the tragic circumstance, including homelessness, involvement with the criminal justice system and

suicides. Also, the issue of significant disability and inability to enjoy life and function has been a major concern and a major cost of morbidity and mortality in our society.

We must maintain an environment that is conducive to innovation and discovery, one that will allow potential breakthrough medications to enter the marketplace in a timely manner. Psychiatry is one area of medicine that does not have a large number of new, novel medication classes developed in recent years. Innovative research has vastly improved treatment of heart disease compared to psychiatric illnesses.

With this as a backdrop, I will briefly make three points about the specific topic under consideration of this meeting determining specific standards for studying long-term effects of psychiatric medications. Although I realize that the first 8 questions in Dr. Laughren's memorandum specifically address major depressive disorder and only the final 2 questions address psychiatric disorders generally, my comments are focused on

psychiatric medications much more broadly.

First, NAMI does not at this time support requiring the accumulation of data on long-term efficacy trials prior to FDA approval of new psychiatric medications. The World Health Organization has documented that 5 of the leading 10 causes of disability worldwide are caused by mental illness and access to evidence-based treatments and intensive community support remains extremely low.

For example, a number of studies have documented that fewer than half of all people with schizophrenia having access to even minimally adequate treatment is a significant issue in this country. Access limitations are equally profound for people with bipolar disorder, major depression, obsessive-compulsive disorder, anxiety disorders and other mental illnesses.

The FDA's process for approving new medications is already quite slow. Many years may pass from the time research on a potential breakthrough medication commences to the time it is

approved. NAMI is concerned that requiring long-term efficacy studies prior to approval would have the effect of further slowing an already overly cumbersome process. This could prove more harmful to the people intended to benefit from these treatments. Ten percent of all people who have schizophrenia commit suicide and only one antipsychotic medication, clozeral, has been shown to reduce that risk to date. Thus, rapid development in approval of new medications for the treatment of schizophrenia is, therefore, of life and death importance.

Second, NAMI does support requiring long-term efficacy studies after psychiatric medications are approved. Serious mental illnesses are chronic in nature. Symptoms may be stabilized but subsequently will recur. Thus, many people, after finding medications that work in reducing their most debilitating symptoms, remain on long-term maintenance doses of these medications.

Understanding the long-term effects of these medications, both positive and negative, is

critically important both to maximize recovery and to minimize risks. Often risks are not discernable until after individuals have been treated with specific medications for extended periods of time. For example, the development of tardive dyskinesia over time varies from one individual to another. For some individuals, TD may develop within months of commencing treatment. For others, it may not occur for years.

Additionally, NAMI believes that long-term efficacy studies should be conducted whenever possible with the financial support of the National Institute of Mental Health, NIMH. Although the results of Phase 1 of the CATIE study were not as broadly useful as we had hoped, we regard the study as the most important research that has been conducted on medications used in treatment of schizophrenia to date, and we eagerly anticipate the findings that will be derived from similar NIH-supported long-term efficacy and safety studies conducted on medications for bipolar disorder, STEP Bipolar, and major depression, STAR-D. We believe

that NIMH should continue to target resources for these important purposes.

Finally, NAMI believes that the use of double-blind, drug withdrawal designs to conduct long-term studies of psychiatric medications puts vulnerable individuals at significant risk and should not be used. Simply stated, if a person responding well to a specific medication wishes to remain on that medication, he or she should not be taken off that medication. This particularly should be the case in studies evaluating the long-term efficacy of medications such as antipsychotic and antidepressant agents. In fact, we have serious questions whether an IRB will or ought to approve studies on antipsychotic or antidepressant medications with designs that involve drug withdrawals or use of placebo.

An appropriate ethical way to conduct long-term studies of antipsychotic medications and antidepressant medications is to evaluate these medications against others that have already been demonstrated to be therapeutic. The CATIE study,

referenced above, is an example of such a study. CATIE was designed as a naturalistic study in which groups of individuals prescribed a number of different medications were allowed over an 18-month period to evaluate both the safety and efficacy of these medications.

It is also important to note that the drug withdrawal or placebo arm designs are not used to study the long-term effects of medications for other life-threatening diseases such as cancer. Discontinuing therapy that has worked is viewed as unethical in the field of oncology. Instead, long-term drug studies in oncology are conducted using an active treatment comparator. We believe that the same standard should be applied to research on medications for the treatment of serious mental disorders.

Clearly, as a primary consumer and family member organization, NAMI's major concern is the safety and well being of those living with mental illness. The FDA is faced with decisions on many difficult issues. In considering these issues, we

ask the FDA to responsibly and carefully weigh the risks and benefits, including the public health consequences, and not to succumb to political pressures imposed by those who oppose psychiatric medications. An action by the FDA that is designed to address concerns voiced by a small but vocal segment of the consumer family member population may have the unintended effect of stifling innovation or delivery of care to the majority of those who suffer.

The National Alliance on Mental Illness is the nation's largest consumer and family member organization with over 200,000 members. We urge you to give this testimony the weight it deserves. Thank you for the opportunity to speak to you today, and I look forward to any questions you may have.

Committee Discussion

DR. GOODMAN: Thank you very much, Suzanne. All right, it is time for us to roll up our sleeves as a committee and get to work. In my relatively brief tenure as a member of this

committee, I am accustomed to more diametrically opposite viewpoints being expressed.

[Laughter]

In sharp contrast today, we have heard more of a chorus, actually a harmonized chorus cautioning us against adopting stringent criteria that may pose barriers to drug development or accessibility/availability to patients.

So, in a way, the rest of this afternoon is going to be made a little bit more difficult for us because we haven't had the opportunity to hear both the pros and the cons of adopting recommendations as we answer these questions posed by Dr. Laughren. So, what I would like to see, as much as possible, in the next hour of discussion among our group is to make sure that we are coming up with some of those other views that may not have been expressed and make sure that we are giving those proper attention before we call a vote. My plan is to call a vote after the break which is scheduled for 3:15. We may be able to do it at 3:00. But I want to have at least one hour of

in-depth discussion to make sure we have covered all bases before we call that vote.

The most important task at hand to achieve our goals today is to vote on the first several questions. I think we will get further than that. I also want to point out, as Dr. Laughren did earlier, that we want to focus our attention on using major depressive disorder. I assume that whatever vote we take at that point would not then be extrapolated to other disorders, but I probably want some reassurance from the FDA on that point. I do think that there is a merit to the notion that has been expressed repeatedly as a theme that one size does not fit all, particularly when it comes to design considerations and ethical considerations. So, I think it makes sense for us to focus our deliberations initially on major depression. I think major depression is the prototype we have for conceptualizing the phases of treatment, breaking it down into the stages between acute, continuation and maintenance. I think Dr. Laughren did a very nice job introducing those

concepts and also cautioning us against a literal interpretation of making those distinctions in clinical practice. Nevertheless, I think major depression serves as a good starting point.

Maybe we should put up the first question, if we could, Karen. As we have this discussion, let's keep these first couple of questions in mind. Actually, on my first reading of this, the differences, as I read them, between questions one and two were too subtle for me to distinguish. I actually did have a conversation with Dr. Laughren to better appreciate the distinction he is making between one and two.

So, in one the question is, is it a reasonable expectation that a sponsor would have accumulated data for both acute and longer--not necessarily long but longer-term efficacy trials at the time of filing an application for a drug for the treatment of major depressive disorder?

The second question is very similar except it states, is it a reasonable expectation that the sponsor must have demonstrated both acute and

longer-term efficacy? So, the distinction between one and two is that one requires that the data have been collected at the time of application. Question two really is a starting point for discussions of what if acute data or positive but long-term aren't, or vice versa.

Again, in my first reading of this question where it says "accumulated data" I believe--and I will ask Dr. Laughren to clarify this, he is referring to definitive data, definitive data that would have been collected that would produce an answer to the question about both acute and long-term efficacy. Is that correct, Tom?

DR. LAUGHREN: Yes, that is correct. What I had in mind here is having a requirement that a company actually conduct valid short-term trials and a valid long-term trial as part of that development program before they file an application, not the outcome of the trials but having actually conducted valid short-term and a longer-term trial.

DR. GOODMAN: Bruce?

DR. POLLOCK: In this first question, just to be absolutely sure, by longer-term efficacy

trial we are not necessarily talking about maintenance trials. You are talking about extending the acute efficacy trial for a longer duration.

DR. LAUGHREN: Well, I am not sure exactly what you mean by extending. We had some discussion about that earlier. Because that takes on very different meanings depending on who you are talking to. What I am talking about is a longer-term trial. It wouldn't have to be of the randomized withdrawal design. It could be, for example, a 6-month study. But I am not talking about taking patients, say, who have responded after 6 weeks and just extending the patients who responded. I think that would not be interpretable. So, I am talking about a valid design.

DR. GOODMAN: Let me just make sure I understand that, Tom. Would you find acceptable a trial that started with an acute trial, say it was

a double-blind, placebo-controlled study, and then you continued the responders in a double-blind fashion for 6 months? Could that constitute an acceptable long-term trial?

DR. LAUGHREN: You mean like responders after 6 weeks would be extended?

DR. GOODMAN: Correct.

DR. LAUGHREN: I think that would be difficult to interpret. Maybe, Andy, you could weigh in on that. You know, I have a problem with randomization having been violated if you are just taking responders and extending them on their own treatment.

DR. LEON: Well, the research question that is addressed by these various designs is driven in part by the point of the randomization. Where does the randomization take place? If randomization takes place at 6 weeks in the trial you were describing instead of at baseline, then we could have balance between the two groups and make a useful comparison. But if randomization takes place 6 weeks before the switch there is no reason

to expect balance.

DR. GOODMAN: Carol, do you have a comment?

DR. TAMMINGA: Yes, it seems to me that the question about what the design would be would depend to some degree on what the question is. I must admit that I thought that the question that Dr. Laughren posed at the beginning of the whole discussion was an important question. So, we now have a treatment for a particular psychiatric syndrome and the doctor and the patient and the family are doing the treatment, like the acute study suggests, and then we get out to 6 months. There really isn't a good deal of data for practicing physicians about what to do at a point like that, being a practicing physician on occasion myself.

It seems to me that if there is going to be research for when and under what kind of circumstances to put people on drug there ought to be information about what to do when they are on that drug for a long time--just leave them on it

for life; step it up; certain characteristics. I mean, it would all differ by illness and it would differ by indication, but I think that that is a really important question. If that is the question that we are thinking about, what kind of design would we have to have in order to answer that kind of a question?

DR. GOODMAN: I think we do need to agree among ourselves in being constant with the FDA's definition of what constitutes a valid longer-term trial before we can answer the question. I think certainly, and maybe this requires more discussion too, but the relapse prevention study using a placebo substitution would be the gold standard. Would you agree with that, Tom and others around the table?

DR. LAUGHREN: Well, I think that is one standard. But, as I said earlier, that is not the only way to get there. I think one could do, as was done with Effexor in GAD, a 6-month trial. That is another valid design. Patients are randomized at day one, some to drug and some to

placebo, and they are continued for 6 months. Another possible design is the design that was done with risperidone for long term, comparing it with haloperidol and beating it. That is looking at time to relapse but that is another valid design.

The question of whether or not one could rely on a non-inferiority trial in schizophrenia is one that needs more discussion but, you know, we may ultimately decide that that is also a valid design. I am not sure that we are there yet. I think there are a number of valid designs beyond the randomized withdrawal. The randomized withdrawal just happens to be the most efficient way to answer the question.

DR. GOODMAN: Danny?

DR. PINE: I guess stepping back a little and thinking of some of the discussion going on right now but then also this morning, at least the way I look at it and the way I read question one, it seems like there are three major points. I think point one and point two pretty much everybody agrees upon--what Carol just said. I think

everybody agrees, you know, that it is a very important question about how long to leave people on medication. It came up in the question of major depression in kids but also major depression in adults, and it sounds like everybody agrees that that is very important, number one.

Number two, it does also sound like--and maybe it hasn't been stated quite as directly but it is the sense that I get, particularly from you, Tom--that the data have been a little slow coming; you know, that there are not enough data on that now that, you know, we wish we had. I would agree with that and I think everybody else would agree with that too.

So, then I guess the real question is, you know, what are the ways to try to put either teeth in that or to kind of push the issue. Related to what you said, Wayne, in the beginning, we have heard a lot of information about what a bad idea it would be to come up with other regulations. I think a lot of people have made really good points about that. But maybe it raises the issue that Dr.

Wang mentioned. Okay, if that is a bad idea, are there other ideas or other things we could do to kind of make the long-term data emerge more quickly, short of regulations or short of things that a lot of people sound like they feel very uneasy about? It seems to me like that is the key issue. You know, we clearly need long-term data. It is clearly not coming fast enough. Is there anything else we can do short of new regulations? I don't know that we have really discussed that at all, except for the brief interchange that you guys had towards the end of the morning that sounded promising.

DR. LAUGHREN: I am open to suggestions. It is hard to know what a middle position would be. Again, just as background here, in the EMEA it is a requirement for filing. Actually, that really goes to question two because in the EMEA you are required to have shown both short-term efficacy and longer-term efficacy. Now, they have accepted a somewhat different trial design--well, it is the same design but it is a different run-in period

than we have proposed. But they actually require a demonstration of both short-term and long-term efficacy. They not only have to have done the trials but they have to have shown an effect over acute and longer-term.

DR. GOODMAN: Could you stay with that point for a moment, Tom, and tell us what is found acceptable by your counterpart in the EU as a definitive longer-term study in depression?

DR. LAUGHREN: It has to do entirely with the run-in period. As I understand it, and industry is here and they can correct me if I am wrong, but my understanding is that they accept a randomized withdrawal trial that involves an open phase where patients are treated for 8-12 weeks and are in responder status then for a relatively shorter period of time.

DR. GOODMAN: I am sorry if I am belaboring the point, but then they go into a relapse prevention design? Is that what you are saying?

DR. LAUGHREN: Yes.

DR. GOODMAN: For what period of time? If anybody else has the answer to that, that will be fine.

DR. LAUGHREN: I have the guidance document right here. An 8-12 week period, an open period, and a randomization phase of up to 6 months. So, it is presumably long enough to have events and that is really what drives the duration of the randomized phase.

DR. GOODMAN: Jean Bronstein?

MS. BRONSTEIN: This is a question that I just need some information about. When we were looking at studies on suicidality last time we were unable to compare one drug to another drug because the designs were so different. Is that in part what we are looking at today, that we want some consistency so we can gather that kind of information? That is just a point of clarification.

DR. LAUGHREN: The question we are asking the committee is whether or not--again, the first question as I intended it is, is it reasonable that

we would expect a company who is developing a drug for major depression, at the time that they file the application to have conducted both valid acute studies and a valid longer-term trial? Is that a reasonable expectation for them to have accomplished those trials? Not necessarily demonstrated longer-term efficacy but having first of all accomplished those trials, completed the trials using a valid design?

DR. MCGOUGH: I remain a little unclear. I mean, I see acute response and long-term response as two different things, and acute response is certainly important. And, I still don't really see what the need is to change. What are we lacking now with our current system? Where is the big problem?

DR. LAUGHREN: The issue is that at the time that a drug is approved for depression right now, in most cases all the clinician has is short-term data when we know that patients who respond after a period of several weeks, a month or 6 weeks--we know that those patients will be

continued longer term on that drug. You know, most clinicians are going to do that whether or not there is longer-term data. So, they are doing that without benefit of having any empirical evidence to support that. It is a question that you have to decide.

Again, as I pointed out, in Europe they have decided, for whatever reasons, that that is necessary to approve a drug for depression, to have not only done the studies but to have shown both short-term and longer-term efficacy. So, that is really the question.

Again, in fairness, most programs do eventually do a long-term trial and, in the vast majority of cases, those trials succeed. So, that should be factored into your decision about this. But the fact is that at the time that antidepressants are approved in this country right now, at this point in time, in most cases--not in every case but in most cases we don't have any longer-term efficacy data.

DR. GOODMAN: I would be interested in

hearing from a representative from industry what the current incentives are to conduct those long-term efficacy trials, other than that the FDA are requesting them. I would assume that there are some advantages to the additional labeling. DR. GILLER: First of all, I would say that I think very frequently the data on long-term efficacy is provided in a timely fashion. There are sometimes delays that are not simply because of conducting a clinical trial but sometimes actually negotiating the protocol with the FDA. So, I think we certainly would welcome some notions about how to do this more effectively.

Partly, these long-term studies are sometimes done voluntarily; sometimes they are a Phase 4 commitment at approval. There is the incentive, if you will or the competition, about providing that information in the label to be on par with other compounds that are also used in long-term treatment.

Just one other comment about the length of time patients are on medication. Dr. Tamminga, I

think your point is a good one from the clinician's perspective but now we are starting to get, to a certain extent, into course of illness and treatment in general, not specifically around a particular medication.

DR. GOODMAN: Earl, before you step down, it is clear to me that this requirement would increase cost of drug development. What is less clear is how much longer, what kind of delays it would introduce in getting a drug to the FDA for an NDA. If you knew in advance that you had to do it, couldn't you start those studies along with the acute trials, and wouldn't there be enough time to meet that new expectation?

DR. GILLER: Well, I think you have heard from some of the presentations that to start at the same time as the acute studies would be probably unethical and unsafe because you are not even sure about what the dosing is and you would like to develop the safety first.

It isn't as much the cost because the cost of the study is going to be the cost of the study.

It is the staging of those costs and also it is the staging of the information from a clinical perspective. Let's be sure we have something that is effective acutely before we go on to longer-term treatment. Again, I think industry, by and large, does start to do those studies if the protocol is negotiated partly through Phase 3 and into Phase 4. It is just a question of staging it to bring the information along at what we think is a timely and relevant point.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: I just have a question for Tom about the regulations in the sense that in your question it is about do people have to have completed the long-term trial before they make the application. Do you have the ability to say you have to have the long-term trial in operation at the time and then report the results later? I mean, could you have a scenario where somebody is saying we are doing a trial and you will have to tell us the results when it is finished, in a year?

DR. LAUGHREN: This is policy; it is not

regulation. So, I mean, clearly, we could do any of these things. I mean, that would be a possibility of insisting that somehow we have evidence that the trial is under way at the time that a company files the application. But it is not quite the same as having the study completed, knowing that they have actually followed through and completed the trial. One can never know, if a trial has been started, when it is going to be completed and the data cleaned and analyzed, and so forth.

DR. GOODMAN: Dr. Wang?

DR. WANG: This morning you sort of alluded to the fact that there is no sanction, there is no mechanism for ensuring that these long-term studies are done after approval. Is that pretty much the reality?

DR. LAUGHREN: Again, Phase 4 commitments for long-term efficacy trials usually are followed through on.

DR. WANG: But just delayed?

DR. LAUGHREN: They are delayed. I am not

aware of any actual mechanism that we have to enforce Phase 4 commitments but, in fairness, they are generally completed; they are generally done.

DR. WANG: This is just sort of a follow-up to Dr. Pine's question. It seems that you are either limited, or would like to have something in the pre-approval process to ensure that this data, which everyone seems to agree is useful and needed, gets generated. What is the range of possible sorts of ways to encourage this? One that you said is requiring a complete study and that in itself has dangers, in addition to what we have heard from the industry side. Just to complete a study, as you saw with the antidepressant trials done in kids to extend patent life--the quality might be so low that you don't know what a negative study means. What other possibilities are there in either requiring that you agree on an approvable design before approval for a long-term study, requiring actual initiation, or maybe requiring that some percentage of patients be enrolled already--but some intermediate so that

there is a good faith effort and you know that the trials are being taken seriously and they will happen in a timely fashion, but not simultaneous with approval for the acute claim?

DR. LAUGHREN: Those are all possibilities but none of them guaranties that the study will actually be completed. I mean, I think the proposal that came up earlier is that somehow FDA would have some authority to revoke the approval if a company didn't meet its commitment. That would take legislation and new regulation. We don't have that authority as of this point in time.

But again, in fairness, these trials generally are done. The issue here is whether or not it is acceptable for the clinical community to wait, you know, two to three, to four years to have those results.

DR. GOODMAN: Dr. McGough?

DR. MCGOUGH: Clinically I would just I would dissuade a physician or a house officer from ordering a study or a test unless that result was going to make a difference in management. I am

just here, thinking if you order these two tests, an acute and a long-term test, and one came back positive and one came back negative--to be more specific, if the acute study comes back positive and the long-term test comes back negative, would you deny approval or would you still approve it? I mean, I am just wondering if this would really matter. I am trying to see how this would really matter in terms of your ultimate decision depending on how the two arms might come out, together or different.

DR. LAUGHREN: That is question two and, you know, we are soliciting your advice on that. Again, if you look at EMEA, the way I read their guidance document, they do require actual evidence of both short-term and long-term efficacy to approve an antidepressant. They do require that. Again, as we have discussed, you know, depression is a chronic illness.

DR. MCGOUGH: But would a novel treatment for unremitting, severe acute depression be not worthwhile if somehow it doesn't maintain that for

6 months or more? That is what I am struggling with.

DR. LAUGHREN: That is a fair question.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Does FDA policy currently define--I am actually concerned about these definitions of acute and longer term--do you define what the range is for an acute trial? It always seems to be about 6 weeks but is that actually defined? If a manufacturer came in with a shorter duration or a longer duration I think many of us would consider that 12 weeks or 6 months could reasonably fit into a definition of an acute trial. For longer-term efficacy you are talking, certainly in late life depression, about several years of maintenance treatment.

DR. LAUGHREN: Well, the difficulty here is that all of these questions are inter-related and the later questions deal with the design issues of how long the studies need to be; how long the run-in period needs to be. There is not much controversy about acute studies in depression.

Company-proposed studies are always 6-8 weeks. We never see any variation from that these days. So, that is really not so much an issue.

The real issue here in terms of design is the question of how long patients need to be in a responder status before they are randomized. That is really the controversial issue here. We had proposed something longer. You have heard a lot of arguments today why it might not be necessary to have such a long run-in period. I don't know the answer but that is one thing that we are asking your advice on.

DR. GOODMAN: Dr. Pine?

DR. PINE: Going back to the issue of the range of possibilities, it sounds pretty clear that there is, you know, no feasible way to "revoke" an indication. What about thinking about other incentives that would, you know, make it so that there was to loss of a possible benefit if a company didn't do it? You know, not withstanding all the problems of the 6-month exclusivity with the pediatric studies, what if there were some

incentive to publicly disclose the results from a long-term study? Again, I wouldn't have any idea what the range of the incentives are but, you know, if a company really stood to lose an incentive if they didn't produce this data but there was, you know, something along the lines of extension of patent exclusivity if they did publicly disclose the data?

DR. LAUGHREN: Well, as we discussed earlier, I think one of the incentives for completing a trial and getting a positive result is that the company gets to put that information in labeling. This is obviously a very competitive field so it is an advantage to a company to have a longer-term claim.

In terms of negative consequences of not completing the study, I suppose Phase 4 commitments are listed on some kind of public list. Beyond that, I am not sure what it would be.

DR. GOODMAN: I am not completely sure what added value there is to the kind of trial that looks like it would count as a longer-term trial to

the EU. If you have 6-8 weeks of acute treatment and then you do your relapse prevention, as you have pointed out and others--I know it is a debatable issue, but without that stabilization period in between, if you have a greater relapse on placebo it would seem that what you are proving is that the drug was really working in the course of the acute trial. You still haven't, in my mind, established and given any additional information about long-term efficacy. It is a way of establishing on the back end of the acute trial that it was working on the front end. I don't know if others would like to comment on that. Agree or disagree on that? Dr. Sachs?

[Several participants say "agree."]

DR. SACHS: You have just stated one of the principles that I think we all agree with 100 percent. There is a very different object to a maintenance trial than a continuation of an acute effect trial.

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

DR. RUDORFER: I want to add something. I hope this isn't too idiosyncratic, putting on my clinician's hat. The other concern that I have

about the whole concept of the randomized withdrawal--well, there are two. One was alluded to. I think the ethical question, certainly with more chronic conditions, could be a problem. I don't think that is a rate limiting step in depression if we are talking about instituting a randomized withdrawal at a point where removal of a drug might be felt to be clinically indicated.

However, I am thinking when I wear my clinician's hat and I am talking to someone about stopping medication, unless there is some pressing reason, I think in really long, drawn out, slow terms about reducing a dose very slowly over a period of weeks, with the idea that if we appear to be running into turbulence we could back up again. So, I think that even in depression, on the one hand, in my mind there could be an ethical problem if there is a risk in essentially inducing an iatrogenic recurrence.

This also goes back to one of my early questions about DSM-IV, which is that major depression is much more heterogeneous than we often give it credit for. I worry, and I don't know if the European experience can be informative to us but I worry that if longer-term efficacy

requirements are instituted that trials not be skewed more towards patients who have less severity of illness; who have less history of relapses and recurrences and essentially might simply look better over the long haul or be more likely to stick with a trial or essentially further remove efficacy trials from the real-world experience.

DR. GOODMAN: Catching up, Dr. Winokur?

DR. WINOKUR: Thanks. I have several points I would just like to run through quickly. Several of the committee members have already commented about a number of areas that we really need more information about, such as long-term effectiveness. The question that has occurred to me is what information is crucial prior to initial regulatory approval as opposed to information that

may come up later and certainly be very important.

Secondly, I think there are a couple of aspects which we have seen that demonstrating efficacy in acute situations is very challenging. When Dr. Potter mentioned the review by Khan, that certainly brought that out and Dr. Laughren acknowledged that as well. The other study that comes to mind recently as an example is the Russian coworkers medical algorithm project, a benchmark study which is an effectiveness paradigm, you know, real world, where they found 25 percent response in this more heterogeneous group with major depression.

So, getting response in and of itself is still a challenge in this field. But I think we also heard that once we have people demonstrated to respond in a short-term trial, with limited studies admittedly that have been done, there is not much of a signal of a problem with maintaining that response, and I think Dr. Laughren agreed with that.

So, to me the much more pressing issue and

concern is the one that, Dr. Goodman, you started out with this morning about the really pressing need for more timely and comprehensive safety data, and it is of less concern to me that beyond a demonstration of acute efficacy intrinsically in every case there should be a requirement for longer-term maintenance or long-term efficacy.

DR. GOODMAN: Tom, could you comment on that? It is my understanding that you do collect that information. That is a requirement already. But, please, clarify.

DR. LAUGHREN: Yes, we always have longer-term safety data at the time of an initial filing. ICH has a guidance document and that is ordinarily followed. You have to have at least 300-600 patients for 6 months and 100 for a year. So, we always we have that for a new chemical entity.

DR. WINOKUR: I am sorry, I was really referring to improving that with more rigorous post-marketing surveillance. That was my point.

DR. GOODMAN: I think in part what you are

saying is if part of the impetus, and I was trying to explore this earlier, has to do with safety concerns that emerge post-marketing and to deal with that using a different fashion through post-marketing surveillance. Dr. Tamminga?

DR. TAMMINGA: One of the arguments that was made this morning that seemed important to me was that the speed of drug development is an important thing. People this morning did emphasize the speed of novel drug development--not that we have really many novel drugs around--and that we are speeding forward with a lot of pretty typical compounds. But given the case that we have novel compounds, we would really want to get those to market quickly. So, I thought that was really sort of a reasonably powerful argument. When I was trying to understand what that would be weighted against, I am not quite sure whether that is weighted against the ultimate availability of any long-term data or whether it is weighted against just delayed long-term data.

From what you say, Tom, for most of the

companies, if there is a commitment to Phase 4 delivery of long-term maintenance data, that eventually comes around. So, from my point of view, I don't know that I would necessarily require long-term data right at the point of approval as long as there was a commitment in the shorter long term, rather than in the further long term, if the tradeoff was speed of drug development. So, I was kind of trying to weigh those kind of things.

On the other hand, not many of us, other than you, have a real idea about near long term, far long term, or whether the FDA would then have much regulation over the design of the trials. I mean, could one maintain supervision, if you will, over the design of the data?

DR. LAUGHREN: Well, we do have a lot to say about the design. Companies submit protocols and we give them feedback and on a critical trial like a long-term efficacy trial they would want to get our buy-in that it was a design that we accepted. So, we do have a lot to say about that. Again, in terms of Phase 4 commitments for

longer-term efficacy trials, we have always added that to the initial approval letter and in most cases we eventually get those data.

DR. GOODMAN: Jean?

MS. BRONSTEIN: Tom, would it be reasonable for the FDA to require that longer-term data be available within two years of the first approval?

DR. LAUGHREN: There wouldn't be any way of enforcing that.

MS. BRONSTEIN: But could it be stated as the guideline and expectation?

DR. LAUGHREN: Well, we do usually put a time frame in the approval letter for Phase 4 commitments. There is a time frame but there is no regulatory authority really to enforce that.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Since we are just in this question focusing on antidepressants, are you aware of there ever having been a case of a antidepressant that passed mustard in an acute trial that failed in a maintenance study?

DR. LAUGHREN: I believe there have been some negative longer-term trials for antidepressants. I am not aware of any for

schizophrenia. I would have to look very hard.

DR. POLLOCK: But the clinical point I think is that you have assured us that safety data is systematically collected at the time of release, but I think it is almost a universal belief, jut talking about depression, depending on a particular type of patient and whether that patient has histories of recurrent depression; whether they are elderly at first onset. But, certainly, if somebody has responded acutely they are going to be maintained. It depends on the individual patient characteristics rather than the true or generalized efficacy of the drug. You can construct a maintenance trial to enrich it for those at risk of recurrence.

So, I really am concerned about whether this game is worth the candle that you want to invest. But there is a tremendous concern amongst those who believe that those patients who responded

to a medication, again depending on the characteristics of that patient, that they should be maintained for efficacy but our concern is with this new entity and do we really have safety data in, in my case, elderly patients that extends out to 6 months or a year. Particularly among the elderly, what happens in terms of hyponatremia and risks of movement disorders, and that sort of thing, if it has been routinely collected for that particular antidepressant.

DR. LAUGHREN: Yes, the quantitative requirements are not as clear for subgroups of the population like the elderly as they are for the general requirement for having so many patients exposed for so long. We generally will have some but I can't say precisely.

DR. GOODMAN: It seems to me that in many cases in which I have entertained the need for a relapse prevention study it is really in response to a different question. It has to do with at what point can you safely withdraw the medication; at what point can the patient be prevented from

relapse.

You mentioned before that one of your concerns about the current policies is that although, for the most part, companies are compliant with conducting the studies it takes too many years to get the information. Look at a case in depression, the work by Kupfer and Frank, how long did it take them to really collect the kind of information that we now use to help us guide how long to continue treatment? I think it must have taken at least five years; maybe it took more than five years because when you get into the field and you are asking the question about a particular patient, it is an individualized decision of when is it safe to discontinue this medication that apparently worked in the beginning. And, how do you make that decision? You make it on the basis of, yes, empirical studies such as the ones that have been conducted in depression about previous treatment history, severity, those kinds of factors, but it took a very long time to gather those data in a very large sample in order to be

able to answer those questions that help tell you at what point is it safe to stop the medication.

I guess I am returning to this question of added value. How much more are you going to learn about doing an acute trial followed by relapse prevention? I think it is still going to take you years to really answer some of the questions that are most pertinent to the clinician. Dr. Leon?

DR. LEON: Thanks. Well, I am a little confused following on what you just said, Wayne, and a few others. Now I am becoming a little more confused about the state of the knowledge about relapse prevention. Because, on one hand, from what Dr. Rudorfer said, it sounded to me like he continues treating. As a clinician, he is concerned for his patient. He is risk aversive and he continues to treat because it is working right now, but he apparently doesn't really have the data to make the decision. And, I have heard that from some other people.

Then, from Tom I hear but these data are eventually provided by each of the pharmaceutical

companies when they make the commitment. So, it seems like we should have the data--not me but the clinicians should have the data available if those data are provided. But I don't hear that that is being translated or it is not being used in clinical decision-making. Instead, it is more of this universal belief that I heard about that what worked for acute will continue to prevent relapse.

Actually, in the relapse prevention time there is a very, very long risk period. If you take person-years, it is a very, very long risk period for each patient to be at risk of relapse. As I say, I am not sure but it sounds like the literature really doesn't guide the clinician to make that decision. So, I think there is general agreement that we need the data but it doesn't sound like it is getting out there to the clinicians.

DR. GOODMAN: Gail?

MS. GRIFFITH: I would have to say I agree with Dr. Leon and also with you, Dr. Goodman. I would suggest that for the stakeholder it is

actually irrelevant to a certain degree. As you point out, the risk of relapse can be anything from, you know, 2 months to 12 years. So, it does become less relevant.

I think that what is important to the stakeholder is the risk/benefit analysis with respect to safety above all, as opposed to efficacy. We have somehow gotten into a thicket over the efficacy argument over the safety argument. DR. GOODMAN: Dr. Tamminga?

DR. TAMMINGA: I think that it would be important to remember that whereas long-term efficacy derived from acute efficacy might be pretty solid--we might be able to do that pretty solidly for drugs that we all know--all the SSRIs, all the antidopaminergic antipsychotics. But for the novel drugs, which industry is really seeking, we wouldn't be able to predict long-term efficacy from short-term efficacy with very much reliability so we would need--I don't know about right at the time of approval but the field would certainly need those data.

DR. GOODMAN: I think that is an excellent point.

DR. MEHTA: I just want to reemphasize one

other point, and that is the time line. Keep in mind that if we are talking about a 6-month withdrawal period and 6-month treatment, that is one year. To enroll patients will take another year and to discuss the protocol will take another 6 months. So, we are talking about 2.5 to 3 years to complete the study. That is usually the time for a Phase 3 program. So, what we are talking about is starting these type of studies right at the beginning of the Phase 3, which is not feasible medically or financially, for that matter.

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

DR. PINE: There is just one other thing I would say, just to second what Carol said. You know, it does sound, at least to me, fairly clear that everybody agrees that there is an advantage to getting these kind of data but it doesn't sound like the risks of discouraging, you know, getting

new drugs into the market outweighs any of the advantages of the regulations that I have heard. So, I would be interested to hear anybody else who had a really good rationale for it.

DR. GOODMAN: I thought what Carol might be saying is to consider different standards perhaps for novel agents, maybe a more stringent standard. That would be an implication at least of what you said, to have an extra degree of confidence because we don't understand the long-term mechanism quite as well, or at least it hasn't been demonstrated clinically to have another way of confirming longer-term efficacy with those compounds.

DR. TAMMINGA: I haven't really thought of the way to do it or the way to define what is a novel compound. In my area, clozapine might actually have different kind of characteristics than other antidopaminergic antipsychotics. So, there are differences even within therapeutic areas of drugs, but there certainly would be differences between some new antiglutamatergic drug for

instance and our usual antidopaminergic antipsychotic.

DR. GOODMAN: I am not quite ready to call a vote, but what I would like to do is hear from any committee member who would like to argue for adopting this measure as stated. They can do that in earnest or they can do it as devil's advocate, either way. I would like to hear the view point expressed in favor of adopting this new stringent standard.

[No response]

Give it a few more minutes!

[Laughter]

DR. LEON: This is leaning in that direction but not quite there. Earlier I asked about antidepressants that have indications for long term or relapse prevention. Are there any that have an indication for relapse prevention--this gets to the second question really--that do not have indication for acute treatment?

DR. LAUGHREN: The only one is lamotrigine

for bipolar depression.

DR. GOODMAN: There is a device too--a little different division of FDA, but vagus nerve stimulation was approved for long-term prophylactic treatment or treatment of resistant depression, but it does not have an acute indication.

DR. LEON: That is not relapse prevention, is it?

DR. GOODMAN: No, it is augmentation. Dr. Tamminga?

DR. TAMMINGA: Well, I would just take a stab at making a comment. I think that everybody thinks that the data for acute and long-term efficacy trials is reasonable to have for any single drug. Question number one doesn't say that you have to have finished both acute and long-term efficacy trials at the time of filing. So, one could interpret the answer to question number one that you have to be finished with one or the other, with the other one in progress.

DR. GOODMAN: Let me interject. That was my first assumption but I am pretty clear that the

intention is that the data is not only completed but analyzed and presented together as part of the NDA.

DR. LAUGHREN: That was certainly our intent in that question, that the studies will have been completed, data cleaned, data analyzed. Whereas, the outcome of that is question two, clearly, our intent in question one is that they would have done the studies.

MS. GRIFFITH: And that they would have been definitive is what you said earlier.

DR. LAUGHREN: That is right, valid trials.

DR. GOODMAN: But with one caveat, that I think if we are using the standard used in Europe, the long-term trial that would count would be going directly from acute into relapse prevention without a long intervening stabilization period. Right?

DR. LAUGHREN: Right. When we initiated this policy change sometime ago we had in mind a different design. We had in mind having patients stable for a much longer period of time but, again,

it is hard to separate these questions, one from the other. You know, we have had a lot of discussion this morning about whether or not there is really any advantage in having a longer stabilization period before randomization. It is not entirely clear to me what the right answer there is.

DR. GOODMAN: Let's assume for the moment, just as a point of discussion, that the FDA's definition of a long-term trial would require some fixed stabilization period in addition, would your answer to this question be any different? For example, if the definition of an adequate trial, a definitive trial would be acute 6-8 weeks and then, say, 2 months stabilization before relapse prevention? Does that change our thinking at all? Dr. Pine?

DR. PINE: First of all, it doesn't change my thinking but then I guess, second of all, you know, listening to all the possible advantages for arguing in favor of the question, the only thing that I have really heard--

DR. GOODMAN: I haven't heard any in favor. What were they?

[Laughter]

DR. PINE: I guess the only thing that I have heard, and again this is more kind of a straw man argument--the only thing that I have heard said is that either the long-term data is not coming at all, which is clearly not the case because we have heard that that is not the case, or it is not coming in quickly enough. I mean, that is the only argument in favor of it that has even remotely come forth and I don't think that there is much support even for that.

DR. GOODMAN: Jean?

MS. BRONSTEIN: The one argument that I am hearing is that it would give the FDA teeth. I am not proposing that but that is the argument that I have heard positively for this, that that would then give the FDA the ability to enforce it.

DR. PINE: Teeth to get the long-term data which, it sounds like we already think we might be getting.

DR. POLLOCK: I agree with what Dr. Tamminga said earlier, that for a novel compound we may not have the confidence that if somebody responds in 6 weeks that response might persist into 3 months or 6 months, and we certainly won't have as clear or as much safety data as we need on

this novel agent, or we need more intensive data on this novel agent.

But I think what I am concerned about is that the longer-term sort of straight efficacy trial where somebody who has responded is continued under double-blind conditions for at least 6 months, that I think is different from putting in the maintenance trials where there is a placebo withdrawal. The two things are blended.

DR. GOODMAN: My understanding is Tom isn't going to count that. Could you clarify, Tom?

DR. LAUGHREN: You are talking about continuing responders?

DR. GOODMAN: continuing responders in a double-blind fashion.

DR. POLLOCK: No, you don't have to break

the blind at 6 months. I mean, presumably people who have not responded or are not doing well will drop out but you don't have to close the study or at least break the blind, I think, at 6 weeks.

DR. LAUGHREN: You are talking about a 6-month placebo-controlled trial in depression where patients are continued on placebo for 6 months?

DR. POLLOCK: Well, presumably they would only be continued on placebo if they had deteriorated or had failed the study.

DR. LAUGHREN: What would the endpoint in that trial be?

DR. POLLOCK: Sustained response in those who had responded at 6 months.

DR. LAUGHREN: We haven't actually seen that design in depression. It is an interesting possibility.

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

DR. GILLER: Certainly, I think a long-term study like 6 months of active versus

placebo would give you a bit more maintenance of effect, but the major concern is the dropout rate. Recall the information that I and others showed that people tend to drop out fairly quickly. The validity of the study often depends on having enough patients left in the study to be able to analyze what happens overall. LOCF is not always the best way to do it. At the end of 6 months, you know, you are going to start off with a lot of patients and you are going to have very few left. It is not going to tell you that much more, except that if you can distinguish between active drug and placebo at 6 weeks you will very likely be able to do it at 6 months as well.

DR. GOODMAN: Thank you. Let's suppose for the moment that we vote no as a committee on this after we take the vote. How do we explain that to the public in layman's terms, that we made it permissible that an antidepressant, in this case, be brought on the market that has been shown effective only for 6-8 weeks? It has been shown safe beyond that but we know, in fact, clinicians

are prescribing it for extended periods of time, 6 months, maybe years. How do we explain our rationale in simple terms for adopting that? Gail?

MS. GRIFFITH: I think we really need to go back to looking at the risk/benefit analysis and the safety concerns. I think if we suggest that longer-term efficacy has not been proven definitively, the decision then goes to the clinician and the patient. I mean, it becomes a matter of the practice of medicine. It is not a regulatory issue and it is not really a public health issue. It goes to the basis of practice and whether or not the clinician deems and the patient deems that he or she is well enough to discontinue use, or whether or not the drug is still working.

We talked about this in the SSRI discussions about not wanting to dictate the practice of medicine and there is so much of this efficacy question that goes directly to that. So, I think we emphasize the safety issue. It is a risk/benefit analysis that the patient makes.

DR. WANG: I would say that from the

clinician's perspective, I think what is most important is that someone is in acute distress and we know we have the means to address that. We have some comfort level that the long-term risks of staying on this medicine in terms of safety are minimal. Then it becomes really the clinician's understanding of whatever disorder we are dealing with and a careful, ongoing assessment of the patient and careful titration down, if necessary, or initiation of another treatment if the treatment effect begins to wane.

DR. GOODMAN: The other thing I would add, and I think this has been alluded to earlier, is that I think there is a role for the NIMH to fill in the gap. In fact, that is what happens now. That is what funded the work that has informed us so well about what criteria to use about how long to maintain treatment and now to individualize, how to tailor continuation of treatment. So, I think there will continue to be a role for the federal government to fund studies that will help us learn more about which patients need to be continued on

medication and which can be discontinued. Dr. Rudorfer, did I say something offensive to you?

[Laughter]

DR. RUDORFER: No! They wouldn't let me bring the checkbook today! I just want to amplify, Wayne, that what we have learned in recent years, and others have alluded to some of our big effectiveness trials--CATIE and STAR-D and STEP-BD--is not a matter that certain kinds of research are necessarily better than others; it is that some are better in answering different questions. One of the ways I am framing our discussion here today is that the regulatory-oriented efficacy trials are excellent at the short-term questions that have been addressed up to this point, and I am wondering really if what we are saying is that once we get to longer term where real-world considerations come in such as, again, the heterogeneity of patients, the co-morbidities that exist in the clinic in people who tend to be screened out of efficacy trials, people who are treated in non-traditional settings,

all the issues that tend to come to the fore after drugs are on the market or whether, in fact, the continuation of the industry-sponsored efficacy trials is simply not the right vehicle for doing them. And, maybe we need a new public/private partnership kind of paradigm to get at those.

But, again, it seems to me, at least from my point of view, that I would agree with the basic premise that the longer-term efficacy data are necessary and are important I think to all of us. I think the question simply is what is the best way to accomplish that. I have questions about whether longer-term efficacy trials under the auspices of the FDA is the best way.

DR. GOODMAN: We will have a few more comments and then I am going to call for a vote. Dr. Tamminga?

DR. TAMMINGA: Well, I would never speak against the NIMH having a bigger role in various kinds of clinical studies. I think one thing that the CATIE trial told us was that it really confirmed previous drug company pharmaceutical

trials because the outcome of the CATIE trial was pretty similar to what we all knew already from all of the efficacy trials that were done by pharmaceutical companies.

I would hate to see pharmaceutical companies think that they didn't have any role in defining the long-term application of their drugs and that that would really be switched over entirely NIMH. The NIMH would have a role in some kinds of questions but the pharmaceutical company would still retain responsibility to continue on to demonstrate to physicians who are using their drugs what the proper way to use them is.

DR. GOODMAN: I wasn't suggesting that we would be dividing up the world of acute and long term between industry and between NIMH. I didn't mean that at all. In fact, I think there are some examples, VNS is one of them, where there will be places for where the FDA would be approving a medication or intervention for long-term management rather than acute efficacy. Dr. Leon?

DR. LEON: Could I go back to the issue of

teeth, the FDA's teeth? An alternative strategy might be on the label to indicate that although you are giving an indication for acute treatment--in one of your questions you say you don't mention anything about longer-term trials. You might explicitly mention, or could you explicitly mention that longer-term use or relapse prevention has not been studied?

DR. LAUGHREN: We do regularly.

DR. GOODMAN: Dr. McGough?

DR. MCGOUGH: I think the question of, yes, we know how to put people on medicine but we don't really know how to take them off is a very good question. But just looking at depression, to design a study, there are all sorts of other factors--the age of the patient; how many past depressions has that person had. Would withdrawal after 6 months really make sense if someone cycles every 5 years? I mean, it seems to me almost that there is no sense in doing a study unless it can reasonably answer a scientific question, and I am not sure you could define a study of one year or

two years that would truly help in that way.

DR. GOODMAN: Unless there is any objection, I will close general discussion and move to individual votes. I think I would actually like to start with a comment from one of our non-voting members. Dr. Mehta, would you tell us your opinion on this question?

DR. MEHTA: The last chairman asked me the question even though I cannot vote, suppose I was to vote, how would I vote and what the reasons are. In this particular case I would vote no. I think you can take solace in the sense that there are a lot of other areas of medicine where you have data only for acute treatment. For example in angina pectoris, all the studies done are in general about 8-12-week studies. Patients, of course, get the drug for a long, long time. Similarly for diabetes, arthritis, hypertension, and you can go to disease after disease where clinical studies are done for 3 months, 6 months, sometimes one year and, of course, in real life the patient gets the drug for a long time. There is no evidence of

long-term efficacy for most of these drugs.

DR. GOODMAN: Thank you. Dr. Rudorfer?

DR. RUDORFER: I concur. I would vote no.

DR. GOODMAN: You are voting no?

DR. RUDORFER: Yes, I vote no. Again, I think it is an important issue and I think what we are hearing, at least in the case of major depression, is that there are data supporting longer-term efficacy but I think in terms of new drugs coming to market this is not the best approach to get that information.

DR. GOODMAN: Thank you. Dr. Leon?

DR. LEON: I also vote no, and I agree with what Matt just said.

DR. GOODMAN: Gail?

MS. GRIFFITH: I vote no.

DR. GOODMAN: Dr. Tamminga?

DR. TAMMINGA: Well, I vote no with a little bit of a reservation, that there could be some kind of commitment with as much teeth as possible for the long-term data to actually become available. But I wouldn't necessarily see it as so

very important that that be there right at the time of the acute approval.

DR. GOODMAN: I vote no. I don't see the added value. I see mostly disadvantages to adding this policy requirement in reducing incentives and availability of new medications and slowing down the process. I certainly, along with my neighbor from Texas here, make it clear that we do need more data on long-term efficacy not only in depression but other disorders. I just don't think that this is the right approach and I think it is going to hurt consumers rather than help them. I also think that the kind of studies we are talking about will help confirm our notion of acute efficacy but won't add that much in terms of important clinical decisions about when is it safe to discontinue treatment, and those require a different kind of design and take a longer period of time, larger sample sizes, etc., and I don't want to place that hurdle on the front end as long as we have the safety data, and I think we are already acquiring that. Dr. McGough?

DR. MCGOUGH: I vote no. I think the long-term open-label safety data is essential. I think the biggest challenge is keeping people in

those studies, not figuring out when to drop them.

DR. GOODMAN: Dr. Wang?

DR. WANG: Yes, I would vote no. I don't think we need a requirement for a complete study. It may even lead to poor quality long-term studies. But I think we do need something less drastic that preserves the sponsors' incentive to do rigorous long-term studies. You know, in order to gain a competitive edge, ideally it would incentivize you to do a long-term study to gain an indication or separate yourself from the competitors. I personally favor something like agreeing on an approvable design at the time of approval and/or actually initiating it at the time of approval.

DR. GOODMAN: Dr. Winokur?

DR. WINOKUR: I vote no. I would also emphasize the importance of more long-term data. I think there might be creative research designs that companies can use to gain an advantage in labeling

for indications as well as for maintenance support. I reiterate that the safety issue is important. I know we are getting more safety data pre-marketing but I think more creative and systematic ways to follow an experience when it is out in larger populations, less kind of restricted in terms of other morbidities and drug use is a really crucial issue.

DR. GOODMAN: Thank you. Jean Bronstein?

MS. BRONSTEIN: I also vote no. I just want to highlight the importance of patient safety and getting that data to the consumer as quickly and as fully understood as possible.

DR. GOODMAN: Daniel Pine?

DR. PINE: I vote no, and I think the only thing that I would add in communicating the message to the public is to state that a lot of this discussion, and I think ultimately the vote, at least partially reflects the concern with how important it is that we do everything we can to as soon as possible address the need for really better treatments for mental illness and, at least from my

own perspective, that speaks as strongly to the no vote as anything else that I have heard.

DR. GOODMAN: Thank you. Delbert Robinson?

DR. ROBINSON: I vote no for the reasons that have been sort of enumerated. I think the longer-term data we all agree is very, very crucial, but the really informative studies to get that out are going to take a period of time and I don't think that it is worthwhile for a drug that has acute efficacy to be held up for that. I share Dr. Wang's concern that if we made this as part of the regulation we might get a lot of long-term studies that weren't done very well and with worse quality.

DR. GOODMAN: Thank you. Bruce Pollock?

DR. POLLOCK: Yes, I also vote no, but I also wanted to underline something I said earlier about safety of these medications in elderly patients because I have certainly seen in the history of even largely benign class of drugs, the SSRIs, that the kind of safety information

concerning medical problems, such as hyponatremia or risk of gastrointestinal bleeding or bleeding after surgery--that these things came out in a very unsystematic and sporadic way and it would have been better to have gotten that more prospectively or in a more regulatory fashion.

DR. GOODMAN: Thank you, all. I want to give Karen some time to tally the votes.

[Laughter]

DR. TEMPLETON-SOMERS: I am working on it!

DR. GOODMAN: It is unanimous with 12 "no" votes. Yes, Gail?

MS. GRIFFITH: Dr. Goodwin, I just wanted to devote a second to thinking about how does this get communicated. I know we touched on how we convey our sense to the public but, as we all saw with the SSRI debate, not only was it miscommunicated to the public, but I think it had some deleterious effects and there was a precipitous drop-off in prescriptions. I would hate for this debate to be misinterpreted in any

way. So, I am wondering is there a way to suggest that yes, indeed, there is long-term efficacy and although we only have about 75 percent fulfillment from the sponsors it is better grounded then one might think. My fear is that this will be yet another run-away issue where it looks as though the FDA was asking efficacy data and, you know, the committee said no and the FDA is going to be put upon to prove that, you know, you are once again doing the public a service. So, how exactly does this get construed through the FDA and out to the public?

DR. GOODMAN: Remember too that we are advisory to the FDA.

MS. GRIFFITH: Right.

DR. GOODMAN: They are still free to make a decision about their own policies. Tom?

DR. LAUGHREN: Well, the full transcript of this meeting is publicly available so people can see for themselves what thinking went into this. There will also be a summary document on the meeting that will be available. I think personally

that it was a thoughtful discussion and I understand how you arrived at your decision. I don't think we will have any great difficulty communicating this.

DR. GOODMAN: I am trying to adhere to the logic of your questions here. We voted no for question one. We don't get to question two in the way it is currently formed.

DR. LAUGHREN: We changed it however.

DR. GOODMAN: But we changed it. You took away the qualifier.

DR. LAUGHREN: Right.

DR. GOODMAN: So, let's go to question number two. We took away the qualifier so it is not contingent on the response to the first question any longer. But given the outcome, is it a reasonable expectation--well, I don't think it makes sense to vote on this.

Let me make sure I understand this. I think really what you are asking is the second parts: Are there situations that would arise where you would grant approval for acute or long term but

not both? Obviously, a sponsor can elect to present data. There is nothing stopping them from presenting data for both acute and long term at the time of original submission. So, I think that is really the question, if they do, what are the options for the FDA? I guess you want the input from this committee. Would we entertain advising you to independently address acute and long-term efficacy? Tom, do you want to elaborate on that?

DR. LAUGHREN: Yes, I don't know that it is necessary to vote on this at this point. I think it is fairly clear. If we are not requiring both acute and long-term efficacy at the time of initial approval, then obviously we can approve only for acute use, and we already have approved only for maintenance for lamotrigine so I don't know that it is necessary at this point to have further discussion on that.

DR. GOODMAN: I agree that we shouldn't take a vote, but any discussion? Dr. Wang?

DR. WANG: I think if there is a way to highlight whether a long-term study has been done

or not, and also the results of it, that is part of unleashing the competitive energies of industry. I don't know what the bounds are for labeling to communicate this, but that is one way to incentivize the sponsors to do these studies, to basically get an advantage.

DR. LAUGHREN: Yes, sometimes it is difficult to know what to do with a negative study. If a study has not been done well or, for example, what we have called failed studies--I am talking now about acute studies, if you have a 3-arm trial and you compare a new drug with a standard drug and placebo and neither drug beats placebo we consider that a failed trial that is uninterpretable. There was probably something wrong with the conduct of the trial, and we would not be inclined to describe that in labeling. But if a study looked like a reasonable trial, reasonably well conducted and failed to show a longer-term benefit and there was no active standard in that trial, I think we probably will describe that in labeling. I think at this point in time we probably will do that.

DR. GOODMAN: I would like for us to take a 15-minute break at this point. It will certainly give me time to collect my thoughts about how to

proceed. My inclination when we get back is that we can either engage in discussion about design of studies or we can reframe that first question in terms of a different disorder and at least have some discussion about whether our answer would be any different if it wasn't major depression. So, let's take a 15-minute break.

[Brief recess]

DR. GOODMAN: This is the last segment of today's committee meeting. I just want to see if everybody on the committee is here, and they are not. Let's wait a minute or so. We will go ahead anyway and we will let the latecomers get caught up by their neighbors.

I have a few ideas about how I think we should proceed. First of all, because we are not paid by the hour I don't think that we need to go to five o'clock as scheduled. So, if we end earlier and we feel we have covered all the ground,

that is fine from my perspective unless there is anybody who disagrees, and I doubt there will be.

I think it is worth touching on the question would our answer be any different if we were talking about something other than depression, but I don't feel the need to take a vote or belabor that discussion. So, that is one thing I would like to touch on.

Number 12 is something that intrigues me. It has to do with the extrapolation between adult or pediatric and I think we should at least have some discussion about that question.

But before we do any of those, I thought that it would be very helpful for this committee to make a statement and vote on it. I think it is certainly true that the public can go to the web site and read the transcripts about what every individual said and how they arrived at their vote. It is not quite as effective, I don't think, as writing a statement expressing what I think would be our strong feeling that there is a need for additional long-term efficacy studies in not only

depression but other psychiatric disorders, and some notion about how we would go about acquiring that information, or at least what bodies or entities need to work together in order to achieve that end.

So, if we could take the next ten minutes or 15 minutes--maybe somebody is that good a wordsmith that we could do it faster, but to help draft a statement that we could all stand behind, or at least most of us can, and take a vote on it. That would be the only other item that we would vote on today. Is everybody amenable to that?

Why don't we just start a discussion. In part, this is addressing the question about how is the public or how is the consumer going to read what we did. Here the FDA was going to raise the bar to ensure long-term efficacy and we said no, don't do that; you don't need to do that. Again, we have all been very clear about the reasoning and the balances that went into that decision, but I would like to be able to express succinctly what we see as the future direction and recommendation.

Carol?

DR. TAMMINGA: Well, one of the reasons why that was at the basis of my vote--my vote was no in the context of the present drugs that we have available because we have extensive experience with SSRIs, antidepressants, with our current mood stabilizers, some of our current antipsychotic drugs. But as soon as we would get really novel compounds in an area, I think that we should add that we would advocate for both long-term as well as acute studies for those compounds with novel mechanisms of action.

DR. GOODMAN: So, you would place the emphasis on novel compounds. I was thinking of speaking in broader terms, and perhaps as we craft that we could say especially for novel compounds. Other comments?

DR. POLLOCK: Could we say that we recognize the need for greater information to guide clinicians for the treatment of individual patients as to the risk and benefit of their continuing on medication?

DR. GOODMAN: Could you restate that?

DR. POLLOCK: We recognize the need for greater information to guide clinicians with regard

to the need for individual patients to be maintained on their treatment for which they have had an initial response.

DR. GOODMAN: That is a terrific start and we will start from there as the draft, as the first sentence. The second question I think should point to the future direction about how to accomplish that.

DR. MCGOUGH: And I would expand that a little bit more to Dr. Rudorfer's point earlier. Really, you know, I think what we are talking about is long-term effectiveness studies where we haven't so carefully screened people for homogeneity where we are dealing with co-morbidities, dealing with issues of patient compliance and the long-term tolerability. That it really needs to be done to inform practice.

DR. GOODMAN: Dr. Winokur?

DR. WINOKUR: I have processed a lot of

the discussion as really taking into account the arguments that we really need more effective treatments. I think that was especially encapsulated in Dr. Sachs' presentation. We also talked it in terms of some of the work in depression. So, I think it was a choice to really prioritize encouragement of new treatment options, even if initially, for acute treatment. There was also a strong emphasis on the importance of following that up with more long-term efficacy, but it was a decision weighing the option to really prioritize encouraging development of new and more effective treatments.

DR. GOODMAN: Let me try to read back to you what we have so far: The advisory committee recognizes the need for additional information to guide clinicians with regard to--

DR. POLLOCK: Let me change that to "inform clinical practice."

DR. GOODMAN: Is there a second person that could put this on the screen? That really works a lot better as a group process. Is there

somebody who could put that up? You need to see it; hearing it doesn't work. In the meantime, some of you can work on the next sentence about how to accomplish this end. We are counting on you, Dr. Wang.

DR. WANG: I am not good at wordsmithing but maybe an intent to support the FDA's initial efforts in this regard, not to reject that intent and that goal, and then offer something prescriptive. So, in addition to supporting the intent, encouraging the FDA to modify or adapt their current drug approval process to encourage this obtaining sort of clinically relevant--

DR. POLLOCK: Then we go back to the question we voted on.

DR. WANG: But it sounds like no one was happy with the mechanism proposed but everyone has concurred that getting this data, this long-term data to inform clinical decision-making sooner would be a good thing. So, in terms of Dr. Goodman's suggestion for what do you tell the public, you know, right now it is pretty negative.

We just say no. Something prescriptive that conveys that everyone thinks it is a good idea to try to expedite this data--what mechanisms do we have? The FDA has, as we are hearing, limited tools in its box, but among those tools what might be useful?

DR. GOODMAN: So, perhaps we can start by saying we commend the FDA for its attempt to acquire--

MS. GRIFFITH: How about recognizing the need to acquire? We commend the FDA for recognizing the need to acquire?

DR. GOODMAN: Additional information on long-term efficacy.

DR. PINE: Or, we encourage the FDA to continue their efforts, something like that. We are supporting them looking for a mechanism.

DR. POLLOCK: Particularly with regard to drug safety.

MS. GRIFFITH: To what?

DR. PINE: We encourage FDA to continue their efforts to--what did you say, Bruce?

DR. POLLOCK: Particularly with regard to drug safety. You said "gather information.

DR. PINE: Gather information--

DR. GOODMAN: No. Let's not commend the FDA.

[Laughter]

If we start doing that we lose all credibility so let's leave them out of this!

MS. GRIFFITH: How about the committee recognizes the need--

DR. GOODMAN: Yes. Yes, I think so. Let's keep it in our own voice. How are we doing, Carol?

DR. LEON: Well, further work is needed. We haven't gotten to the point of what is the design that would help us gather the additional information that the first sentence says we need. So, further work--I am not dictating this sentence at all; I am discussing this, that further work is needed. What design will get us that information? Maybe in some other forum we need to discuss--

DR. GOODMAN: The second part is about how

to acquire the additional information, how to mobilize or marshal. Dr. Giller, it seems that you might have an idea? We all know what we want to say. We want to get it just right.

DR. GILLER: I would just like to really make the point that, as you saw this morning, industry really supports the importance of long-term data. As somebody who has spent years in academia and years in clinical practice, I am speaking not only for myself and for Pfizer but for the thousands of other people who are developing drugs because we think they are important. Look back on the slides. We think long-term data is important, period.

So, I would say this committee supports the need for and the importance of long-term data to better inform patients and clinicians about the use of medication after acute treatment and going into long-term treatment. How can we do it better? I think we could use expert consensus workgroups looking at what types of clinical trials will best deliver that information.

We were hearing that we have to do something to kind of beat industry over the head. Well, there is an incentive. The system is already

there and it works. If you have long-term information in your label, then you can talk to physicians and patients. If you don't, you can't. So, it is a competitive advantage; it is a clinical advantage.

The problem is we have been hearing that, well, sometimes this information doesn't get there for two to four years. Well, that could be speeded up, and part of the way it could be speeded up is to have some expert consensus panels work to see how fast we can get it done.

DR. GOODMAN: Let's talk a bit more about what our recommendation is for a forward thinking plan to mobilize resources. Are we asking the NIMH and industry and other groups to partner in this process? Comments on that?

DR. PINE: If we are not talking about what FDA should do I don't think that we should be talking about what NIMH should be doing.

DR. LEON: Does the FDA organize sponsor workshops to discuss something like this?

DR. LAUGHREN: We have had workshops in the past. Actually, we have had some joint workshops, very useful workshops, with NIMH and I think that would be a useful way to pursue this. I

mean, part of the advice that we have gotten today is that we need to look at this issue in different indications because the issues are so different. Just as an example, with schizophrenia the notion of considering non-inferiority trials is a very interesting one. It takes a separate group of people who are expert in that topic to discuss that. So, I think that is probably the way that we will pursue this, dividing it up into separate indication areas and pursuing means to get some kind of a discussion of that, assembling appropriate experts. Exactly how we do that is something we will have to work out. Maybe Matt and I can probably talk about that.

DR. TAMMINGA: Who is responsible to inform clinical practice?

DR. GOODMAN: Some of the journalists in the audience may be able to do a better job. This is not pretty but I think it is probably something we could stand behind.

DR. TAMMINGA: Are we going to say who we think should inform clinical practice?

DR. GOODMAN: Microphone, please.

DR. LEON: For empirical support.

DR. GOODMAN: I think it is satisfactory

the way it is. Last chance?

DR. WANG: We encourage ways to further research because everyone agrees, you know, more research is good in this area. I think there have to be some concrete mechanisms for the FDA to promote this. It sounds like possible regulatory actions or mechanisms aren't ideal, but something.

DR. LAUGHREN: What I understood the advice to be is that we should assemble the experts that we need to improve the methods of obtaining data in the different areas that we have talked about, again, you know, thinking in terms of specific indications and how the approaches might

differ depending on the different indications. That means gathering together experts in the different areas. That is something that we can do.

DR. POLLOCK: I am not sure what the need of empirical support--the need for improved methodologies to inform, or improved methodologies and mechanisms of support that might inform--I am just not sure I like "need of empirical support." Data, great need for data and improved methodology.

DR. GOODMAN: How would it be if we say research efforts by industry, NIH and other government agencies to further research in this important area? Is that acceptable to some of the industry representatives? Is that good enough?

Let's start from the other side. We are voting on whether to accept this statement by our committee.

DR. POLLOCK: Yes.

DR. ROBINSON: Yes.

DR. PINE: Yes.

MS. BRONSTEIN: Yes.

DR. WINOKUR: Yes.

DR. WANG: Yes.

DR. MCGOUGH: Yes.

DR. GOODMAN: Yes.

DR. TAMMINGA: Yes.

MS. GRIFFITH: Yes.

DR. LEON: Yes.

DR. RUDORFER: While empirical is one of my favorite words, I do fear that many people in the public will not understand what that means.

MS. GRIFFITH: How about "the need for evidence?" "The need for evidence to support"...?

DR. POLLOCK: Yes.

DR. GOODMAN: I like that.

DR. TAMMINGA: Shouldn't we specify this important area? Shouldn't we say something concrete? Long-term efficacy?

DR. GOODMAN: Just long-term treatment is probably okay. Do we need to recast votes? I don't think so. Dr. Rudorfer, are you now prepared to vote?

DR. RUDORFER: Almost! Did we want to use the word safety in here anywhere? Long-term

treatment efficacy and safety?

MS. GRIFFITH: Could I suggest that that might open a can of worms. I hope not.

DR. GOODMAN: We weren't talking about that.

DR. TAMMINGA: We are already assured that that happens.

DR. RUDORFER: Okay. Final question, at the risk of over-reaching and I am just thinking for myself here, "we encourage efforts"...do we want to use a word like "collaborative efforts?"

DR. GOODMAN: I love it. Good work.

DR. RUDORFER: Yes.

DR. GOODMAN: He had to get in the last word, so to speak! That is our last vote for today. Special thanks to Dr. Tamminga. Karen is computing the results here, but it looks like it is unanimous in favor, 12-0. We are going to save it now because we don't want to go through that painful process again.

Some discussion about whether our vote would be any different on the first question if it

were another psychotic disorder besides depression. Another way of asking is, is there a vote of "no" about a requirement for both long-term and acute efficacy data to be presented at the time of new drug application apply to all psychiatric drugs? Again, we are not going to take a vote on this. Any reason to consider any of the other conditions differently? Carol?

DR. TAMMINGA: Well, it seems like a big generalization and a big leap. I think that certainly my thought would be that in the context of our discussion today and in the context of our current active drugs, it might be safe to make a limited statement like that but not to extend it much beyond our present treatment armamentarium or our present major psychiatric diagnoses.

DR. GOODMAN: Dr. McGough?

DR. MCGOUGH: I think if we had voted yes on the question, then the discussion would be one size doesn't fit all and different natural courses of different illnesses really require different types of considerations. But since we rejected

this in the case of depression, I think it is even more so that this needs to be considered on an individual basis, and I can't think of any other disorder when I would insist on long-term efficacy data prior to giving an acute approval.

DR. GOODMAN: Dr. Pine, you are nodding your head?

DR. PINE: I would just agree with what Jim said, everything he said even in children. I would agree that I think it would be a mistake to apply the question one statement in any disorder that I can think of, really for a lot of the same reasons that we discussed with adults. I would be very concerned about limiting the implementation of trials or getting new medications available.

DR. GOODMAN: Any industry representatives disagree with that? Dr. Giller, come forward, please.

DR. GILLER: I am not going to disagree because I think it certainly make sense. I did want to comment though on the concern about new mechanisms of action, which I think is something

that is related to potential restrictions. I think that for some particular new mechanisms of action there may arise certain concerns about efficacy, as there are about safety, but in general I would suggest that, as Dr. Sachs has said, what gets you well keeps you well, and we know that through the antidepressants with a couple of mechanisms of action--the benzodiazepines, the SSRIs which are a bit more selective; in schizophrenia D2, and now D25h, D2a; in bipolar disorder lithium and anticonvulsants. So, there are a lot of mechanisms of action that were at one time new MOAs.

Hopefully, one of the things we will be doing is bringing forward new compounds with new mechanisms of action and if the hurdle, as we have heard, is even higher for new mechanisms of action it is even less likely that those are going to come forward. Again, we re not just talking about a delay; we may be talking about people just not investing in them at all. So, I would suggest that a new mechanism of action in and of itself is not a reason to say you need long-term efficacy at the

same time you need acute.

DR. GOODMAN: I wouldn't represent our discussions of this issue as comprehensive or definitive, but I think I want to get a sense from the committee if any exceptions leap to mind where we would have answered differently in other disorders. I think at first blush the answer is, no, we can't think of any.

There is a series of questions that concern methodology of design, questions about need for stabilization period and the length of that period. Although they are all important questions, I think at this stage, given our answer to the main question, there is no need for this committee to belabor over them. There are plenty of other disorder specific experts that could be assembled that could help inform what would be the best research design to answer questions. Is there agreement that we don't need to discuss them unless, Tom, there was something that you specifically needed us to address?

DR. LAUGHREN: No, I think if we are

moving in the direction of specific groups to deal with specific disorders, that would be the better place to deal with all the issues of design. I am fine with that.

DR. GOODMAN: I would actually like to move to question number 12. We will get it up on the screen. I will read it to you in the meantime: If there are data supporting a longer-term claim for adults for a drug for a chronic psychiatric indication, is there a need to obtain longer-term data for a pediatric indication for this same disorder, or would it be sufficient to obtain acute data for the pediatric population and extrapolate from adult data for the longer-term claim?

I know, Dr. McGough, you wanted to express an opinion on this.

DR. MCGOUGH: I think, while well intended, as I perceive this question the attitude behind it really reflects a bias that has hurt the treatment of kids. There have been attempts to get companies to do studies in children, although many drugs still come on the market without showing

efficacy in children. If a drug is released, it will be prescribed for kids. There is not any question about that.

But the problem as I see it--there are really two. The first is on the claim of efficacy. Just because a child shares the same nosology as an adult, it doesn't mean at all that it is the same disorder. We may call kids major depression, but perhaps one reason why SSRIs have done so poorly in depressed kids is that they are really a different set of kids.

I would argue that in disorders like psychosis, mania--I mean, there is no guaranty at all that when we use that label it is the same thing at all. So, even though you may have a short-term response, it doesn't at all inform the long-term response and, in fact, many kids, say, with psychosis do much more poorly over the long haul with the same medicines that would be fine for someone who becomes schizophrenic at age 18 or 19.

But probably the more important issue is the safety issue. I think earlier in the day we

highlighted the need for safety data out of long-term studies. A nine year-old brain is not the same as a 29 year-old brain. So, there are issues of pharmacokinetics; there are issues of developmental neurology that really come to bear. And, I think without good long-term safety data in kids those practitioners are really left in the lurch.

DR. GOODMAN: When I first read this question I was thinking along similar lines as you just expressed about the limitations of drawing conclusions from even acute trials in adults to acute trials in pediatric patients. But the question is very specific in that it is saying once you have obtained the longer-term data in adults, do you have the same problem in extrapolating to longer-term data in children and adolescents?

DR. MCGOUGH: Again, when we say long-term data I think we mean long-term efficacy data and safety data, and I don't think there is any way you can extrapolate safety data from adults into kids or perhaps into geriatric patients.

DR. GOODMAN: Let me ask Dr. Pine to comment.

DR. PINE: I guess I would just echo some

of the things that Jim said. I think that I can't think of a single instance where there has been an adult agent where one can easily and safely extrapolate and feel totally comfortable either with respect to efficacy or with respect to safety. I got the sense, just from talking with Tom and listening to some of the rationale for this meeting right here, that there is a desire to think of other ways to encourage the gathering of more data in kids in general, and specifically long-term data. I would say that whatever regulation you can have to insist that adult data not stand for child data, both with respect to safety and efficacy.

I guess the one other specific example I would point out that we haven't talked about that kind of spells out some of the issues that Jim was raising is the whole issue of growth. So, it is reasonably clear that there is reason to be concerned about the effects of stimulants on

growth, number one, and now it looks like maybe there is some reason to worry about the effects of SSRIs on growth. You know, if we can see in the overall visible stature of a child a differential effect of an agent, we should be even more concerned about trying to discover the mechanisms through which the agents are working in the brain, both in a beneficial way and in a bad way. It really requires a weighing of risk and benefit in studies directly among kids.

DR. GOODMAN: Tom, do you want to respond?

DR. LAUGHREN: Let me just clarify this question. First of all, the topic for today was long-term efficacy, not safety. So, this question is focused specifically on efficacy, not safety. We clearly agree that there is a need for completely separate and much more specific and detailed safety information, including long-term safety information, in kids.

The basis for this question is the following: In a typical situation we have acute data for a disorder in adults; we have long-term

efficacy data in adults. If a company does an acute efficacy trial and obtains acute efficacy data in kids, the question is--for efficacy only--can you extrapolate the long-term adult data, efficacy data, to kids, or does the company need to do a separate long-term study in kids?

Here is why this question is important to companies, this becomes the substance of a written request to gain additional exclusivity. I mean, this is a question for you to give us advice on but basically if you advise us that we do need additional--if you have those three legs of that four-legged chair, if you are telling us that you need to have additional long-term efficacy data in kids we will incorporate that into a written request. But that means doing not only acute studies in kids, efficacy studies, but also long-term efficacy studies in kids.

DR. PINE: Let me clarify my position. I would agree with what I said about the adult studies, that it should not be a requirement that a long-term efficacy study be done for an agent to

have an indication for acute efficacy in kids. But by the same token, I would not recommend that just because the acute data are clear in adults, the acute data are clear in kids and the chronic efficacy data that occur in adults--I would not recommend granting an indication that, you know, the long-term use is indicated in kids.

DR. LAUGHREN: And a company would not get a specific indication. You can't describe a trial that has not been done. But the question is, in terms of issuing a written request, would it be necessary for FDA to ask if a company wants to do pediatric studies and gain additional exclusivity, do they need to do both short-term and long-term efficacy trials in kids to get that additional exclusivity?

DR. PINE: I guess that is more of a nuance point. I think, you know, we would almost want to have a whole other independent discussion along the lines of this morning. I mean, clearly, that as a policy would have advantages, on the one hand, because it would encourage those kind of

studies. On the other hand, you know, I would worry about is it a disincentive for conducting even the acute efficacy trials in the kids.

DR. LAUGHREN: It may well be.

DR. MCGOUGH: If we are not going to require acute and long-term studies in adults, on that logic it doesn't make sense to require it in kids. But I think, you know, in mania and psychosis for sure the long-term response of these drugs is not the same in kids. So, I would just like to make it clear by saying that I don't think extrapolating is fair. Probably asking for those studies wouldn't be fair either given what we decided with the adult world.

DR. LAUGHREN: It is a different setting entirely. Again, we are not talking about granting a long-term efficacy claim in children based on extrapolation from adult data. What we are talking about is essentially whether or not you think we need the data for clinicians to appropriately use that drug in children. If you have acute data in adults, long-term data in adults, and you consider

the disorder--really, in fairness, it is disorder specific. Suppose you are talking about obsessive-compulsive disorder, you have acute data in adults, long-term data in adults for efficacy--again, safety is entirely separate--acute data in kids, do you need to do a separate long-term efficacy trial in kids for a clinician to appropriately use that drug for OCD in kids?

DR. PINE: Let me say this, let's say we are talking about the specific issue of the written request and the 6-month patent exclusivity application, because it sounds like that is really the basis of your question. Right or no?

DR. LAUGHREN: That is one of the results of having a policy but, again, the question is basically a question of what does the clinician need for practice. You should answer that question first. If you think that that is an important need, to have separate data for a clinician to use a drug in kids with OCD, then the other implications really shouldn't matter I suppose.

DR. PINE: Well, I think they do, I think

the other things do matter. For example, I think very clearly, as a clinician, we want to have both acute efficacy data and long-term data in kids, very clearly on the one hand. On the other hand, and we have that case right now with SSRIs, just because we only have acute efficacy data does not mean that we can't use medicines acutely. We are going to. I think that, you know, acute data are better than no data at all. Moreover, let's say we have the situation that a wonderful medication was discovered for OCD and it was used to treat adults with OCD and it worked better than anything else that we had, and a company was deliberating was it worth launching a trial in kids so that the medication could be tried in kids, I would worry that if the requirement was that both the acute study and the long-term study had to be done for any study to be launched at all--I would be very upset as a clinician that that was a disincentive to not get the acute study done, on the one hand. On the other hand, if you could tell me that that isn't going to happen, that you were going to do it

in such a way that whenever we have a great medication come down the road we are going to get both acute efficacy and long-term data in kids and, would I rather just have the acute data or both, of course, I would rather have the acute and the long-term data. So, if is an either/or I want them both. If it is one of the other, then I do not want to sacrifice the acute data for the sake of the long-term data. I don't know if I am answering your question.

DR. LAUGHREN: Yes, it turns out to be a much more complicated question than I had envisioned, and maybe it is one that is better addressed, again, by specific experts in each area.

DR. GOODMAN: Could you state your name for the record?

DR. YEUNG: Yes, Paul Yeung, from Wyeth Research. As a child psychiatrist and as a parent, I would like to commend the FDA and this committee for discussing pediatrics, and I would like to point out that the issues tied to question 12 are similar to question 1 in that a "yes" could

actually have a significant effect on pediatric drug development. So, you know, there has been good discussion about the variability of these disorders in adults but the same obviously holds true for children, that there is a great difference between some of the common outpatient disorders, like ADHD or anxiety disorders, versus some of the other than can be more severe, like schizophrenia, and more rare in pediatric patients.

So, if a blanket policy were implemented requiring long-term data in pediatrics it actually might invalidate some of the power that the FDA has been given through the FDA Modernization Act. You know, the FDA has been able to effectively encourage companies to undertake more clinical studies in pediatrics with the power to manage the incentives. But if it turns out that some of these programs are impossible to do--I will use as an example schizophrenia, so schizophrenia is exceedingly rare in children. If it occurs in 1/10,000 children under the age of 12 and even in adolescents, it is not often diagnosed because you

don't know if a psychotic child who is presenting will develop schizophrenia, or bipolar disorder, or something altogether different. So, it may not be possible to do short-term, let alone long-term studies, in some disorders so these do have to be handled on an indication by indication basis. So, we do agree that there does need to be more long-term studies, safety and efficacy studies, in children but this has to vary according to the indication.

DR. GOODMAN: Thank you. Tom, is there anything else that you need this committee to address today?

DR. LAUGHREN: No, actually this discussion has been very helpful to us and I think we have a lot of things to take home with us and think about. I think we also have some ideas about how we might continue our efforts to develop better approaches for getting long-term efficacy data. So, I thank the committee.

DR. GOODMAN: I do want to commend you, although I don't want it to be on the record!

[Laughter]

I want to thank all the other presenters and my fellow committee members for I think a very

thoughtful and productive day. We start tomorrow, a different topic, same room, at 8:00 a.m. I look forward to seeing you then.

[Whereupon, at 4:10 p.m., the proceedings were recessed until 8:00 a.m., Wednesday, October 26, 2005.]

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