

1 scientists would like to actually do, this  
2 type of study that would really be necessary  
3 to establish in the real world the effective  
4 risk-benefit, that is the number of patients  
5 you would need to treat with this and show  
6 that the outcomes for X-number of people with  
7 schizophrenia, that they couldn't get some  
8 other way, greatly outweighed whatever the  
9 harassment of dealing with this event  
10 is -- to really generate the data for that,  
11 I'm not sure what it would take.

12               So we have to make this  
13 terrible -- we have to make this difficult  
14 decision. Is there -- that's why I said is  
15 there a hint, is there a sufficient hint that  
16 this actually might be of greater of people  
17 to take it forward? I don't  
18 understand -- and perhaps our statistical  
19 colleagues can particularly address, I don't  
20 understand how the 5,000 observational  
21 patients is really going to teach us that  
22 much more. But maybe I'm missing something.

1 DR. RUDORFER: Ms. Lawrence?

2 MS. LAWRENCE: Yes, I'd also like to  
3 follow up on Dr. Caplan's comments. I do think  
4 this is a very vulnerable population. And I  
5 always feel that if someone's in some type of a  
6 treatment, it's better than being homeless on  
7 the street and psychotic 24/7. But I am  
8 concerned that maybe this study is too young and  
9 we need more time to look at it, and really to  
10 follow the people that did have these events and  
11 see whether they're in the study still or not.  
12 And I don't know, if they're not in the study,  
13 could they get more information? But really see  
14 what their life is like, because it's not just  
15 the side effect of being sedated.

16 I would imagine somebody that's  
17 injected with the medication could still have  
18 some psychotic thoughts and still be paranoid  
19 and delusional. I mean, I'd like to see more  
20 information and more testimony about what  
21 their day-to-day life was like, not just  
22 related to the sedation, but more of the plus

1 side of being on an injectable rather than  
2 just the negative of the sedation. But I  
3 think it's important to have different  
4 options for different people with the  
5 illness, but the illness has such risks as it  
6 is that you don't want to add more risk to  
7 someone's life.

8 Thank you.

9 DR. TEMPLE: I don't treat these  
10 people, and I'm just going from what I heard. I  
11 gathered nobody had any doubt that for someone  
12 who's poorly compliant, the presence of depot  
13 preparations is a huge and of self-evident  
14 benefit. So the question isn't whether there  
15 should be depot preparations. It's whether  
16 there should be this one.

17 And we have other information. We  
18 have CATIE, which tells you something. And  
19 there have been a number of suggestions that  
20 maybe it's for people who do well on the  
21 oral, maybe you should think about this  
22 problem and discuss it. A wide variety of

1 things.

2 But it sounds like we were creeping  
3 off into whether you need a depot  
4 preparation. And everything I heard from  
5 everybody said that's really not worth  
6 discussing, because you're obviously better  
7 than if you didn't have anything or were very  
8 poorly compliant with an oral. So I guess  
9 I'd urge focusing on whether and how one can  
10 make this risk acceptable, assuming that  
11 depot preparations are needed.

12 DR. RUDORFER: Yes, Ms. Griffith?

13 MS. GRIFFITH: Not to turn the  
14 discussion on its head, but I would suggest that  
15 maybe it would be more worth our while to tackle  
16 3 through 6 and then come back to this question  
17 as to if it were approved and marketed, how  
18 would we enact risk management procedures.

19 I mean, we're starting to get  
20 circular, as you suggested, Dr. Temple. If  
21 we were to go to the questions about efficacy  
22 and safety and then come back to 2, we might

1 be able to resolve this.

2 DR. RUDORFER: Why don't we have the  
3 three remaining people on line and then, I  
4 agree, move on to No. 3. I think the remainder  
5 of our discussion of Question 2 will be  
6 undoubtedly subsumed under that.

7 To Drs. Winokur, Mann, and Leon.

8 DR. WINOKUR: Well, I just wanted to  
9 come back specifically to put in my thought  
10 about Question 2 and the wording. I'm  
11 completely on board with very clear labeling and  
12 even conceivably black box. I would not favor  
13 the secondary status, because I think the  
14 decision to go with the depot preparation for a  
15 patient is something that has to be thought out.  
16 It's very patient-specific, and I think to put  
17 another hindrance in the path of using this  
18 agent for that is not beneficial.

19 I think in the long run, in my  
20 mind -- I mean, and we're going to discuss  
21 the other questions as we come, but it's  
22 going to be the success of the risk

1 management and keeping these incidences where  
2 they are that really in the long run will  
3 tell. But I think we need to be able to use  
4 this agent for the positive that it can do,  
5 including, as an example, for patients that  
6 had done well on oral olanzapine but not  
7 exclusively. I wouldn't agree with only  
8 that, but as an example. And then when you  
9 decide to go to depot, there may be a very  
10 compelling reason to have that be the first  
11 thing to try. And I would not want to see it  
12 set back arbitrarily.

13 DR. RUDORFER: Dr. Mann?

14 DR. MANN: Coming back to the question  
15 of whether it's premature and we need more data  
16 and what it would yield, I think the  
17 5,000-person naturalistic study is not going to  
18 yield very much.

19 That's a personal view. It's going  
20 to be probably more of the same, maybe make  
21 the estimates a little more secure in terms  
22 of risk. But I don't think it's necessarily

1 going to help us to sit around and wait for  
2 that.

3 But what I think would be a more  
4 useful way to spend the time, if the drug is  
5 out on the market or whatever, is to have  
6 data on a rigorous comparison with another  
7 depot preparation, which is what is missing  
8 in the dialogue to support the dialogue  
9 between the doctor and the patient. So I'd  
10 encourage that happening.

11 DR. RUDORFER: Dr. Leon, we are giving  
12 you the last word on this question.

13 DR. LEON: Okay. Well, picking up on  
14 what Drs. Mann and Potter just said, or  
15 responding to Dr. Potter's question, I believe  
16 right now, what are there, maybe 2- or 3,000  
17 person years exposure to this preparation? Is  
18 that the number? Fourteen hundred. So -- and  
19 with this study we'll get maybe 10,000. We  
20 won't because there won't be that many  
21 completers, but 9- or 10,000.

22 So we'll get six times, seven times

1 as much person years exposure, so we'll have  
2 a much more precise estimate of the risk  
3 that'll be seen. So that's the answer.

4 DR. RUDORFER: Thank you.

5 Now we move on to our four voting  
6 questions. As Dr. Laughren mentioned, when  
7 we were setting up this meeting, I took the  
8 liberty as your acting chair to ask him to  
9 spread out the questions some more because I  
10 thought the issues of efficacy and safety  
11 might well differ in the treatment of an  
12 acute exacerbation as opposed to a  
13 maintenance treatment situation, and I didn't  
14 want us to be forced to lump all that  
15 together. So I apologize for the  
16 multiplication of the questions, but I hope  
17 that will help keep things clear.

18 So No. 3, which is up on the  
19 screen, is: Has OP Depot been shown to be  
20 effective for the treatment of acutely  
21 exacerbated schizophrenic patients? And I  
22 believe that refers to the first controlled

1 trial that was presented before us. And I  
2 move in the affirmative if people would like  
3 to have discussion of the acute exacerbation  
4 treatment data.

5 Dr. Leon?

6 DR. LEON: I'm inclined to agree with  
7 you, but I do want to point out there were only  
8 306 subjects who received the OP Depot in that.  
9 And I think for efficacy, that's probably less  
10 of a problem than when we go down two more  
11 questions.

12 DR. RUDORFER: Yes, Ms. Lawrence.

13 MS. LAWRENCE: I would agree with you  
14 also, but I'm not ready to say let's get this on  
15 the market. But I do think there is hope for  
16 it. I do know there is a great need for the  
17 injectables. I think it has shown to be  
18 effective, but I feel like there's still more  
19 testimony and comparison before we really give  
20 it a final vote.

21 DR. RUDORFER: Dr. Laughren, if I can  
22 clarify -- with this question and the following,

1 we are not voting on our position with regard to  
2 potential marketing. Am I correct? We are  
3 asked if we believe the treatment's been shown  
4 effective, it is possible that we could find the  
5 treatment effective, but find the safety  
6 concerns such that it is not ready for  
7 marketing.

8 DR. LAUGHREN: Absolutely.  
9 Questions 3 and 4 are solely focused on whether  
10 or not you think with the data that you've been  
11 presented, it's been shown to be effective in  
12 these two situations.

13 DR. RUDORFER: Okay, thank you. Is  
14 there further discussion before we take a vote  
15 on Question 3, which again is a very narrowly  
16 focused question on the effectiveness of OP  
17 Depot for the treatment of acutely exacerbated  
18 schizophrenic patients, and we're asked to vote  
19 yes or no.

20 This is at least my first  
21 experience with the new voting procedure  
22 where we will vote simultaneously as opposed

1 to sequentially. I believe with the deluxe  
2 model, you can also vote for American Idol,  
3 but I don't know. We're not there yet.

4 So if the panelists will look at  
5 your microphone base, you will see buttons  
6 labeled "yes," "no," and "abstain." Those  
7 who are voting should first press the  
8 "attend" button at the far left. Yes, you  
9 can press it now. Now you can press one of  
10 three choices: yes, no, or abstain on  
11 Question 3.

12 Okay, I'm sorry, I'm told we need  
13 to redo that. Press "attend" again -- yes,  
14 do we want the red flashing?

15 I think we just approved the  
16 marketing of Thorazine.

17 DR. NGO: Drs. Shaffer, Mann, and  
18 Geller, please press your "attend" button.

19 DR. RUDORFER: I understand now we  
20 will go around the table, and if everyone will  
21 please state their name and their vote for the  
22 record.

1           Dr. Potter is not voting, so should  
2 we start with Dr. Geller?

3           DR. GELLER: Barbara Geller, and the  
4 vote is yes.

5           DR. MANN: John Mann. I voted yes.

6           DR. WELLS: Barbara Wells, yes.

7           MS. LAWRENCE: Margy Lawrence, yes.

8           MS. GRIFFITH: Gail Griffith, yes.

9           DR. RUDORFER: Matthew Rudorfer, yes.

10          DR. FOLLMANN: Dean Follmann, yes.

11          DR. LEON: Andrew Leon, yes.

12          DR. CAPLAN: Rochelle Caplan, yes.

13          DR. WINOKUR: Andrew Winokur, yes.

14          DR. NGO: That's a total of 11 yes, 0  
15 no, 0 abstentions, for a total of 11 votes.

16          DR. RUDORFER: Okay, thank you. I  
17 think we're getting the hang of it.

18                 Question 4 is the other side of the  
19 effectiveness coin: Has OP Depot been shown  
20 to be effective for the maintenance treatment  
21 of schizophrenia patients? And again, we saw  
22 one controlled trial and half a dozen

1 open-label continuation studies this morning.

2 Is there discussion on this  
3 question? Again, this is not related  
4 specifically to marketing approval, but  
5 whether we accept that the data we saw have  
6 convinced us of the effectiveness of this  
7 product for this use.

8 Dr. Mann?

9 DR. MANN: I have a question for the  
10 FDA. It sounds like these were two studies with  
11 two slightly -- with two different indications.  
12 I assume that qualifies under two positive  
13 studies?

14 DR. LAUGHREN: Yes, I should give a  
15 little background here. When we make a decision  
16 about this, we are factoring in our knowledge  
17 about acute efficacy and maintenance efficacy  
18 with the immediate release formulation, we would  
19 not -- you know, if these were the only data we  
20 had for this drug, we would not be reaching a  
21 judgment, because we do need two studies. But  
22 typically, it's been our standard when we have a

1 new formulation of a compound that's already  
2 approved for some indication, one additional  
3 study is sufficient to convince us that it's  
4 effective. Actually, here, we have two.

5           You know, oral olanzapine has  
6 several acute studies showing efficacy in  
7 schizophrenia. It has one maintenance study.  
8 Now we have an additional acute study and we  
9 have a maintenance study. So it's actually  
10 better than the usual situation, but it is in  
11 that background of our knowledge about the  
12 immediate release.

13           DR. TEMPLE: Can I just add something?  
14 Actually, Tom, correct me if this is wrong, but  
15 if we were just looking at the oral for the  
16 first time, we would expect two studies in acute  
17 treatment. We usually only demand a single  
18 maintenance study unless there's some reason to  
19 be suspicious or have doubts.

20           DR. LAUGHREN: Yes, that is the  
21 standard as well.

22           DR. RUDORFER: Thank you for that

1 clarification. Is there further discussion on  
2 Question 4, or dare we vote?

3 Okay. We believe you're in  
4 attendance, so you can skip that step and now  
5 just vote yes, no, or abstain.

6 Dr. Caplan, why don't we start with  
7 you, if you'll announce your vote.

8 DR. CAPLAN: Rochelle Caplan. I voted  
9 yes.

10 DR. WINOKUR: Andy Winokur, yes.

11 DR. LEON: Andrew Leon, yes.

12 DR. FOLLMANN: Dean Follmann, yes.

13 DR. RUDORFER: Matthew Rudorfer, yes.

14 MS. GRIFFITH: Gail Griffith, yes.

15 MS. LAWRENCE: Margy Lawrence, yes.

16 DR. WELLS: Barbara Wells, yes.

17 DR. SHAFFER: David Shaffer, yes.

18 DR. MANN: John Mann, yes.

19 DR. GELLER: Barbara Geller, yes.

20 DR. NGO: That's a total of 11 yes, 0  
21 no, 0 abstentions, for a total of 11 votes.

22 DR. RUDORFER: We're due for a break

1 now. May I recommend we take a very short, like  
2 five- to 10-minute break?

3 (Recess)

4 DR. RUDORFER: If the Committee will  
5 regroup, we'll press on.

6 Questions 5 and 6 bring us to the  
7 safety issues we've been discussing  
8 throughout the day, and since I'm responsible  
9 for breaking them into two, if I could have  
10 the first word on No. 5.

11 This is really the essence of my  
12 own concern -- one of my concerns. The  
13 question reads:

14 Has OP Depot been shown to be  
15 acceptably safe for the treatment of acutely  
16 exacerbated schizophrenic patients? And I  
17 have trouble with the benefit-to-risk ratio  
18 in this scenario, for the simple reason that  
19 if a patient has not been shown to be  
20 refractory to all the other available  
21 treatments that do not have this sedation  
22 delirium syndrome risk, then I would think

1 that the benefit-to-risk ratio for most of  
2 those individuals would be away from acute  
3 treatment with a depot preparation.

4 I wonder what others' feelings are.

5 Dr. Mann?

6 DR. MANN: I think that one way of  
7 framing what you're saying is that a patient, an  
8 acutely ill patient, the clinician has an option  
9 of using all the oral medications as well as all  
10 the depot medications. And the choice is much  
11 broader, and therefore, the compelling argument  
12 that John Kane made that many of us found so  
13 persuasive actually doesn't apply in this  
14 situation.

15 DR. RUDORFER: Dr. Potter?

16 DR. POTTER: So are you really saying  
17 that -- again, for the acute exacerbation, you  
18 would want -- I guess the other way to put it  
19 around, because the phrase is acceptably  
20 safe -- clearly, this has a higher side effect  
21 risk than, say, oral olanzapine would in the  
22 same situation. So what are you saying? That

1 in order to feel comfortable with this, you  
2 would want to see something like that?

3 In fact, this did somewhat better  
4 than oral olanzapine on some measures during  
5 this same paradigm. Of course, that study  
6 was not done, right?

7 DR. RUDORFER: Right, that study was  
8 not done, which -- I think that's a very  
9 important point. I mean, the issue is, for this  
10 acutely exacerbated patient that we're asked  
11 about in Question 5, why would one use the depot  
12 rather than oral olanzapine?

13 And again, I interpret the phrase  
14 "acceptably safe" as referencing the  
15 benefit-to-risk ratio.

16 DR. LAUGHREN: Yes, that's absolutely  
17 right. That's inherent in Questions 5 and 6,  
18 that you've already established the benefit.

19 DR. TEMPLE: But can I ask -- my  
20 presumption again -- I don't know anything about  
21 this -- is that somebody who's treating somebody  
22 makes a judgment about whether they'll take the

1 oral and behave properly, and wouldn't use a  
2 depot unless that was true. I have no idea  
3 whether that's so, but isn't that the person you  
4 might use a depot to start with? Someone who,  
5 by history, doesn't take the medicines, or you  
6 have some reason to doubt that they would. I  
7 mean, that would be the population. Whether you  
8 should choose this one is another question. But  
9 is there such a population?

10 DR. RUDORFER: Well, I'll let others  
11 take that first. Dr. Winokur?

12 DR. WINOKUR: I was going to make the  
13 argument along the same lines. This could be a  
14 circumstance of someone that by history has had  
15 a pattern of pronounced noncompliance, become  
16 acutely psychotic in -- they've landed in the  
17 hospital, where you now have a chance to move  
18 treatment in a direction that you have hopes  
19 will be more definitively effective. And  
20 because of the data that we've seen, it's not  
21 only efficacious acutely, but rather quickly, so  
22 it may actually lend itself to an inpatient. I

1 mean, I don't think it would automatically be  
2 the first choice, but I could certainly could  
3 think that it would be a reasonable option to  
4 consider in the context of someone who is  
5 acutely exacerbated but with a clear history of  
6 noncompliance. I think that's a situation we  
7 face frequently.

8 DR. RUDORFER: Thanks.

9 Did I see Dr. Potter?

10 DR. POTTER: To follow up on this,  
11 because again, what we are fundamentally  
12 discussing is the standard that we set for  
13 ourselves to convince ourselves that something  
14 is of value here.

15 And I think that Dr. Temple and  
16 Dr. Winokur both bring up the possibility  
17 that the treating clinicians at the front  
18 line who deal with seriously ill patients  
19 might be in a position to make that judgment  
20 in the absence of formal studies. And so I  
21 guess this judgment is left to the experience  
22 and knowledge of the people of the committee

1 who really have a sense and are actively  
2 engaged in treating a lot of very ill  
3 patients. And how do you capture that sense  
4 of the community? Am I hearing you right,  
5 Dr. Winokur? I think that's what --

6 DR. WINOKUR: Exactly. That's the  
7 exact point I was trying to bring across.

8 DR. RUDORFER: Dr. Mann?

9 DR. MANN: I guess I saw it a little  
10 bit differently. You're raising the longer term  
11 reason for choosing this is the way of getting  
12 the patient acutely under control. But that  
13 again seems to me to be related more to an  
14 approval of No. 6. That seems to be the bigger  
15 driving force. And I still think that with  
16 No. 5, you've got a lot of other choices, and  
17 maybe that is why the two were coupled together  
18 at the beginning. But it seems to me that if  
19 you're looking at the acute treatment of the  
20 patient, you want to make that judgment as one  
21 part of the story. If you're thinking about  
22 what the long-term treatment is and allowing

1 that to influence your choice at the beginning,  
2 that's really the way I was looking at it.

3 That's different.

4 DR. WINOKUR: No, I understand your  
5 point. From direct clinical experience, there  
6 are a subset of patients that we're trying  
7 actively and repeatedly to get them to take and  
8 stay on oral medication, and they're not staying  
9 with that and having acute exacerbations. And  
10 sometimes getting them rehospitalized does  
11 provide an opportunity to kind of move in a  
12 different direction. I think that's a clinical  
13 decision that one has to make carefully.

14 But I think that taking advantage  
15 of a time when they're acutely hospitalized,  
16 and in our place, maybe yours, that we only  
17 have them for a limited period of time before  
18 they're passed along to the outpatient  
19 setting, I wouldn't want to deny that  
20 clinical judgment. I'm not saying that it  
21 should be one that is made with great  
22 frequency, but it seems to me a reasonable

1 option under those circumstances.

2 DR. RUDORFER: Dr. Potter?

3 DR. POTTER: Just because this is  
4 complicated, just to make sure we're all  
5 understanding the same thing -- the acute  
6 studies had patients with PANSS scores of about  
7 100, so they're pretty sick, as I understand  
8 what that means. The patients who were entered  
9 in the maintenance trial had PANSS scores about  
10 55. They were about -- I mean, there was a huge  
11 difference in these patient populations. So if  
12 I understand Dr. Winokur properly, again, what  
13 one is saying is, would one want to include the  
14 possibility that you would make the judgment to  
15 start a person on the maintenance while they're  
16 acutely ill, thinking that this might confer an  
17 advantage -- a way, rather than stabilizing them  
18 with something else only, only allowing that?  
19 And so you always had to stabilize somebody on  
20 something that was oral, and then go through the  
21 process of switching them over to the  
22 maintenance. So that's the contrast we're

1 talking about here, right?

2 I had to think about it, so I'm not  
3 sure if it's self-evident to everybody.

4 DR. RUDORFER: Ms. Griffith?

5 MS. GRIFFITH: In Dr. Winokur's  
6 example, I think one of the things we find the  
7 most troubling is the ability to manage the  
8 adverse event. If that patient is acute, if  
9 that patient is hospitalized, then whatever the  
10 risk is, it is somewhat minimized by detection,  
11 given that the patient is there and stable.

12 DR. RUDORFER: Dr. Shaffer, did you  
13 have a question, a comment?

14 DR. SHAFFER: I just wanted to know if  
15 the word "exacerbation," does that presumably  
16 exclude first-break cases?

17 DR. RUDORFER: Dr. Laughren?

18 DR. LAUGHREN: Again, I think -- let  
19 me describe the patient that I had in mind when  
20 we originally posed the question just for the  
21 treatment of schizophrenia. It's the patient  
22 that Dr. Potter and Winokur have been talking

1 about. A patient who, by history, has responded  
2 to oral medications, perhaps even oral  
3 olanzapine, but fails to adhere to it, and so  
4 ends up repeatedly back in the hospital. And  
5 the question is, do you want to provide  
6 clinicians with an efficient way of getting that  
7 patient on a more effective regimen, which might  
8 be a depot of the same drug?

9 Now, if you wanted to restrict the  
10 use of this drug to patients who'd already  
11 responded to olanzapine, I suppose you could  
12 do that. But again, the question is how much  
13 do you want to do? We seek your advice on  
14 this. How much do you want to do in terms of  
15 restricting the way clinicians could use  
16 these drugs? I think it would be unlikely  
17 that most clinicians would use it as the  
18 first treatment in a first-break patient.

19 DR. RUDORFER: If I could interject a  
20 hypothetical, how does the Committee feel about  
21 something along the lines of restricting the  
22 approval to individuals with a documented

1 history of either nonresponse or poor adherence  
2 to oral medication? I mean, just something  
3 where -- putting the burden on the clinician to  
4 demonstrate that this is an appropriate case. I  
5 mean, my thought is simply, when I was first  
6 presented with the option of is this treatment  
7 acceptably safe for the treatment of  
8 schizophrenia, based on our discussion today,  
9 I'm not comfortable with the idea of this as a  
10 first-line treatment.

11 On the other hand, I think several  
12 individuals, especially Dr. Winokur, have  
13 made very good points in terms of real-world  
14 treatment. And again, trying to find the  
15 right balance is the tricky part. But I come  
16 back to my point that I think this is why I'm  
17 happier discussing Questions 5 and 6  
18 separately, because I think the  
19 benefit-to-risk ratio is different.

20 And if I'm gauging the sense of the  
21 Committee correctly, we're saying we don't  
22 want to absolutely prohibit the use of this

1 drug in the acute exacerbation situation. Am  
2 I reading the temperature correctly?

3 And are people comfortable with the  
4 idea that there should be some limiting  
5 language as opposed to this drug is approved  
6 for the treatment of the acute exacerbation  
7 of schizophrenia?

8 Yes, Ms. Lawrence?

9 MS. LAWRENCE: I do agree with your  
10 last comment, but I do want to say, as a patient  
11 representative, these people do have rights.  
12 Even though they're not well and they're in this  
13 state and you feel that they need to have the  
14 injection as the first offense, I hate to say  
15 that, but that's what I said -- but we do have  
16 to remember that these patients, these people  
17 that have the illness, do have rights, and I do  
18 think for a first-break, it would not be a good  
19 idea.

20 In order to gain a relationship, a  
21 respect, and an understanding of them, and  
22 they of the clinician, we need to be

1 sensitive. And I do think it should not be  
2 for a first-break. And I think also your  
3 point was well-taken, because as much as they  
4 can understand, they have to be educated at  
5 the same time. Thank you.

6 DR. RUDORFER: Thank you.

7 Dr. Leon?

8 DR. LEON: Responding to your earlier  
9 comment, I was curious as to what the inclusion  
10 and exclusion criteria were for the acute study.  
11 They're on page 18 of the briefing document.

12 So the inclusion criteria did not  
13 require nonresponse to another drug. In  
14 fact, an exclusion criterion was history of  
15 resistance to olanzapine. So maybe what  
16 you're saying -- what you said earlier, that  
17 maybe they should first have responded to  
18 oral olanzapine, it's not quite the same  
19 thing. The ones who hadn't responded were  
20 not included here, so these might be somewhat  
21 higher rates than you would have seen.

22 MS. LAWRENCE: If I could make a

1 comment. A lot of times, there are other  
2 injectables that you can give somebody that's  
3 really in an acute state just to calm them down.  
4 It doesn't have to be something like this right  
5 away.

6 DR. RUDORFER: Dr. Caplan?

7 DR. CAPLAN: This also brings up the  
8 issue again that if somebody is in an acute  
9 state, they might not be able to understand all  
10 the implications, the safety implications. So  
11 we sort of get back to the same point.

12 DR. RUDORFER: Right, the informed  
13 consent point.

14 DR. CAPLAN: Yes.

15 DR. RUDORFER: Thank you.

16 Dr. Temple?

17 DR. TEMPLE: I thought Dr. Griffith  
18 was offering the thought that treatment of the  
19 acute episode is usually in a much more  
20 controlled environment, so that the thing you  
21 are the most worried about, which is the  
22 unobserved patient, is rather less worry than on

1 maintenance. And I didn't hear anybody address  
2 that, or maybe I misunderstood it.

3 DR. RUDORFER: I think that's a very  
4 good point, except for the fact that inpatient  
5 hospital stays tend to be so short, that if  
6 we're not sure when this untoward event might  
7 occur, then the patient might well be discharged  
8 at a period of higher risk, for all we know.

9 DR. TEMPLE: I mean, they're -- not a  
10 day or so? I mean, we saw 4 cases out of the 25  
11 that occurred after three hours and nothing  
12 late. So I guess until there's much wider  
13 extent of use, you don't really know for  
14 absolutely certain. But it looked as if the  
15 major risk that people are worried about and the  
16 fear that people won't be observed for the full  
17 three hours, a very legitimate fear, seems less  
18 in this case than in the maintenance case. And  
19 I just wondered what people thought about that.

20 DR. POTTER: I was just going to add  
21 one thing. Again, it's up to people to decide.  
22 Dr. Berkstrom made the point in going through

1 the hypothetical that when the injection, when  
2 it has to be in liquid form, and that's  
3 basically something not that far removed from  
4 water -- and that once you inject it, that  
5 liquid part has to go away, and from a physical,  
6 chemical property, as I understand it, that's  
7 probably pretty much got to be true.

8           So the form in which it's possible  
9 for it to get into the bloodstream however it  
10 does more rapidly and then be dissolved and  
11 get around -- actually can't last that long  
12 was the inference from this. And there's no  
13 data to suggest a late event.

14           So I would agree that the evidence  
15 suggesting post-24 hour events is zero. And  
16 so again -- so, to get to Dr. Temple's point,  
17 perhaps people with even more physical  
18 chemical expertise could comment on this, but  
19 it seems like a pretty sound argument.

20           MS. LAWRENCE: Some of the studies, a  
21 few people did go into comas, so I mean --

22           DR. POTTER: No, the technical point

1 here -- I'm sorry -- the onset has to be, if  
2 it's going to occur, of this event. May be  
3 other things related to olanzapine, but of this  
4 particular event that we're talking about, my  
5 scientific understanding of this is that it is  
6 so -- from everything we've seen and anything we  
7 can infer, it's going have to be in the first 24  
8 hours, and probably even more limited than that  
9 based on the physical chemical properties of  
10 what you're putting into the body.

11 MS. LAWRENCE: Usually, we get 72  
12 hours here in Montgomery County. I don't know  
13 about anywhere else for hospitalization, but I  
14 think that's what we get here.

15 DR. RUDORFER: Dr. Shaffer?

16 DR. SHAFFER: When I asked about  
17 first-break, my concern was really about  
18 something different. It's the kid who's brought  
19 in from the bus station or brought in by the  
20 police without any informants or maybe with few  
21 informants. And the diagnosis appears in the  
22 emergency room to be psychosis. They may say

1 schizophrenia, but in fact, the differential  
2 diagnosis might not have been worked through.  
3 They're eventually shipped back to somewhere,  
4 and I just wouldn't have liked the thought that  
5 they were shipped on a depot medication, if  
6 that's what they'd been given for acute care.

7 DR. RUDORFER: Other thoughts?

8 Dr. Mann?

9 DR. MANN: I think, again, very little  
10 on the safety side by observing one injection,  
11 which is about all you'll see by starting the  
12 treatment acutely as an inpatient. So I think  
13 that the decision to start the patient off on  
14 this as an initial treatment has to be based on  
15 other imperatives, not this.

16 DR. RUDORFER: Are we ready to vote?  
17 The question before us: Has OP Depot been shown  
18 to be acceptably safe for the treatment of  
19 acutely exacerbated schizophrenic patients? And  
20 we will vote with the same procedure. You don't  
21 need to push "attend" anymore to vote yes, no,  
22 or abstain. And when we go around the table,

1 everyone will have a chance to offer any  
2 comments they want.

3 Dr. Laughren?

4 DR. LAUGHREN: I just want to make  
5 sure that the committee, after voting on this  
6 question, you're going to come back and give us  
7 advice about the kind of language you would want  
8 in labeling, to help deal with this issue that  
9 you all seem to be in reasonable agreement  
10 about.

11 DR. RUDORFER: Yes. My thought is  
12 that we would vote on 5 and 6 and then  
13 essentially return to Question 2.

14 MS. LAWRENCE: Can I ask a question?  
15 So our vote -- I guess you answered it then,  
16 because since I'm still hung up on the  
17 conditions of when it be used for an acutely  
18 exacerbated person with schizophrenia, there's  
19 different times, there's different degrees. You  
20 know, it's all in the terminology, so it's a  
21 hard yes or no.

22 DR. LEON: I think my answer to this

1 question really hinges on what the label says.

2 It's pretty --

3 DR. RUDORFER: So do we have a "it  
4 depends" button?

5 I'm sorry, was there a comment?

6 DR. POTTER: Again, since I'm not  
7 voting, and it's changing the question a little  
8 bit, but what I'm hearing is this is extremely  
9 hard to vote on this as worded.

10 DR. RUDORFER: Yeah.

11 DR. POTTER: So if you rephrased it,  
12 has OP Depot been shown to be acceptably safe  
13 for the treatment of acutely exacerbated  
14 schizophrenia, with restrictions, would that  
15 be -- or you could vote up on this. And then  
16 you could just add a separate question.

17 I don't know how you do these  
18 things, Dr. Laughren.

19 DR. LAUGHREN: Alternatively, you  
20 could give us the advice that you're going to  
21 give us on question -- on comment or discussion  
22 issue 2, about how you think the labeling ought

1 to in a sense direct the use of this product for  
2 acute use.

3 DR. POTTER: You mean along with the  
4 answer?

5 DR. TEMPLE: You mean someone who  
6 wanted to say no, would say no, there's no  
7 labeling that would convince me this is okay.  
8 Someone who wanted to say yes would be specific  
9 about the labeling that would satisfy him or  
10 her. Is that what you mean?

11 DR. LAUGHREN: Right, that would help  
12 the panel members to know how they wanted to  
13 vote on this question. Whether or not you could  
14 out -- whatever you're going to come up with  
15 that, in a sense, restricts the use before you  
16 vote. I mean, that's what I'm hearing from you.  
17 They're uncomfortable voting because they don't  
18 know what the implications are.

19 DR. RUDORFER: So if we added in that  
20 phrase "with restrictions," and then we'll have  
21 to discuss and hopefully come to an agreement on  
22 what those restrictions would be.

1 DR. TEMPLE: Sometimes it's very hard  
2 to reach agreement on what the restrictions are.  
3 And we read the whole thing, you know? So the  
4 general sense of whether there's a reasonable  
5 way with some things, and we'll take that into  
6 account in labeling. That's helpful, too.

7 DR. RUDORFER: Okay.

8 DR. SHAFFER: Can we assume that the  
9 word "exacerbation" means it's worse than it has  
10 been?

11 DR. RUDORFER: Yes.

12 Dr. Laughren?

13 DR. LAUGHREN: Maybe you could  
14 rephrase the question. Are there circumstances  
15 under which OP Depot -- would be acceptably safe  
16 for the treatment of acutely exacerbated  
17 schizophrenic patients? And then you could go  
18 back and tell us what those circumstances are.

19 DR. RUDORFER: Yes. Are there  
20 circumstances under which OP Depot would be  
21 acceptably safe for the treatment of acutely  
22 exacerbated schizophrenic patients?

1 I'm told the vote won't count until  
2 the question is formally changed.

3 MS. GRIFFITH: That's at least a more  
4 positive wording than "with restrictions."

5 DR. RUDORFER: Yes. I think there's a  
6 fine line between the labeling requirements and  
7 dictating the practice of medicine, which is  
8 where we don't want to go. And I think what  
9 we're all feeling is that that can be a  
10 sometimes nebulous boundary.

11 DR. TEMPLE: Just to offer a thought.  
12 We like to say we don't control the practice of  
13 medicine, and of course, we don't. But the idea  
14 that we don't influence it by our labeling isn't  
15 realistic either. And everything I've heard  
16 says you really do want to influence it. You  
17 don't want it used casually, you don't want it  
18 used on just everybody when they walk in the  
19 door and aren't going to be observed. There's a  
20 lot of "please don't do this" in it. So for  
21 better or worse, you're influencing the practice  
22 of medicine some.

1 DR. LAUGHREN: But we're sensitive to  
2 the issue, and if you give us a reasonably full  
3 discussion that covers all the different  
4 parameters that you want us to address, we'll  
5 take a crack at trying to craft language that  
6 accomplishes that without appearing too  
7 restrictive.

8 DR. RUDORFER: Okay, thank you. And I  
9 think the other challenge that I think we've  
10 agreed to today is that in a sense, this is a  
11 moving target because the last word is not in.  
12 And so we're basing our judgments today on what  
13 is known now and what might influence the  
14 treatment of patients in the coming weeks and  
15 months. But again, as we've seen new data  
16 emerged, then the judgment certainly of the  
17 Committee and of the FDA might well evolve along  
18 with that new information.

19 DR. TEMPLE: That's what we call a  
20 life cycle approach to drug approval. It's in  
21 these days.

22 DR. RUDORFER: Are we not going to see

1 the new -- you'll just have to take my word for  
2 it. Here's the new version of Question 5. Are  
3 there circumstances under which OP Depot would  
4 be acceptably safe for the treatment of acutely  
5 exacerbated schizophrenic patients? So if you  
6 could vote, yes, no, or abstain.

7 Oh, now it's lit up. Oh, has  
8 everybody voted? Everybody should recast  
9 their ballot. I'm sorry. Please recast your  
10 ballot.

11 DR. TEMPLE: Now it shows an  
12 abstention.

13 DR. RUDORFER: We'll start again.

14 Dr. Geller?

15 DR. GELLER: Barbara Geller, yes.

16 DR. MANN: John Mann, yes.

17 DR. SHAFFER: David Shaffer, yes.

18 DR. WELLS: Barbara Wells, yes.

19 MS. LAWRENCE: Margy Lawrence, yes.

20 MS. GRIFFITH: Gail Griffith, yes.

21 DR. RUDORFER: Matthew Rudorfer, yes.

22 DR. FOLLMANN: Dean Follmann, yes.

1 DR. LEON: Andrew Leon, yes.

2 DR. WINOKUR: Andy Winokur, yes.

3 DR. CAPLAN: Rochelle Caplan, abstain.

4 DR. NGO: That is a total of 10 yes,  
5 1 abstention, for a total of 11 votes.

6 DR. RUDORFER: Okay, thank you.

7 Now, the final question, No. 6.

8 Has OP Depot been shown to be acceptably safe  
9 for the maintenance treatment of  
10 schizophrenic patients? Are there comments  
11 or discussion on that, or any concern with  
12 that wording?

13 Dr. Laughren?

14 DR. LAUGHREN: Do you want to consider  
15 the same language change for that question?

16 DR. RUDORFER: We certainly could, so  
17 that they're in synch. Certainly. So are there  
18 circumstances under which OP Depot would be  
19 acceptably safe for the maintenance treatment of  
20 schizophrenic patients? Are people ready to  
21 vote on that? I think we discussed that.

22 DR. NGO: And then there's the change

1 in the question.

2 DR. RUDORFER: Oh, okay. Hold off,  
3 the question has to be formally changed. I  
4 guess this would be better if there were a  
5 little more suspense with this question, but --

6 DR. LAUGHREN: The question needs to  
7 be further modified there. You're working on  
8 it? Okay.

9 DR. RUDORFER: We're ready to go  
10 around again.

11 Dr. Caplan, if we could start at  
12 your end?

13 DR. CAPLAN: Rochelle Caplan, abstain.

14 DR. WINOKUR: Andy Winokur, yes.

15 DR. LEON: Andrew Leon, yes.

16 DR. FOLLMANN: Dean Follmann, yes.

17 DR. RUDORFER: Matthew Rudorfer, yes.

18 MS. GRIFFITH: Gail Griffith, yes.

19 MS. LAWRENCE: Margy Lawrence, yes.

20 DR. WELLS: Barbara Wells, yes.

21 DR. SHAFFER: David Shaffer, yes.

22 DR. MANN: John Mann, yes.

1 DR. GELLER: Barbara Geller, yes.

2 DR. NGO: That's a total of 10 yes, 0  
3 nos, 1 abstention, for a total of 11 votes.

4 DR. RUDORFER: Okay, thank you.

5 Would anybody like to pick up the  
6 discussion on what in fact the circumstances  
7 that we would like to be reflected in the  
8 labeling should be?

9 Dr. Geller?

10 DR. GELLER: I have a question for the  
11 FDA. There must have been a similar discussion  
12 about not using it for a patient who had never  
13 been on oral, or for a patient like Dr. Shaffer  
14 described where you don't know the history. How  
15 is it worded so -- or was it worded so that you  
16 wouldn't be giving depot, like, to somebody with  
17 their first episode, or somebody who hadn't been  
18 tried on oral or whatever?

19 DR. LAUGHREN: The only language that  
20 is typically in depot formulations now is asking  
21 clinicians to give a patient at least several  
22 doses of immediate release of that particular

1 drug to make sure they tolerate it before you  
2 put a depot in. But you're obviously wanting to  
3 go well beyond that. And that's what we want to  
4 understand is what sorts of -- what are the  
5 circumstances under which you think it would be  
6 appropriate to use this depot, either in an  
7 acutely exacerbated patient or for maintenance?

8 DR. GELLER: So there's nothing in the  
9 wording for the haloperidol and the other  
10 preparations that says it wouldn't be used in  
11 somebody having a first-break?

12 DR. LAUGHREN: No.

13 DR. RUDORFER: Dr. Caplan, did you  
14 want to make a comment?

15 DR. CAPLAN: In terms of the wording?

16 DR. RUDORFER: Yes.

17 DR. CAPLAN: I think one of the things  
18 that's important is we need to have evidence of  
19 nonadherence, so that this is a patient with a  
20 history who has repeatedly gone off medication.  
21 I think in terms of exclusions, we want to make  
22 sure that this would not be a woman who is

1 postpartum, even though she's had prior  
2 episodes, but she shouldn't be in the immediate  
3 postpartum period. And also, the example like  
4 Dr. Shaffer mentioned. In other words, if this  
5 is a youth who doesn't have anybody who can who  
6 is -- what's the word? A parental or  
7 nurtural somebody who can make an informed  
8 decision for them.

9 DR. RUDORFER: Going to Dr. Shaffer's  
10 case, which I totally agree with, I'm  
11 wondering -- and I'll direct this to  
12 Drs. Laughren and Temple -- DSM-IV schizophrenia  
13 by definition is a chronic disorder. I mean,  
14 one needs to be ill for six months, so that  
15 presumably, the young person brought in by the  
16 police from the bus station would not in all  
17 likelihood, without an informant, literally meet  
18 those criteria.

19 Has there ever been an instance  
20 where that kind of wording was modified or  
21 strengthened in some way? In other words, if  
22 the label reads treatment of schizophrenia as

1 defined by DSM-IV, is that sufficient to be  
2 making the statement that this should not be  
3 someone with two weeks of a psychotic  
4 illness?

5 DR. LAUGHREN: That is the way it's  
6 worded now. No, the answer's no, we've never  
7 gone beyond that to try and clarify that.  
8 Again, it's generally left up to the clinician  
9 as to who is going to get treated. But it  
10 does -- it is indicated -- it would be indicated  
11 for schizophrenia, which of course, as you  
12 mentioned, is defined in terms of duration.

13 DR. TEMPLE: But you collectively  
14 might have a series of considerations you could  
15 identify in labeling that might lead you to  
16 choose this drug. For example, a history of not  
17 taking it. I don't know what they are, but you  
18 do. And those kinds of things can go on  
19 labeling. What would push you in this  
20 direction? That's one of the possibilities.

21 MS. LAWRENCE: I was just wondering if  
22 Lilly, in their training, if it gets to be that

1 point, is doing any special wording? Or would  
2 that come from us to them -- if we wanted to  
3 advise them as to the type of training they  
4 would be giving clinicians, do they have any  
5 input on that?

6 DR. TEMPLE: We usually think of the  
7 sort of primary focus as the labeling. Any  
8 training they give needs to be compatible with  
9 that. They could add things to it, of course,  
10 but any limitations or considerations that you  
11 all think ought to go in there, our first  
12 thought would be that those should be things  
13 that go in label. And as Tom said before, we  
14 try to balance useful advice with not overdoing  
15 it.

16 DR. RUDORFER: Dr. Caplan, you had  
17 another comment?

18 Drs. Mann, Geller, and then  
19 Winokur.

20 DR. MANN: I think it would be fair to  
21 write, in addition to the adherence statement,  
22 "not known to be resistant to olanzapine."

1     Though (inaudible) is also an exclusion  
2     criterion in the efficacy studies, so we have no  
3     idea if it makes any difference -- has any  
4     therapeutic benefit in that kind of patient.

5             DR. RUDORFER: Right, thank you.

6             Dr. Geller?

7             DR. GELLER: The reason I'd asked what  
8     the FDA had in the other labels was, I think we  
9     want to consider, do we really want to go above  
10    and beyond the labeling for similar  
11    preparations, for similar issues? So that it's  
12    left up to the clinician to know better than to  
13    give a depot to Dr. Shaffer's patient. And  
14    should we instead -- and perhaps more usefully  
15    for the FDA coming to a label, center the  
16    discussion on what makes this drug different  
17    from the other preparations.

18            DR. RUDORFER: Dr. Winokur, and then  
19    we'll come back to Dr. Shaffer.

20            DR. WINOKUR: I think the issue of  
21    nonadherence or compliance is clearly crucial.  
22    And I would even consider putting something in

1 about repeated, because nonadherence or poor  
2 compliance is so common that -- I don't know,  
3 that the first time that happens is enough to  
4 kind of jump to the depot.

5 I would not on the other hand favor  
6 putting in something about being treatment  
7 refractory, because I think that that's a  
8 different issue. And conceivably, patients  
9 who are treatment responsive -- but the big  
10 issue is nonadherence -- could benefit.

11 DR. RUDORFER: Thanks. Dr. Shaffer?

12 DR. SHAFFER: I think the notion that  
13 the average psychotic teenager has two weeks of  
14 observation is pretty idealistic. They usually  
15 get their first antipsychotic within hours of  
16 presenting at the emergency room, and so I think  
17 that it would be helpful and advisable to  
18 preclude people who don't meet criteria for  
19 schizophrenia or who have psychosis not yet  
20 diagnosed or under investigation, that this is  
21 not indicated for that, something of that sort.

22 DR. LAUGHREN: But if the indication

1 is for schizophrenia, that is not sufficient to  
2 direct clinicians to that population?

3 DR. SHAFFER: It might be. But in  
4 practice, the diagnosis is usually made there,  
5 and then on the basis of the nature of the  
6 presentation.

7 I know that we're not here -- well,  
8 you do say that we are here to make medicine  
9 better. I think that would be one way around  
10 doing it; that is, you're not meeting  
11 criteria for schizophrenia. But acute  
12 psychotic states are not that uncommon and  
13 they usually treat it parenterally, and I  
14 think that this might be a tempting  
15 treatment.

16 DR. LAUGHREN: Part of the question  
17 is, is the advice that you're giving us, does it  
18 apply more broadly than to this product? Is  
19 this advice for all antipsychotic products?

20 DR. SHAFFER: No, for all depots.

21 DR. LAUGHREN: For all depots. So  
22 that's -- I guess that's a --

1 DR. SHAFFER: A bigger issue.

2 DR. LAUGHREN: I guess what we're  
3 looking for is, given the particular risk for  
4 this product, how can you help us craft the  
5 language for this product that would help  
6 clinicians to direct it somewhat more narrowly  
7 than they might otherwise? I mean, we're not  
8 here really to rewrite the labeling for all the  
9 depot products.

10 DR. SHAFFER: Correct. I understand.  
11 Well, then you'd probably have to mandate some  
12 period of a short observation.

13 DR. POTTER: To catch up on  
14 Dr. Shaffer's last point, I was just going back  
15 to the sponsor's proposed labeling, I guess, and  
16 the research. Again, I'm not sure how the risk  
17 management plan is formally reviewed, and the  
18 extent of which the information that a sponsor  
19 translates from the labeling -- I don't know if  
20 something more has emerged from the more  
21 traditional way of handling this. But  
22 fundamentally, as I read this, the sponsor has

1 said they have a three-hour post-injection  
2 precautionary period, that itself would appear  
3 to be -- potentially to be a very strong  
4 message, depending on how it was presented. And  
5 actually, maybe Dr. Laughren can clarify -- I'm  
6 not aware of anything else which carries that  
7 directive.

8 Is that strong a direction coupled  
9 to anything else, as it is sort of laid out  
10 here, and obviously someone could beef this  
11 up even more than written.

12 DR. LAUGHREN: Certainly, there's  
13 nothing like that for any other depot product.

14 DR. TEMPLE: But I think you can  
15 fairly safely assume that something like that's  
16 going to be in.

17 DR. POTTER: I guess my point is, I  
18 want to try and make a point to the Committee,  
19 is even the sponsor is proposing much stronger  
20 language than is associated with other  
21 compounds. And I think, as a sponsor, one would  
22 not want to incur risk of not fully informing

1 people of all the risk.

2 DR. RUDORFER: Your two analogies that  
3 come to mind -- they're not perfect, but just to  
4 move our discussion along -- we've seen on some  
5 hypnotic products a language actually directed  
6 to the patient along the lines of do not take  
7 this product unless you have X-hours to devote  
8 to sleep.

9 The implication being that it might  
10 not be a safe product to use if after a  
11 shorter period of time, one attempts to drive  
12 or otherwise function.

13 The other analogy that comes to my  
14 mind are steroid-based products for asthma,  
15 which usually include in the labeling wording  
16 to the effect of this is a maintenance  
17 treatment, not meant for treatment of an  
18 acute exacerbation. And again, these don't  
19 translate precisely, but I think that's part  
20 of the direction we're moving, that  
21 essentially -- if I'm reading the sense of  
22 the Committee correctly, we're not talking

1 about a product that would typically be used  
2 in an emergency room, that this is part of an  
3 ongoing treatment package.

4 Now, it's true, we have agreed that  
5 there are circumstances under which an acute  
6 exacerbation might be appropriate. But  
7 again, the context, if I understand  
8 Dr. Winokur and others correctly, the context  
9 again would be one of ongoing treatment, not  
10 somebody who showed up in the emergency room  
11 and is acutely psychotic. So we're going to  
12 give you a shot.

13 The other part of that, again, that  
14 Ms. Lawrence and Dr. Caplan and others were  
15 pointing to is -- which I don't want us to  
16 lose sight of -- is that whole informed  
17 consent part, which I don't think we're going  
18 to get directly into our labeling  
19 recommendations, but I think we want to leave  
20 implied, which is, to the greatest extent  
21 possible, we would want the patient to be  
22 involved in the decision-making process. And

1 again, that brings me back to the point, as  
2 Dr. Potter was mentioning, people in the  
3 maintenance study were not that acutely ill  
4 at the time that they made their decision  
5 that weighing the potential benefits and  
6 risks for themselves -- perhaps with input  
7 from family or friends -- that this was the  
8 right decision to make. Which, of course, is  
9 not a part of the treatment of acute  
10 psychosis.

11 But if I can put two things on the  
12 table to move us along. On the one hand, is  
13 there agreement that some language reflecting  
14 nonadherence, perhaps repeated nonadherence  
15 to oral antipsychotic treatment, should be  
16 part of the labeling in terms of the  
17 indication for the use of this product?

18 Dr. Caplan?

19 DR. CAPLAN: I want to ask you a  
20 question for clarification. We voted on No. 5,  
21 and that was for acute exacerbation. So the  
22 wording then should also include that. In other

1 words, because I assumed then the use would not  
2 only be for acute exacerbation, but also for  
3 nonadherence without acute exacerbation, but  
4 patients who are not taking their meds.

5 DR. RUDORFER: Right. Well, do you  
6 think the nonadherence issue should be part of  
7 the treatment of -- well, we agreed that there  
8 were circumstances under which we thought this  
9 product was acceptably safe. Do you think the  
10 labeling should reflect that if you're in an  
11 acute exacerbation situation, that part of the  
12 inclusion criteria should be the evidence of  
13 nonadherence to oral treatment?

14 Dr. Temple?

15 DR. TEMPLE: In something like  
16 that -- again this goes a little bit to the  
17 practice of medicine -- you could have actual  
18 evidence of nonadherence. That would make  
19 everybody happy. Could there be other reasons  
20 for anticipating poor adherence that the  
21 treating physician might have that might also be  
22 considered? I mean, again, I'm talking totally

1 about something I have no idea about. But you  
2 wouldn't want to overnarrow it if there were  
3 legitimate reasons for worry that weren't the  
4 known history. That's all I'm saying.

5 DR. RUDORFER: That's a good point.

6 Dr. Mann, do you want to address  
7 that?

8 DR. MANN: Kind of. I also like the  
9 idea of nonadherence somehow worked into this,  
10 because I felt very persuaded by John Kane's  
11 presentation. But I also think that that allows  
12 for avoiding Dr. Shaffer's problem with the  
13 acutely ill underevaluated patient because  
14 you're then forced to have a patient that's had  
15 enough of a history that you can evaluate  
16 nonadherence. It also allows you to determine  
17 that the nonadherence is not because of side  
18 effects that characterize olanzapine  
19 particularly, like the patient doesn't like the  
20 weight gain that they're getting on medications.

21 I don't know how much of that needs  
22 to be articulated in the labeling language

1 and how much of that is just common sense.  
2 But steering the clinician a bit in that  
3 direction -- and I think that if the patient  
4 has a history of having had a good trial on  
5 oral olanzapine and not responded  
6 therapeutically, then that must certainly  
7 undermine the argument for putting them on  
8 this preparation. And maybe we can think of  
9 a couple of other things that could flesh  
10 this out a bit.

11 DR. RUDORFER: Is the sense of the  
12 Committee that labeling should reflect a history  
13 of a lack of response to an adequate trial of  
14 oral olanzapine should be reason to avoid this  
15 product?

16 DR. LAUGHREN: I think we could  
17 probably come up with a long list of things.  
18 Part of my discomfort with this is partly that  
19 some of these things seem like quite common  
20 sense. I mean, why would a clinician put a  
21 patient on a depot form of olanzapine if they  
22 have a history of being resistant to olanzapine?

1 I mean, we could put that in there, but do we  
2 need to put it in there? I'm a little  
3 bit -- because the list then could become very  
4 long.

5 I was just wondering, in terms of  
6 an efficient way of doing this, maybe an  
7 alternative would be simply to say you  
8 ought -- given the risks with this drug, you  
9 ought to think about other options before you  
10 choose this drug. In other words, it's sort  
11 of a close to second-line, almost like  
12 ziprasidone, maybe one and a half line.

13 You know, give clinicians pause  
14 before they go with this drug, rather than  
15 trying to put together a very long list of  
16 criteria and circumstances that -- I mean, we  
17 could do that. I'm just not sure how  
18 efficient that is.

19 DR. RUDORFER: Let me switch gears a  
20 little. I think what we had agreed to earlier,  
21 but I don't know that we conceptualized that  
22 into labeling language, is this whole issue of

1 appropriate monitoring at the time of the  
2 injection. I think we're in agreement on two  
3 things. One, that I think we all wanted to see  
4 language to that effect. And two, I think we're  
5 in agreement that that in itself is probably as  
6 rate-limiting a step as one would see on  
7 labeling.

8 DR. LAUGHREN: Well, it will  
9 definitely have that requirement for an  
10 observation period, to focus specifically on  
11 detecting this event during the period of  
12 greatest risk for it occurring. The other part  
13 of this is whether or not you go beyond that, to  
14 further, in a sense, restrict the use of the  
15 drug. And what, in other words, define what  
16 those circumstances would be when it would be  
17 reasonable to proceed with using this  
18 formulation.

19 DR. TEMPLE: There are various ways to  
20 do that. As Tom said, for ziprasidone, we  
21 didn't say you have to fail on something else.  
22 We said when you're choosing your drug, think

1 about it. Some other treatments that work also  
2 don't cause QT prolongation, and you want to  
3 take that into account when you pick. There are  
4 various ways of doing that that leave a certain  
5 amount of intelligent discretion but kind of  
6 tell them what to worry about. And we can work  
7 on that or write that, if you think that's a  
8 good idea.

9 DR. RUDORFER: Dr. Potter.

10 DR. POTTER: Again, I was just going  
11 to elaborate on the last question you asked of  
12 those people who are actually closer to clinics,  
13 to the large clinics in treatment settings -- if  
14 you impose an observation period which you don't  
15 have to do for any other treatment you're  
16 administering, what would that do operationally  
17 to your willingness to select a particular drug?  
18 I mean, I'll flip it around just to dramatize  
19 the point, I guess.

20 Under what circumstances would you  
21 be -- I mean, will -- by saying that, will  
22 you so restrict the use that nobody will ever

1 get it, because nobody wants to spend the  
2 resources necessary to have a patient  
3 observed for this period of time? I'm  
4 exaggerating, but just to make the point.

5 DR. RUDORFER: Ms. Lawrence, and then  
6 Dr. Geller.

7 MS. LAWRENCE: I do think it needs to  
8 be addressed on the labeling, because I don't  
9 think it will be part of the marketing for this  
10 product. I don't think -- no, I don't know that  
11 in an ad campaign, Lilly is going to -- well,  
12 maybe they will -- indicate this risk. That's  
13 not a real plus. I think legally, they have to,  
14 but I'm sure it's not going to be on the major  
15 ad.

16 DR. LAUGHREN: Yes, it will be. Yes.

17 DR. TEMPLE: Among other things, drug  
18 advertising reports to me. We'll make sure.

19 DR. RUDORFER: Dr. Geller, did you  
20 have a comment?

21 DR. GELLER: Just in terms of  
22 Dr. Potter's comment about which patients might

1 be willing to stay for three hours. I think we  
2 all see people who come from a very long  
3 distance, and that would really be a problem for  
4 them to drive in to the major medical center and  
5 then spend a few hours waiting. But we also see  
6 a lot of people who live locally, and they might  
7 decide to go have pizza in the hospital  
8 cafeteria and so forth for a while and then  
9 drive home. So I think there probably will be  
10 people who will be able to manage it, probably  
11 more so in areas like where I live where  
12 back-to-back traffic is not this similar issue.

13 DR. RUDORFER: Are we in agreement  
14 that this -- in some ways, this is like a  
15 clozapine kind of discussion? That we're saying  
16 that the safety issues for this product, as we  
17 understand it today, are above and beyond  
18 existing depot antipsychotics, and therefore, a  
19 more restrictive use would be appropriate, at  
20 least until we know enough that we can better  
21 control or prevent that? In which case, it's  
22 certainly possible in the future if this

1 sedation delirium syndrome becomes a nonevent,  
2 then the benefit-to-risk ratio changes and  
3 presumably the labeling would follow.

4 Is there a sense of the Committee  
5 that we want the labeling to reflect the  
6 monitoring period, for example, the  
7 three-hour?

8 DR. TEMPLE: Yes, you really can  
9 assume that. That will be prominent, and I  
10 doubt Lilly disagrees.

11 DR. RUDORFER: I just wanted the  
12 Committee to be on record, because I think that  
13 will subsume a number of other issues.

14 DR. TEMPLE: On the other matter, it's  
15 a tough judgment to know whether you should make  
16 something explicitly second-line or have to  
17 fail. We did for clozapine because we  
18 considered a granular cytositis to have a  
19 mortality in the neighborhood of 10 percent,  
20 which meant about 1 in 1,000 people we thought  
21 might die. It hasn't worked out that way  
22 because of monitoring, but that was a very high

1 level of worry.

2           And there are other circumstances.  
3 We have a channel blocker called deperdil (?)  
4 that's only for people who failed on other  
5 therapy, because it causes torsadapon (?), so  
6 that's easy. Some things are lighter than  
7 that and we don't go quite as far.

8           And we -- both of us have described  
9 what we did for ziprasidone, because we  
10 didn't really have any evidence that anybody  
11 had actually died, but we were nervous. So  
12 it sort of says think about these other  
13 things. And then we need your help in  
14 figuring out what the location is of this  
15 one.

16           DR. RUDORFER: Dr. Geller, then  
17 Dr. Wells.

18           DR. GELLER: Just a distinction I see  
19 between ziprasidone and the situation with  
20 what's called here "profound sedation," which  
21 again goes back to the comments that Dr. Caplan  
22 is making, that there is a concern that the

1 neurological events that happen during the event  
2 might in fact impinge upon the cognition. And I  
3 think in some ways, that may bring it to a  
4 somewhat higher level of concern than  
5 ziprasidone. Not to the level with clozapine,  
6 but perhaps higher than the level with  
7 ziprasidone.

8 DR. RUDORFER: Thank you.

9 Dr. Wells?

10 DR. WELLS: These restrictions and  
11 limitations that we're talking about, will that  
12 go in the precautions section in the labeling?  
13 Or do we need to talk about that?

14 DR. TEMPLE: Well, there isn't a  
15 precaution section in the labeling anymore.  
16 It's warnings and precautions, so it would go in  
17 there. And one question to be resolved is  
18 whether it's part of a boxed version of that,  
19 too? But it'd be pretty prominent, I would  
20 think.

21 DR. LAUGHREN: And also, if we were  
22 also using the same kind of language, for

1 example, that we used on ziprasidone, it would  
2 also go in the indication section.

3 DR. RUDORFER: The sponsor had used  
4 the terminology, a bolded warning. Do you want  
5 to -- can you orient us to the distinction, and  
6 if you have any feelings about your experience  
7 with the different versions of warnings?

8 DR. TEMPLE: Yes. We have various  
9 ways of seeking to emphasize things. If our  
10 highest level of noise is to put the warning in  
11 a box, which means it's at the very front of  
12 this section called Highlights, which is part of  
13 the new labeling. And frequently, in an  
14 expanded version in full labeling, it's very  
15 prominent. And actually, we make some effort to  
16 have the version of it that's in the highlights  
17 be short and sweet and bulleted so that  
18 everybody understands what's going on.

19 Things that are at a somewhat lower  
20 level of sense of urgency might be bolded in  
21 the regular warnings and precautions section.  
22 They, too, would show up in the highlights in

1 a prominent way, under warnings. And we try  
2 to balance making everything bold and nothing  
3 is bold, you know? So we try to do that.  
4 But I think we're talking about, as Tom says,  
5 things that would be prominent in both the  
6 indication section -- that is who it's  
7 for -- and how to use it. So there'd be a  
8 fair amount of discussion of this limitation  
9 and the reason for it.

10 There'd be a detailed description  
11 of these sedation events or whatever we're  
12 going to call them, also.

13 Bolding is used to emphasize  
14 things.

15 DR. RUDORFER: Dr. Shaffer?

16 DR. SHAFFER: I just wanted to say  
17 something because I've been wanting to say it  
18 for a long time, which is that I don't think  
19 that we really know the neurology of these  
20 events. We know that one person had a Babinski.  
21 We know that some of them went into coma. We  
22 don't really know what the neuropathology is.

1 And we don't know if there was raised  
2 intracranial pressure. Is this a drug which  
3 could be doing that?

4 The assumption that it was simply  
5 just a replication of the normal range of  
6 activities that the drug will manifest is  
7 quite a daring one. And I just hope that  
8 there's going to be more investigation of  
9 these events, that we don't really have any  
10 CSF results, I don't think, and I hope that  
11 we can get a better understanding of the  
12 neurology of the events.

13 DR. RUDORFER: Dr. Potter?

14 DR. POTTER: Yes. To get at  
15 Dr. Shaffer's comment, I guess that is one thing  
16 that could be part of an observational study,  
17 not only greater precision around the estimate  
18 of events, but additional information on  
19 subsequent sequelae. I guess I could -- one  
20 could imagine that. That would be an  
21 opportunity. I don't know if the sponsor would  
22 be willing to do that, or is invested in doing

1 that, but that's a different question. But  
2 scientifically, I guess you might do that.

3 DR. RUDORFER: I think it's safe to  
4 say that the Committee certainly endorsed the  
5 sponsor's plan to further study and hopefully  
6 better understand this problem, that this is  
7 sort of implied in their comments. What I'm  
8 hearing -- I'm sorry, do you --

9 DR. TEMPLE: No, I was just going to  
10 say more than half of the people have these  
11 episodes stayed on therapy, so that at least  
12 somebody observed them. And perhaps we need to  
13 look at how they looked more closely. I don't  
14 remember.

15 DR. RUDORFER: The way I'm putting  
16 this together we keep coming back to the  
17 all-important benefit-to-risk ratio. I think  
18 we've agreed today that there's probably greater  
19 than 1 percent incidence of this serious adverse  
20 effect of people using this product. And I  
21 think what we've been trying to do here this  
22 afternoon is to craft a message of saying that

1 the potential benefit, which we think is real,  
2 has to be of sufficient magnitude as to overcome  
3 that. I think that we're saying there certainly  
4 are people with very serious psychotic illnesses  
5 for whom the potential benefit would outweigh  
6 the risk of this syndrome, serious as it might  
7 be.

8           Obviously, we want to work toward  
9 understanding and minimizing that syndrome,  
10 but in the meantime, I think we're concluding  
11 that we want to avoid casual use of the drug.  
12 And I think that we're saying labeling that  
13 would include language with reference to  
14 nonadherence -- again, whether that's  
15 documented or fear of -- I'm not sure we  
16 quite resolved, because again, I don't think  
17 we want to leave a window there again for  
18 casual use.

19           But assuming we kind of nail that  
20 down, it seems to me that between the history  
21 of nonadherence and the requirement for the  
22 three-hour monitoring, I think that that

1 pretty well narrows the thoroughfare to where  
2 our comfort level is.

3 Dr. Laughren?

4 DR. LAUGHREN: Nonadherence probably  
5 would apply to any depot, right? I mean,  
6 ordinarily a clinician would think about a depot  
7 formulation if nonadherence was an issue. Is  
8 there anything beyond that here that you think  
9 we ought to think about? Again, coming back to  
10 the question, should a clinician think  
11 about -- if a clinician is thinking about a  
12 depot, should a clinician think about other  
13 depot forms before going to this one?

14 DR. RUDORFER: Ms. Lawrence?

15 MS. LAWRENCE: I do think our comment  
16 before about having been on olanzapine should be  
17 part of it, too. Because I don't know that a  
18 doctor would put somebody on this one if they  
19 had not responded to the olanzapine orally. It  
20 wouldn't make sense to me.

21 DR. RUDORFER: Dr. Potter?

22 DR. POTTER: I was going to say that.

1 That seems hard to do without a clear area to  
2 argue one way -- to that way, without clearer  
3 data. I mean, I don't know how much of it is  
4 anecdotal or real, but the number of studies in  
5 which we have as a field -- or have been able to  
6 execute studies, either publicly funded or  
7 industry funded, to actually show the fraction  
8 of patients who seem to be well-controlled with  
9 one particular medicine and who are not that  
10 well-controlled over long periods of time that  
11 we're talking about here -- these mirror  
12 designs, that you'd have to do a year on one and  
13 then a year on another and all this kind of  
14 thing, there just aren't enough of those, I  
15 think, to justify restricting a person to, say,  
16 you have to show that you failed on one of the  
17 other depot medicines before you would even  
18 consider that. That would seem to me fairly  
19 extreme based on the data.

20 DR. RUDORFER: Dr. Temple?

21 DR. TEMPLE: One could write something  
22 less directive than that and say that there

1 ought to be some reason you pick this, such as  
2 failure to respond to other things, a  
3 particularly good response to the oral, and the  
4 "such as" means there could be other reasons  
5 that you might choose that. We do things like  
6 that sometimes.

7 DR. RUDORFER: Presumably, if there's  
8 language to the effect that data to date  
9 suggests that there may be safety concerns  
10 beyond those of other existing depot  
11 preparations, would that be saying the same  
12 thing as what you're saying before in terms of  
13 you might want to look elsewhere first?

14 DR. TEMPLE: Well, my thought is that  
15 as was done with ziprasidone, you'd introduce it  
16 by saying this drug has a particular problem;  
17 that is, approximately 1 percent of all patients  
18 over the course of their treatment will have  
19 this episode. Therefore, you should think about  
20 why you're picking this drug. And some is still  
21 to be written, of course, but something like  
22 that. It's not unprecedented.

1 DR. RUDORFER: Dr. Winokur?

2 DR. WINOKUR: I just wanted to put in  
3 the pitch, I think again, that we not recommend  
4 putting it as a second tier among the depot  
5 options. But even clinical judgment -- again,  
6 there need to be important clinical reasons to  
7 decide to go to depot, and within that there can  
8 be valid reasons -- certainly, one being a good  
9 response to oral olanzapine is one, but there  
10 could be others to choose.

11 And I just don't think there's a  
12 valid reason to automatically recommend  
13 putting it behind among the depot options. I  
14 think that link with the careful risk  
15 management -- which we all agree is  
16 crucial -- is the way I'd recommend.

17 DR. RUDORFER: Thank you. Dr. Mann?

18 DR. MANN: I'd agree with that, and I  
19 would add another reason for doing that. For  
20 example, while this preparation has this  
21 disadvantage of this pronounced unpredictable  
22 sedation, it also does have a clear advantage, a

1 likely advantage, in terms of EPS, for example.  
2 So if you had a patient that's had several  
3 relapses and has been treated for a long time  
4 and is prone to EPS, and then you look at the  
5 choice of the other depot preparations, you  
6 would want to steer the patient potentially more  
7 in this direction.

8           So having some warnings and having  
9 some restrictions is okay, but we also need  
10 to leave the clinician enough room to make  
11 these judgment calls.

12           DR. RUDORFER: Right. I think that's  
13 part of the dilemma of steering medical practice  
14 without directing it. And I think, in a funny  
15 way, it's almost as if it's not the good  
16 clinicians we have to worry about. We need to  
17 direct clinicians that we are concerned might  
18 otherwise just not pay enough attention.

19           So when we talk about it -- and  
20 Dr. Laughren made a valid point, why should  
21 we have to tell people don't use depot  
22 olanzapine in a patient who didn't respond to

1 oral? And I'm thinking, well, the answer is  
2 that in many settings, the treating clinician  
3 hasn't read the chart and doesn't have a clue  
4 whether the person ever had a trial of oral  
5 olanzapine. So it's almost like having to  
6 remind people sometimes of the obvious.

7 Dr. Wells?

8 DR. WELLS: I know we talked about a  
9 three-hour observation period. I'm not sure if  
10 we intended for all of that be in the clinic. I  
11 personally would be comfortable with a one-hour  
12 observation period in the clinic, and then  
13 perhaps the person could be discharged with  
14 another adult who can be responsible for  
15 providing some monitoring over the ensuing two  
16 hours.

17 DR. LAUGHREN: Yes, I think that's the  
18 option that the sponsor has proposed. We'll  
19 have to consider that as we look to the  
20 possibility of labeling.

21 DR. RUDORFER: Would anybody else like  
22 to provide some input to the FDA? Are there

1 other recommendations you'd like us to discuss?

2 DR. LAUGHREN: No, this has actually  
3 been very, very helpful. I think you've  
4 discussed all the issues, certainly, that we  
5 intended you to and some more.

6 So thank you very much. It's been  
7 very helpful.

8 DR. RUDORFER: Then I, with the power  
9 invested in me as acting chair, pronounce us  
10 adjourned.

11 (Whereupon, at approximately 4:31  
12 p.m., the PROCEEDINGS were  
13 adjourned.)

14 \* \* \* \* \*

15

16

17

18

19

20

21

22

