

1 stimulant drugs. We don't know about the
2 cataplectic narcoleptics who weren't. So, I wanted
3 to reflect what we actually looked at, the
4 scientific evidence.

5 DR. KATZ: And, would that be the basis
6 for your no vote as well?

7 DR. SIMPSON: Well, mine is really that
8 they reduced cataplectic events. I guess my
9 understanding of treating it is that they couldn't
10 sort of cure it.

11 DR. PENN: May I just clarify? I didn't
12 mean cure. My motion was not cure, nor did I say
13 monotherapy.

14 DR. KATZ: Right. From the point of view
15 of an effect, you know, that sort of language only
16 being applied to a cure, the vast majority of
17 things we treat and give claims for in indications
18 are for symptomatic, non-curative treatment. So,
19 it is perfectly acceptable for us -- and I think it
20 was implied in Dr. Penn's motion that to vote yes
21 you wouldn't necessarily have to conclude that the
22 drug cures it or wipes these attacks out, but just
23 that there is a decrease in these attacks compared
24 to the control.

25 DR. FALKOWSKI: And you can call it

1 monotherapy but what the subjects were in these
2 studies were subjects with the condition that were
3 already under medication for this condition. So,
4 to take that leap to say, well, therefore, if you
5 have people with this condition who are not on
6 stimulant drugs, does that follow? I don't believe
7 it does.

8 DR. KATZ: We will take that under
9 advisement.

10 DR. KAWAS: The next question, has the
11 sponsor demonstrated efficacy of Xyrem for the
12 proposed indication to reduce excessive daytime
13 sleepiness in patients with narcolepsy? The floor
14 is open for discussion on this point.

15 At the risk of putting myself back in the
16 same place as last time, I would summarize what we
17 have seen today with regards to excessive daytime
18 sleepiness that there was one study, in a
19 double-blind fashion, that showed subjective
20 changes in sleepiness with the Epworth Scale, and
21 that would be the GHB-2 study. The other study
22 which is being held up as a pivotal study with
23 regards to daytime sleepiness was the Lammers
24 study, which is a small study. Otherwise, I feel
25 that the evidence with regards to daytime

1 sleepiness was very weak at best, in particular,
2 the only study that proactively made daytime
3 sleepiness the primary outcome measure as well as
4 using objective measures with the MSLT was, in
5 fact, negative. All the other studies were open
6 label. So, here I have a little more --
7 considerably more difficulty actually seeing that
8 the sponsor has demonstrated efficacy for daytime
9 sleepiness. So, what are the committee's thoughts
10 on this? What are the committee's comments on
11 this? Jerry?

12 DR. WOLINSKY: As I tried to point out
13 before, I think this is such an enriched patient
14 population for purposes of the endpoints that were
15 studied, it is hard to know that one could
16 generalize daytime sleepiness effects in a full
17 population of narcoleptics. So, I agree that the
18 data is weak and it is also in a very enriched
19 population.

20 DR. KAWAS: I am not sure I understand.
21 For clarification, enriched with what? You mean
22 enriched for cataplexy?

23 DR. WOLINSKY: Enriched for cataplexy
24 which is not present in all narcoleptics and is not
25 always present at this frequency. So, I don't

1 think that we would know. I would not know as a
2 clinical that if I had a narcoleptic with sleep
3 attacks or daytime sleepiness but no cataplectic
4 attacks whether I could expect the drug to work or
5 not, and I saw no data to tell me that I could.

6 DR. KAWAS: Any other comments? Any other
7 thoughts before we call the vote on this question?

8 DR. PENN: I move that the company has not
9 provided information to prove that daytime
10 sleepiness is affected by Xyrem, and I would make a
11 comment on my motion, that if the company sees this
12 as an important thing they can do a post-approval
13 study on that specific item and that would be
14 appropriate. I was leaning at the beginning of
15 this to think that there was too much need for full
16 proof on an orphan drug that this might be the case
17 and I was going to give them the benefit of the
18 doubt, but considering the potential for abuse in
19 patients who will say they are just sleepy and the
20 regulatory problems with that, I think we had
21 better be quite strict on this.

22 DR. KAWAS: Can you make that motion
23 without the addendum?

24 DR. PENN: No, no, the addendum is just my
25 comment.

1 DR. KAWAS: Good. Give me the short
2 motion.

3 DR. PENN: They didn't prove their point.

4 DR. KAWAS: The language is has the
5 sponsor demonstrated efficacy of Xyrem for the
6 proposed indication to treat excessive daytime
7 sleepiness in patients with narcolepsy? So, a vote
8 of yes the way I just worded it would suggest that
9 the company has shown efficacy, similar to the last
10 vote. A vote of no would suggest that the company
11 has not shown efficacy for that particular
12 indication. So, all in favor of yes, the company
13 has shown efficacy for the indication of daytime
14 sleepiness, please raise your hand.

15 [No show of hands]

16 All in favor of no?

17 [Show of hands]

18 Let the record show that it was unanimous.
19 It might be the only time today.

20 DR. TITUS: And enter nine names please
21 into the record.

22 [Drs. Penix, Van Belle, Penn, Kawas,
23 Wolinsky, Roman, Falkowski, Simpson and Lacey voted
24 against the motion]

25 DR. KAWAS: Now, the second question that

1 the FDA has asked us to vote on is has the sponsor
2 established the safety of Xyrem when used for the
3 proposed indication for which substantial evidence
4 of effectiveness has been submitted?

5 Now, given our previous vote, we are
6 talking about substantial evidence for the
7 effectiveness to treat cataplexy, and I want to go
8 ahead and put in here that I think most of the
9 committee members have been of the opinion that the
10 substantial evidence is almost exclusively in the 9
11 g dose range. So, I think we are talking about has
12 the sponsor established safety of Xyrem when used
13 for cataplexy at a dose of 9 g per day, for the
14 most part. The floor is open for discussion on
15 this question.

16 DR. SIMPSON: Could one of the physicians
17 put the adverse events that one can see in the 9 g
18 in perspective?

19 DR. KAWAS: Let me let Dr. Katz and Dr.
20 Mani answer the question. Dr. Katz?

21 DR. KATZ: Yes, this is why the dose which
22 you think is effective is important. It might be
23 useful, before you decide whether or not the safety
24 has been established at 9 g, to have a look at what
25 the total exposure at the 9 g dose is and whether

1 or not you think that is acceptable, as a first
2 step, independent of whether or not it seemed to
3 have been tolerated, with enough people at 9 g with
4 sufficient duration. So, I don't know if the firm
5 could put up a slide. I think Ranjit has an
6 overhead.

7 DR. KAWAS: Slide 67 from the company,
8 updated ISS database, summary patient exposure by
9 dose. By my calculations we are talking about 60
10 years, person years of exposure on the 9 g dose
11 from the integrated data set.

12 DR. MANI: I am sorry, I don't believe it
13 is patient years, is it? It is the number of
14 patients.

15 DR. KAWAS: Well, I calculated it because
16 there were 13 patients who had been on it for 2
17 years or more and 34 patients who had been on it 12
18 months or more. So, it was just 2 times 13 plus
19 34. That is the way I came to the 60 person year
20 estimate. I actually didn't give them any credit
21 for the 6-month exposure.

22 Actually, I have a question to ask of the
23 company, do each years subsume the others? So, the
24 13 individuals who were in the 2-year category, are
25 they also included in the 62 who are in the 6-month

1 category and the 34?

2 DR. REARDAN: Yes, I believe that is
3 correct, Dr. Kawas, the 13 patients would be
4 included in the 34, and the 34 would be included in
5 the 62.

6 DR. KAWAS: So, the math is more
7 complicated than I made it out to be, actually. It
8 still comes to about 47 patient years of exposure
9 by my calculation. I believe that the standard
10 generally if it is considered acceptable is
11 considerably higher than that. Perhaps Dr. Katz
12 would like to comment on that, particularly in the
13 case of an orphan drug with a relatively small
14 patient population.

15 DR. KATZ: Yes, the typical minimum
16 requirements for an application for a standard drug
17 that is not an orphan -- we will start there
18 because we have such standards written, is at least
19 1500 patients total or subjects total, with at
20 least 300-600 for 6 months for a chronic disease
21 and at least 100 for a year. That is the standard
22 ICH minimum data package for safety.

23 As you point out, this is an orphan
24 condition. I guess the company estimates the
25 prevalence of narcolepsy patients with cataplexy is

1 about 25,000 or 24,000, something like that. And,
2 we had agreed prior to the submission of the NDA
3 with the company that, because it is an orphan with
4 a fairly small prevalence, that they wouldn't
5 really have to have the full data set that a
6 typical NDA would have, and we agreed that a total
7 of about 500 would be in the ball park. It is
8 understood that at least some significant
9 percentage of those patients should be at a
10 therapeutic dose because the safety accrued at the
11 dose that is less than therapeutic isn't
12 particularly contributory.

13 So, while I don't believe -- the company
14 can correct me if I am wrong, but I don't believe
15 we set in stone what would the minimum numbers be
16 that would be sufficient for either 6 months or a
17 year or total active therapeutic dose. I don't
18 believe we signed a contract about that, but I
19 think the implication is that a big chunk of the
20 data ought to be at therapeutic dose. So, I can't
21 give you an absolute answer but I will throw it
22 back to you and ask would you think that the
23 exposure at the therapeutic dose that you have seen
24 is sufficient to characterize the safety profile
25 reasonably and that we could write labeling that

1 would adequately inform prescribers about what the
2 panoply of risks is at 9 g?

3 DR. ROMAN: Could that be solved with a
4 post-release very strict follow-up on these
5 patients, Dr. Katz?

6 DR. KATZ: We really have to be assured
7 that the drug is safe in use at the time of
8 marketing. We cannot rely on post-marketing data
9 to say, well, we will find out if it is safe in
10 use. We have to make a decision about whether it
11 is safe in use as described in labeling, whatever
12 that is going to look like, at the time of
13 approval. There may be additional information we
14 would like to have in Phase IV but the fundamental
15 finding of whether or not it is safe in use must be
16 made prior to approval.

17 DR. ROMAN: A second point that I would
18 like to make is that probably you can say that up
19 to 9 g per day, not that there is sort of the
20 middle of the road -- probably it would be
21 recommended to start with a lower amount and
22 increase according to tolerance and effects, but it
23 is up to 9 g per day. That is sort of the upper
24 limit. It happens to be the most effective one and
25 sort of therapeutic dose but probably you would

1 like to start with the lowest possible amount.

2 DR. KAWAS: I think the company shares
3 your interest, but my take on this is we don't want
4 to put out there that a drug is efficacious at one
5 dose and safe at another. I mean, I think it is
6 incumbent on us to feel confident that both of
7 those characteristics go with whatever dose we
8 think is appropriate.

9 In response to your question, Dr. Simpson,
10 and I don't know if I understood it correctly but
11 you said what is the clinical significance, is that
12 from the perspective of a clinical?

13 DR. SIMPSON: Well, that is part of it.
14 Just speaking as a statistician though, the safety
15 evidence isn't there with those kind of numbers,
16 obviously. I mean, I think everybody knows that.

17 DR. KAWAS: I think that is really more
18 the question that is on hand here --

19 DR. SIMPSON: Yes.

20 DR. KAWAS: -- because from the
21 perspective of a clinical, this drug actually --
22 you know, if you didn't tell me what the drug was
23 and just showed me ten safety profiles that have
24 gone by this committee in the last decade, or
25 whatever, I suspect this would look like one of the

1 best ones. Nobody died from it. No major
2 laboratory abnormalities were detected. But it is
3 very, very, very few subjects that we are talking
4 about, and I think that is considerable concern to
5 us.

6 DR. SIMPSON: There actually was one
7 suicide which could be attributed to this.

8 DR. KAWAS: It still puts it in probably
9 the best of the ten. Dr. Katz?

10 DR. KATZ: Dr. Racusin, on our safety
11 team, just reminded me of sort of a simple rule
12 that we use to decide what sort of size of a risk
13 you can cap with a given exposure, it is called the
14 rule of thirds, but basically with a cohort of 60
15 patient years you could be comfortable with ruling
16 out a risk of no greater than 1/20, which is
17 --what? -- 5 percent. So, in other words, there
18 could be a rate of 5 percent of something bad with
19 a cohort of 60 that you would not have even seen in
20 that cohort. So, just to sort of give you an idea
21 of what sorts of potential risks are there that we
22 might not have seen yet with this cohort size.

23 DR. VAN BELLE: Just a small correction,
24 Dr. Katz. I believe that it should be 3/60, which
25 is 15 percent rather than 20 percent.

1 DR. KAWAS: Do we have any other comments
2 before we give a shot at trying to vote on the
3 safety?

4 DR. WOLINSKY: I very much share your
5 concern about approving the drug at one effective
6 dose and then saying the safety is really at a
7 lower dose than what is effective. On the other
8 hand, I do think that we have some reasonable data
9 on the efficacy side that says that the dose ranged
10 somewhere between 6-9 g is effective for a
11 substantial proportion of patients, which we then
12 give us not roughly 50 years of patient exposure
13 but closer to 200 years of patient exposure.

14 DR. KAWAS: I agree with that comment, Dr.
15 Wolinsky, but I really would want to point out that
16 almost all of the SEs appear at the 9, not at the 6
17 range. So, you know, you are stacking the deck a
18 little.

19 DR. WOLINSKY: I thought actually, as I
20 saw the listing of the adverse reactions, they
21 clustered in two modal distributions. One was at
22 the high range and one was, surprisingly, below 6.

23 DR. KAWAS: Actually, maybe we will take a
24 look at that. Could Xyrem put up slide number 70
25 for us, updated ISS database does distribution of

1 adverse events?

2 [Slide]

3 I think that is what you are talking
4 about. It is not a perfect dose response. I mean,
5 something pops up in the middle, the 6 range
6 actually in terms of SAEs at 12 percent for the 6 g
7 dose.

8 DR. WOLINSKY: And if I heard correctly,
9 and I don't know how they were distributed, at
10 least some of those serious adverse events were
11 cataplectic episodes.

12 DR. KAWAS: But even then, I mean, I would
13 point out that we are talking about a 3-fold
14 increase in discontinuations due to AEs in the 9
15 versus the 6. I mean, it is a 3-fold difference.

16 DR. WOLINSKY: I take your point.

17 DR. PENN: On the other hand, once again,
18 that looks like a pretty safe drug to me when you
19 are only talking about 15 percent of people
20 dropping out for AEs, and the real-life situation
21 is that these patients are going to be titrated up
22 to the 9 and, as we saw from that graph of the
23 unacceptable information from the standpoint of the
24 study results, in experience over a number of years
25 you can run patients certainly at lower doses than

1 9. So, I think that should be influencing our
2 opinion of the safety data.

3 DR. KAWAS: Thanks. Dr. Katz?

4 DR. KATZ: Yes, I think the critical
5 question here is not whether those numbers at 9 g
6 are acceptable or not, although that is an
7 important question, but to me the question is --
8 and you have certainly been talking about that, do
9 you have enough experience to be comfortable at the
10 dose you think is effective. I think, I mean my
11 sense of what people are saying -- you didn't vote
12 on it yet, but my sense is that you felt that at 9
13 g there just isn't really that much data. I don't
14 want to preempt your vote, but it sounds like the
15 general consensus was there wasn't enough data
16 there -- forget about what the data actually
17 showed, but there just wasn't enough to be able to
18 be comfortable that we have adequately
19 characterized the safety at 9, which is what we
20 have to do. The only vote you took on
21 effectiveness was effectiveness at 9 g. So, if you
22 think it is useful to reopen a discussion about
23 whether or not you think there is effectiveness at
24 6 g, and if you do, then you have considerably more
25 exposure to think about. So, that is your call. I

1 mean, Dr. Wolinsky suggested that he thought there
2 might be some evidence of effectiveness at 6. I
3 don't know how the others feel, and I leave it up
4 to you as to whether or not you want to reopen that
5 question because if you do think there is
6 effectiveness at a lower dose, it increases your N
7 from the point of view of safety. So, I just throw
8 that out.

9 DR. KAWAS: I actually think that is
10 probably worth our doing. With regards to
11 effectiveness at 6 g, what are the thoughts of the
12 committee? I will start by saying that I suspect
13 that there is effectiveness for at least many
14 patients at 6 g, partly for all the reasons that
15 other members of the committee have said, but also
16 because there appears to be a fairly prominent
17 dose-response curve not only in terms of AEs but
18 also in terms of efficacy. And, what isn't
19 factored into a total dose is the levels of
20 particular patients, the weights of particular
21 patients or whatever, but the data shows me that at
22 least a subset of patients appear to be responding
23 at least in some of the trials to 6 g. Dr. Katz?

24 DR. KATZ: Study 21, the withdrawal study.

25 DR. HOUGHTON: That is the slide that I

1 would really like to show if I could.

2 DR. KATZ: The dose there was 50 mg/kg, is
3 that correct? What was the distribution of doses
4 in that study?

5 [Slide]

6 DR. HOUGHTON: This is shown here. There
7 was an equal distribution of patients at the 6, 7.5
8 and 9 g and if you look at that paradigm of acute
9 withdrawal, the response to placebo randomization
10 is obviously very robust at 6 and 7.5 g, as it is
11 at the 9 g. The problem with the GHB-2 study is
12 that it is only a 4-week study and the slope of the
13 line hadn't plateau'd at the end of 4 weeks. When
14 we did apply that to open label, even though it was
15 open label we still saw the maximum nadir at 8
16 weeks. So, if you then take a group of patients
17 who have been on active treatment for a very long
18 time and are then randomized to placebo, if you
19 believe that is a support for long-term efficacy
20 then efficacy is supported at 6 g and 7.5 g.

21 DR. KAWAS: Would members of the committee
22 like to comment on this data or any other data
23 showing efficacy or non-efficacy at 6 g? Yes?

24 DR. SIMPSON: I do think that this trial,
25 in fact, is very impressive. I just want to remind

1 everybody of the caveat of this, that the people
2 that you were looking at long-term exclude all
3 those people who have dropped out for adverse
4 events.

5 DR. KAWAS: I think that is a very good
6 point. I mean, this was a study done in responders
7 rather than just random narcoleptics. Individuals
8 in this group represented probably are individuals
9 who felt they were getting benefit or saw benefit.

10 DR. SIMPSON: And provided the drug is
11 safe, then in fact this might be a fair rule to
12 look at to say, yes, the drug is effective.

13 DR. MANI: I would just like to point out
14 that these comparisons are not of randomized
15 groups.

16 DR. KATZ: They are not randomized to
17 dose.

18 DR. MANI: They are not randomized to
19 dose.

20 DR. KATZ: It is obviously a randomized
21 study. So, they are not randomized to dose in the
22 sense of typical dose response. These are doses
23 that presumably they had been responding to in open
24 experience, and there is not as balanced across the
25 doses, that is true. And, the numbers are quite

1 small on each dose. On the other hand, you have
2 already decided that in toto it is a study that
3 demonstrates effectiveness.

4 DR. KAWAS: I mean, I think even though we
5 all recognize these are responders, the fact that a
6 group of individuals on 6 g who, when withdrawn,
7 showed this effect at least told me that there was
8 a subgroup that did respond, as I said before, to
9 6. The question is how big is that subgroup, and
10 when we are talking about indications and efficacy
11 do we feel that on the whole 6 is a dose to which
12 people respond based on all the evidence that we
13 have seen so far?

14 DR. FALKOWSKI: And I would also like to
15 say I am a little uncomfortable with the idea of
16 saying that we have so many patient hours for most
17 drugs but, because this is orphan status, we have
18 it but we don't have -- Dr. Katz' remarks -- but we
19 don't have any numbers. Well, that, to me, puts
20 the sponsor in a difficult situation about, you
21 know, what is adequate in trying to develop a new
22 drug and it makes it very difficult for us here to
23 try to reach a conclusion. Enlighten me, here.

24 DR. GUILLEMINAULT: Can we make a comment,
25 as a sleep expert, on the issue?

1 DR. KAWAS: I am sorry, who is speaking?

2 DR. GUILLEMINAULT: Yes, can we make a
3 comment on that issue as sleep experts?

4 DR. KAWAS: Please. Yes, you are on the
5 air.

6 DR. GUILLEMINAULT: Okay. The comment
7 that I want to make is that currently there is no
8 drug for cataplexy which is at a fixed dosage.
9 None. Because there is a certain amount of
10 variability from patient to patient, and a patient,
11 for example, can respond at 20 mg of fluoxetine or
12 60 mg of fluoxetine. In general terms, it is
13 unrealistic to believe that there will be a single
14 dose which will control all cataplectic attacks for
15 all narcoleptic patients. So, you have dose
16 ranges, and I think that that is what these studies
17 are showing. Looking at the data that you have,
18 efficacy for some patients is at 6 or for some
19 patients at 9. And, that is the clinical
20 experience, 20 years of clinical experience. That
21 is the best that you are going to get. So, your
22 efficacy for some is 6 and for some is 9. All
23 drugs used for cataplexy are like that. All
24 patients respond following that scheme.

25 DR. KAWAS: Thank you. Dr. Katz, would

1 you like to comment on Dr. Falkowski's concerns
2 about the orphan status?

3 DR. KATZ: The only written rules that I
4 am aware of which talk about numbers that are
5 adequate, or are potentially adequate, for an NDR,
6 or for a typical NDR, there are no numbers written
7 down anywhere as policy or guidance.

8 So, as I say, had agreed that a total of
9 500 was appropriate -- we, the company and the
10 division.

11 DR. FALKOWSKI: So they came up short.

12 DR. KATZ: Well, that is the question we
13 are asking. There was, on our part, that at least
14 a big chunk of that would be at a therapeutic dose.
15 So that is why we are asking you whether or not you
16 think it is adequately characterized.

17 I just want to make one other comment with
18 regard to the 6-gram effectiveness and to ask the
19 company just -- should make this explicit, although
20 I think Dr. Trout said it a couple of times.

21 In Study 2, the p-value for the 6-gram
22 versus placebo contrast was 0.0529, or 0.053, I
23 believe. That was including a correction for
24 multiple comparisons given the three doses.

25 So you have one study which, basically,

1 has a p-value of 0.05 at the 6-gram dose; right?

2 And then you have what you have seen. So I just

3 remind the committee of that.

4 DR. FALKOWSKI: And that was the four-week

5 study, the GHB-2 study; right? Okay.DR. KATZ: i

6

7 DR. KAWAS: Any final comments before we

8 take a vote on the sponsor establishing the safety

9 of Xyrem when used for the proposed -- well,

10 actually --

11 DR. SIMPSON: Would it be appropriate to

12 do a revote on the efficacy?

13 DR. KAWAS: Not revote, but we can do

14 another vote on whether or not the panel thinks

15 that there was efficacy demonstrated at --

16 DR. SIMPSON: A dose between 6 and 9.

17 DR. KAWAS: Well, I think we will have to

18 say either a dose of 6 or a dose of 7.5 or

19 something like that.

20 DR. KATZ: Well, if you conclude it is

21 effective at 6 and you have already concluded it is

22 effective at 9, it would be sort of odd if it

23 wasn't effective at 7.5. So, if you just want to

24 vote it at 6, we will take it from there.

25 DR. KAWAS: Okay. We are voting on 6.

1 Has the sponsor demonstrated efficacy of Xyrem for
2 the proposed indication to treat cataplexy at the
3 dose of 6 grams per day? All in favor? All who
4 agree that the efficacy has been demonstrated,
5 raise your hand.

6 [Show of hands.]

7 DR. KAWAS: Let's start and identify
8 yourself as we are going around.

9 DR. SIMPSON: Simpson.

10 DR. ROMAN: Roman.

11 DR. WOLINSKY: Wolinsky.

12 DR. LACEY: Lacey.

13 DR. KAWAS: All who do not feel that the
14 company has demonstrated efficacy at 6 to treat
15 cataplexy, raise your hand. Start identifying at
16 that end.

17 DR. PENIX: Penix.

18 DR. VAN BELLE: Van Belle.

19 DR. PENN: Penn.

20 DR. KAWAS: And I am the lone abstention,
21 I think.

22 DR. FALKOWSKI: Over here.

23 DR. KAWAS: Oh; and Falkowski. So we have
24 a split committee for you on 6. If I vote, I break
25 it. Actually, I am fairly convinced that there is

1 efficacy at 6. So Kawas.

2 Now, safety. We are now talking safety
3 between 6 to 9. We are now talking about a lot
4 more patient hours, patient years. The floor is
5 open for discussion for safety between 6 and 9
6 grams a day.

7 DR. PENN: Can the company give us the
8 number of patient years exposure 6, 7, 9, total
9 because we can't do it from your data that we have
10 seen here. How close to the magic 500 are you?
11 Patient years; excuse me.

12 DR. KATZ: Not patient years. 250
13 patients greater than six months, if I added that
14 up correctly. That is without Dr. Scharf. This is
15 now with, so the numbers are bigger. Without Dr.
16 Scharf, I calculate about 250 patients for at least
17 six months. Is that about right?

18 DR. VAN BELLE: I got 399.

19 DR. KATZ: Greater than six months?

20 DR. VAN BELLE: Yes.

21 DR. KATZ: At 6 and above? We can just
22 split the difference.

23 DR. VAN BELLE: How many Ph.D.s does it
24 take to add nine numbers?

25 DR. KATZ: I am not a Ph.D. I can't be

1 expected to. Can you put the slide back without
2 Dr. Scharf?

3 DR. KAWAS: I come to about 150 patient
4 years of exposure just looking at the individuals
5 who were on at 12 months or more.

6 DR. REARDON: This is the data without Dr.
7 Scharf included from the ISS.

8 DR. KAWAS: I think it is important that
9 we know exactly what we are looking at so thank you
10 for pointing that out to us. On the other hand, I
11 will say that it is to -- my personal impression
12 was that Dr. Scharf's data, although it was the
13 most extensive and the longest term, was collected
14 the least systematically. Given some of the other
15 issues that were brought up about it, it is
16 probably to your advantage to stick with this
17 dataset in terms of AEs.

18 Okay; then the vote is about to be called
19 for. If the sponsor has established the safety of
20 Xyrem when used for the proposed indication at the
21 dose of 6 to 9 grams per day. All who think yes,
22 raise your hands.

23 [Show of hands.]

24 DR. KAWAS: Wait a minute. Something very
25 funny just happened here. It seemed like more

1 people were willing to say it was safe at 9 than
2 are willing to say it is safe at 6 to 9? Let me
3 try again. Who thinks it is safe, raise your hands
4 now.

5 [Show of hands.]

6 DR. KAWAS: Identify yourself from that
7 end.

8 DR. ROMAN: Roman.

9 DR. WOLINSKY: Wolinsky.

10 DR. PENN: Penn.

11 DR. KAWAS: Kawas in there. Anyone else?

12 Who does not think it is safe, raise your hands,
13 that safety has been demonstrated, established
14 safety at the dose from 6 to 9 raise your hand now?

15 [Show of hands.]

16 DR. KAWAS: Has not been demonstrated to
17 your satisfaction. Falkowski, Simpson, Lacey,
18 Penix? Anyone else?

19 DR. VAN BELLE: Van Belle abstains.

20 DR. KAWAS: And one abstention. We are
21 really helping a lot.

22 DR. KATZ: I didn't count. Was that a
23 split?

24 DR. KAWAS: Right down the middle. Really
25 helping.

1 The third question that the FDA has asked
2 us to consider is the adoption of a risk management
3 plan necessary for the safe use of Xyrem. I would
4 like to focus us on that question. First, in a
5 yes/no way rather than the details of whether or
6 not, of what belongs in a management program if we
7 think yes, or what doesn't belong if we think yes.

8 DR. FALKOWSKI: I thought part of our
9 discussion was going to be different elements of
10 that.

11 DR. KAWAS: That is the next part. First,
12 let's decide do we need a risk-management program,
13 yes or no. And then, if we do, what should be the
14 elements. Jerry?

15 DR. WOLINSKY: I think there are really
16 two issues here. I wish there weren't, but there
17 are two. One is the risk-management program and
18 whether it is critical for the patient population
19 in which the drug seems to be indicated. I
20 actually don't think that is important.

21 Then the question is is there a risk-management
22 program that is necessary for the
23 concerns about the societal risk at large. There,
24 I think the answer is absolutely yes. Because of
25 that conflict, we may be in an unusual position if

1 we favor this drug, favoring, potentially, making a
2 precedent step in which we put unusual controls on
3 physicians and patients, more so than we have had
4 in the past.

5 I am not sure there is anything wrong with
6 that, but I am not sure that this is a large enough
7 forum in which this question should be addressed.

8 DR. KATZ: There certainly are precedents
9 for risk-management programs being necessary for
10 the safe marketing of the drug. I don't know that
11 there are many, but there are certainly -- and I
12 think you heard about some. So there is this
13 precedence for a risk-management program.

14 Now, the details--I don't know
15 specifically which details you are thinking about--may make
16 this more of a precedent. But, certainly,
17 risk-management programs of this type or similar
18 type have been used and have been approved.

19 DR. WOLINSKY: I don't disagree with that,
20 but I think we are talking about whether or not
21 there is an inherent problem with the drug in terms
22 of the efficacy, safety level that we are seeing.
23 Most of the risk-management programs that I am
24 aware of that have been put in place have been put
25 in place for the protection of the patient not the

1 protection of society.

2 DR. KATZ: Again, you have made a
3 distinction which we have not yet explicitly made.
4 It is a fair distinction. I am not sure everyone
5 agrees that there would be no need for a risk-management
6 program if it was just--if you weren't
7 worried about the societal questions. But it is a
8 fair point for sure.

9 DR. PENIX: Also, isn't it the difference
10 in the fact that this is a controlled substance and
11 the other drugs are not that the safety measures
12 that are put in place for the protection of the
13 patients are usually not controlled substances. So
14 that may be a difference in this particular case.

15 DR. WOLINSKY: This is controlled, but I
16 am not sure that the controlled substances have
17 this much potential control on them is what we are
18 suggesting here.

19 DR. FALKOWSKI: I have a question which is
20 has the FDA ever been in a position where they have
21 a drug coming before them that has already been
22 scheduled? This seems to be unique.

23 DR. LEIDERMAN: Could I just answer a
24 couple of these questions?

25 DR. KAWAS: Please, Dr. Leiderman.

1 DR. LEIDERMAN: Let me refer you to a
2 table. It is actually the last page in your blue
3 FDA briefing package book. It actually lists
4 several examples of risk-management plans for
5 different drugs that come from different classes
6 and for different therapeutic indications that are
7 all in place for various safety reasons within the
8 FDA, and they range from other controlled
9 substances, potent opiates in the case of Actiq and
10 fentanyl, to mifeprex and thalidomide. The risks
11 and the intended protected individuals may be
12 different in each case. Obviously, in thalidomide,
13 the risk isn't to the patient but to the accidental
14 fetus. Similarly, much of the consideration in
15 Actiq, which is a potent opiate, was concern for
16 other individuals within the household and, again,
17 not for an opiate-tolerant severely debilitated
18 pain patient.

19 So, to answer Dr. Penix' question, in
20 fact, or Dr. Falkowski's, some of these have been
21 already scheduled drugs. I think what is unusual
22 but not absolutely unique is to start out with a
23 drug that is basically in Schedule I and then to be
24 bringing it into the therapeutic arena but, again,
25 it is not entirely unprecedented either.

1 DR. KAWAS: Thank you. I can't help but
2 point out that it is probably unprecedented, but
3 this drug has gone from over the counter, a
4 completely unregulated food supplement that could
5 be bought by anybody ten years ago to Schedule I,
6 which seems to me even more unusual.

7 So we are back to the question about the
8 adaption of a risk-management plan necessary for
9 the safe use of Xyrem. I think the comments that
10 have been made, that Dr. Wolinsky made, was it may
11 not be necessary for the safe use but it is
12 necessary for other reasons.

13 Can we amend what we vote on, whether or
14 not it is necessary, period, for whatever reasons
15 and vote on it in that regard?

16 DR. KATZ: Yes; I would prefer you did,
17 actually.

18 DR. KAWAS: Okay. The real question is is
19 a risk-management program necessary. I have a
20 feeling we are ready to vote on that. So I will
21 call the question. All in favor say aye.

22 [Chorus of ayes.]

23 DR. KAWAS: No?

24 DR. PENN: No.

25 DR. KAWAS: Let the record show that Dr.

1 Penn voted no. Any abstentions?

2 [No response.]

3 DR. KAWAS: Dr. Penn, do you want to give
4 your comments, since you were the descending
5 opinion.

6 DR. PENN: I think this is a very
7 complicated issue and I don't think we can resolve,
8 at the end of a committee meeting, the
9 responsibilities toward the general population of
10 controlling the drug and the FDA controlling it for
11 a group of patients.

12 I see that the whole issue is being
13 distorted in the same way that drugs for treating
14 pain have been a problem and that is if we limit
15 the drug with all these regulations, that the
16 patient population, which is quite small, will not
17 be served.

18 That certainly has been true with narcotic
19 drugs over the years, that many, many physicians
20 have underprescribed narcotics for a long period of
21 time. I think we will see the same here except
22 there won't be the same push to get it accepted by
23 cancer patients. The narcolepsy group is much too
24 small.

25 So it is going to be a very hard balance.

1 I also worry about the idea of "voluntary" ways of
2 doing this. They are not voluntary on the company.
3 The company wants to get the drug out and they
4 realize that they can't do it unless there are
5 societal controls on the drug and they are willing
6 to do it.

7 But I don't like the precedent of the drug
8 company deciding for a physician whether, for
9 example, somebody 17-years old will get the
10 medication or whether somebody, because of
11 different metabolism of the drug, might not be used
12 on a slightly higher dose than 9.

13 Those are things that we have
14 traditionally let the treating physician do and we
15 have also not let the company choose who are the
16 treating physicians. So I think this is something
17 that needs a large amount of debate and that is why
18 I was being obstinate and voting no on this without
19 qualification.

20 DR. KAWAS: Thank you. Rusty?

21 DR. KATZ: Just as far as the dose and the
22 limitations, that is something that can be
23 discussed in the context of what type of risk-management
24 program you think needs to be in place.
25 You could have a risk-management program that

1 doesn't say you cannot ever give a dose greater
2 than 9 grams.

3 In a typical drug, when we have labeling,
4 we have information that the drug is effective or
5 safe only up to dose X, we don't usually say, "You
6 can't possibly give any more." We just say, "Here
7 is the data. There is no data above dose X."

8 So it isn't part and parcel of any risk-management
9 program that you would automatically
10 limit the dose. I supposed you could, but it is
11 not presupposed that that must be the case.

12 DR. PENN: But you might limit age. The
13 other thing is who is going to make these
14 decisions. We were given this in the context of a
15 very particular type of risk management. I think
16 the devil is in the details in these types of
17 situations and to vote yes or no is very difficult
18 without knowing exactly what details we are talking
19 about. They make major substantive differences.

20 DR. KAWAS: Let's go on.

21 DR. KATZ: That is why I wouldn't ask you
22 to vote on the details.

23 DR. KAWAS: That is what I was going to
24 say. Let's go on to the details. I want to remind
25 the committee, particularly because of the lateness

1 of the hour, if there is a detail that is not
2 important to you, please don't fill up too many of
3 the airwaves with it so we can get to the ones that
4 are important to you.

5 So the first one is should there be a
6 requirement for additional safeguards; i.e.,
7 keeping drugs in a locked storage space in the
8 patient's home. Just for a straw vote to begin
9 with. How many people think that there should be
10 the requirement for a locked cabinet in the
11 patient's home? Anyone who thinks yes? Straw
12 vote. Anyone who thinks no? Straw vote.

13 I think we have got a clear preponderance
14 here. I think I will at least express my thinking
15 is that we don't require patients to keep Demerol
16 or Valium or Halcion or anything else in a closed
17 cabinet, many of the drugs that are potentially at
18 least as abusable as this.

19 Having said that, I think that almost all
20 drugs belong in a locked cabinet. That is the real
21 issue here and I am not sure to what extent
22 requiring it would make one difference or another.

23 So, should there be a requirement for
24 additional safeguards? Can I say, in general, that
25 the committee felt that that was not essential, necessary.

1 Should there be additional warnings on the
2 labeling of the dose cups and/or bottle? Any
3 comments?

4 DR. WOLINSKY: I heard something that I
5 thought was very insightful from one of the people
6 who talked to us in the public session and that it
7 would be useful if there was some distinguishing
8 feature about the bottles that could not easily be
9 counterfeited and this was be in everyone's best
10 interest.

11 DR. KAWAS: Thanks. I assume that would
12 be something that the company would do to the
13 bottle rather than something the patient--

14 DR. WOLINSKY: I assume so.

15 DR. DYER: Are the dose cups to be labeled
16 because those are not? So additional would be
17 additional to that or additional to what is
18 required by law, because they should definitely be
19 labeled.

20 DR. KATZ: If I can just interject. I
21 don't think there is anything required by law.
22 This is what the patient keeps at home. Right now,
23 I think they are just as you see them. There is
24 nothing on them. There is no labeling of any sort;
25 is that right? They are just blank?

1 DR. KAWAS: Would the company like to
2 comment? Is any additional labeling planned for
3 the dose cups? Or maybe it is about to be planned
4 for the dose cups?

5 MS. ENGEL: Actually, no. As you know,
6 the poison-control system nationwide is going to a
7 central 800 number as well as having a logo that is
8 "Mr. Yuck" like but better tested for kids. That
9 we expect to be ready in October. At that point,
10 the central pharmacy will put into each of the
11 packages three stickers, one for the bottle and one
12 for each dose computer that will include that "Mr.
13 Yuck" type symbol plus the central 800 number for
14 the entire poison-control system nationwide.

15 DR. DYER: My concern is that if the
16 bottle ever leaves the little dose caps--if you go
17 away for a night, I am going to take my two doses
18 with me. If they are separated from that bottle,
19 no one is ever going to know what it is.

20 MS. ENGEL: As I said, there are three of
21 those labels that will go, so one for each--no; it
22 does not.

23 DR. DYER: It needs to say what it is. If
24 you go stay at a friend's for the night and you
25 have narcolepsy and you take those two bottles with

1 you, child-resistant caps are designed to keep
2 children out for one to two minutes. That is it.
3 Somebody will get into that and, if they do, there
4 is no way to know what it is.

5 When they call that number to the poison
6 center, they say, "I have a bottle with a "Mr.
7 Yuck" sticker on it." It needs to say Xyrem and
8 now many milligrams.

9 DR. KAWAS: I would like to call the
10 question. Should there be additional warnings on
11 the labeling of the dose cups and the bottle of
12 GHB? Do I need to separate those two out or can I
13 put the dose cups together with the bottle.

14 Let's start with should there be labelings
15 on the bottles. All in favor raise their hands?

16 [Show of hands.]

17 DR. KAWAS: Is that almost unanimous? No?
18 Labels on the dose cups saying that it is Xyrem or
19 GHB or something. That is unanimous, please note
20 on the record.

21 How about should there be additional
22 warnings on the dose cups and/or bottle of GHB? I
23 am not sure, maybe I should ask, what is the
24 definition of additional? What is supposed to be
25 on there already? Dr. Katz?

1 DR. KATZ: I think we are probably mostly
2 thinking of the cups. There was supposed to be
3 nothing on cups. So anything you put on is
4 additional. I don't know about the bottle. I
5 don't know if we were thinking specifically about
6 the bottle. I assume that has all the usual
7 required statements, whatever they are.

8 DR. KAWAS: Are you satisfied by our vote
9 that there needs to be labeling on the dose cups?
10 I think, though, I am starting to feel from the
11 committee that there is some expression of wanting
12 certain kinds of warnings added? No?

13 DR. DYER: If I could just add in, by law,
14 you have to have "Keep out of reach of children,"
15 "Don't take with depressant drugs," "Avoid
16 hazardous machinery." So those kinds of standard
17 things would be on there and I don't know that
18 anything else would be required.

19 DR. KAWAS: Dr. Lacey?

20 DR. LACEY: If this is a scheduled
21 substance with implications for--legal
22 implications, why wouldn't we put that type of
23 warning in as few words as possible there. Maybe
24 it would deter someone.

25 DR. DYER: There is already a requirement

1 for "Federal law prohibits dispensing of this drug
2 to other than who it is prescribed." There is
3 already a label like that required on
4 prescriptions.

5 DR. PENIX: It could also attract certain
6 people as well, I think.

7 DR. KAWAS: Yes; these warning labels have
8 a mixed response. Can we move on to special
9 concern or advice regarding limitations on the
10 quantity supplied at any one time. Perhaps the
11 sponsor can correct me but my recall is that it is
12 going to be dispensed at one month and then--a
13 maximum of one-month supply at a time? Is that
14 correct?

15 DR. REARDON: We had proposed to the
16 agency initially to start at one month with each
17 patient. As the patients and pharmacists get
18 experience, that might be extended to three months
19 or could be kept to one month.

20 I think the FDA is asking should there be
21 a regulatory or legal description on the length of
22 period that a Schedule III drug should be
23 prescribed.

24 DR. KAWAS: Rusty?

25 DR. KATZ: I am not sure we meant that

1 question to be generic with regard to any Schedule
2 III. We want to know whether or not, in this
3 particular risk-management program, there ought to
4 be a provision that says you only get one month at
5 a time, or you only get three months at a time. We
6 just wanted to know what you felt about that.

7 DR. KAWAS: The floor is open for
8 discussion. First, do people think there should be
9 any restrictions on the amount, period, and then we
10 can discuss the timing. So straw vote. All people
11 who think that we should be talking restriction of
12 some sort or another raise their hand. And people
13 who don't think we need to be talking restriction
14 on length of time, raise your hands.

15 We have got a roughly split straw vote
16 with the probable preponderance on the no time
17 limit. Does that help enough?

18 DR. KATZ: Sure. If that is what you
19 think, it is helpful. I can't guarantee we will
20 agree.

21 DR. KAWAS: Having worked in sleep
22 laboratories as well as doing other physician
23 things where certain drugs--I mean, my personal
24 rule has been that drugs that have the kind of
25 potential for trouble, of which there are many,

1 many, many of them already in our armamentarium, I
2 never give out more than one month's supply with
3 three refills.

4 DR. FALKOWSKI: That is why I think that,
5 particularly with this, we need to be cognizant of
6 that and that there should be a limitation on that.
7 That is all I wanted to say. And I also don't know
8 where it comes in, or where this discussion
9 happens, but I really believe that a drug, if you
10 look at the third page from the back of the
11 materials the FDA provided about just the
12 scheduling criteria for drugs, that this drug,
13 although it is efficacious for people with
14 cataplexy, with narcolepsy or else on stimulant
15 drugs, that it clearly--

16 DR. KAWAS: Your point it getting lost.

17 DR. FALKOWSKI: It should be in Schedule
18 II. I believe it should have the dispensing
19 restrictions that are more consistent with a
20 Schedule II drug and I don't believe that would put
21 undue burden on the patients because most of them
22 are already on Schedule II drugs because they are
23 on methamphetamines or other drugs.

24 Somehow, I wanted to say that today.

25 Thank you.

1 DR. KAWAS: Do you feel satisfied with
2 what you have heard on that question, Rusty?

3 DR. ROMAN: Claudia, one more point is how
4 are the patients going to be selected. I think
5 would should at least mention that the patient
6 should have a clear diagnosis of narcolepsy with
7 polysomnogram and MSLT

8 DR. KAWAS: You are jumping to Question 6,
9 but why don't we go ahead and do that since I agree
10 that is an important point and I am worried we
11 won't get to it.

12 So what are your thoughts?

13 DR. ROMAN: That patients should have a
14 recent polysomnogram followed by MSLT in order to
15 confirm the diagnosis of narcolepsy.

16 DR. PENN: Who is going to decide whether
17 it really is narcolepsy or not? The government?
18 The company? The person who reads the test? The
19 doctor that is taking care of the patient? That is
20 why I mean the details are very important. You can
21 say that it sounds good that we should have a
22 diagnosis, but these are important points.

23 DR. KATZ: Can I just clarify what we
24 meant?

25 DR. KAWAS: Thank you.

1 DR. KATZ: We meant the treating
2 physician, in other words, would make the
3 diagnosis. We certainly, obviously, are not going
4 to get involved in the diagnosis of a patient from
5 where we sit. The company didn't anticipate that
6 they would either if I can speak for them.

7 No; we just meant do you think that the
8 patients have to have a bona fide diagnosis, does
9 the physician who is writing the prescription have
10 to assert, in writing, before the prescription will
11 be filled that, yes, this patient has narcolepsy.

12 Then you can throw this apart and say do
13 they have to assert that the patient has cataplexy
14 and that is what you have decided the effectiveness
15 data supports. So that is a subtlety or nuance of
16 the question you can get to. But specifically with
17 regard to who is going to make the diagnosis, if
18 you meant that question seriously, we meant the
19 prescribing physician.

20 DR. KAWAS: Response to that? Dr. Roman,
21 do you want to give your opinion and then Dr.
22 Wolinsky has a question or comments.

23 DR. ROMAN: I think that there are
24 diagnostic criteria that are sort of fairly well
25 accepted, at least here in the USA. The question

1 of should it be a certified polysomographer or
2 should it be one of the certified centers in the
3 nation, we will start getting into the problem of
4 what happened with the patient who lives in the in
5 the middle of nowhere and has no way to get to the
6 next sleep center at 500 miles.

7 DR. KAWAS: Excuse me, but that is not
8 what Dr. Katz asked you. He wants to know do you
9 think the physician needs to certify, however they
10 come to this decision, that the person has
11 narcolepsy, that they need to certify up front,
12 this person definitely has narcolepsy.

13 DR. ROMAN: One of the speakers mentioned
14 that it is relatively simple to get a sleep attack
15 and narcoleptic episodes that are real enough to
16 fool the best unsuspecting doctor. So, since we
17 have objective ways of making a diagnosis of
18 narcolepsy, I think we need to use that for the
19 protection of the public at large.

20 DR. KAWAS: Thanks. Jerry?

21 DR. WOLINSKY: I think this actually
22 frames what is my concern from before about
23 protecting, or treating patients and protecting
24 society. Now I want to get back more to protecting
25 people who are treated. That really gets to an

1 issue that we run away from in this country and
2 that is, if we want to be able to push the envelope
3 to be able to provide drugs that may be helpful for
4 patients with true orphan diseases, we probably
5 also have to say that we are willing to make sure
6 that those people have what they say they have and
7 that the drugs are being used in the context of the
8 set of patients in whom they were originally
9 tested.

10 It is one thing to talk about hemorrhoid
11 cream but it is another thing to talk about a drug
12 with a narrow therapeutic window and a diagnosis
13 which can be made with accuracy by experts most of
14 the time and could be misapplied by others a lot of
15 the time.

16 This becomes a critical issue so that if
17 someone is not willing to monitor this, all that we
18 do, in looking at the hard science of what is
19 presented to us, flies out the window as soon as
20 the drug gets approval.

21 DR. HAGAMAN: Can I make one quick
22 comment? I think, as a physician treating these
23 patients, if they have had a PSG and MSLT in the
24 past, there is really no need to bring them back in
25 for another one. At that point, you have to trust

1 the physician's judgment that yes, they do have a
2 diagnosis of narcolepsy, they have had the PSG MSLT
3 done.

4 DR. WOLINSKY: I don't think the panel was
5 questioning that at all.

6 DR. MIGNOT: Especially because, in such
7 cases, you will have to stop medications which is
8 another problem.

9 DR. KAWAS: I don't think that was being
10 suggested. So let's move on if we could, please.

11 DR. SIMPSON: I don't know if this fits
12 under it, but the way the question is worded,
13 should there be restricted prescribing for the
14 product. I just want to put in a plea for
15 prescribing for children. As far as I can see,
16 there have been no pharmacokinetic studies in
17 children and children's pharmacodynamic and
18 pharmacokinetic profile can be very different from
19 adults.

20 So, given its complex pharmacokinetic
21 profile, as it is, I would be very concerned if it
22 was prescribed in children based, as is usual, on a
23 way to a BMI.

24 DR. KAWAS: I am not sure that we have
25 answered your question. Actually, I still have a

1 question that I want the committee to focus on
2 unless Dr. Katz feels otherwise. Is it important
3 that we decide whether or not it needs to be
4 restricted to people with cataplexy as a component
5 of their illness?

6 DR. KATZ: I am not sure whether or not
7 you think you have made some sort of recommendation
8 about whether or not it needs to be restricted to
9 patients with narcolepsy globally yet. Do you
10 think you have, because I didn't hear it if you--

11 DR. KAWAS: No; I don't think we have.
12 You are talking now about certifying that the
13 person has narcolepsy, at least on some signature
14 level.

15 DR. KATZ: We did not put in how we you
16 would know that the patient has narcolepsy. We
17 anticipated that the physician would make the
18 diagnosis appropriately. We didn't ask--I don't
19 think we did anyway--about whether or not there
20 should be specific diagnostic criteria that they
21 have checked off or they have had a recent, or ever
22 had a polysomnogram.

23 We anticipate, for purposes of this
24 question, that the diagnosis would be up to the
25 physician to make appropriately without any

1 additional specific requirements, but I suppose you
2 could say patients must have a history of
3 polysomnography and other tests, a multiple sleep
4 latency test or an MPT before they can be
5 prescribed this.

6 You could decide that you think that that
7 is appropriate. We left it open intentionally.

8 DR. KAWAS: I think the committee needs to
9 discuss that particular point. I want to make the
10 comment, though, before we get too far, I would
11 tend to leave it open and I recognize all of the
12 things of modern medicine that all of the people in
13 this committee are familiar with because we sit at
14 major medical centers.

15 But there are people with narcolepsy and
16 cataplexy at places that do not have access to
17 sleep-disorder centers and polysomnography. I
18 think that needs to be kept in mind or discussed on
19 some level as we are cogitating about this.

20 DR. ROMAN: The problem is that you need
21 to go through the differential diagnosis of
22 excessive daytime sleepiness and the differential
23 diagnosis of cataplexy. In most cases, that is
24 going to require at least a polysomnogram, a sleep
25 test, to rule out obstructive sleep apnea,

1 restlessness, and what have you.

2 So, in most patients, at least those who
3 present for the first time to get this medication,
4 I don't see how you can avoid doing these tests.

5 DR. BLACK: I hate to interrupt, but a
6 point that I think is worth bringing up is that the
7 condition indication here is cataplexy. Cataplexy
8 is a clinical diagnosis not confirmed by any
9 testing or MSLT. If you are going to limit it to
10 cataplexy, I think it is important to recognize
11 that you can't make any verification on the
12 diagnosis with MSLT as far as the cataplexy goes.

13 DR. KAWAS: Since we have you up there,
14 what percentage of people have isolated cataplexy
15 without narcolepsy and sleep attacks?

16 DR. BLACK: It is incredibly rare.

17 DR. KAWAS: Thanks.

18 DR. BLACK: Incredibly so. But, on the
19 other hand, the incidence of cataplexy and
20 sleepiness without an MSLT that confirms it is a
21 modest subset. In other words, if you have
22 cataplexy, you won't necessarily have two sleep-onset REM
23 periods on your MSLT, so we need to keep
24 that in mind so that we don't potentially limit
25 folks with true sleepiness and cataplexy and

1 narcolepsy that don't show the MSLT findings.

2 It is not 100 percent specific or
3 sensitive.

4 DR. KAWAS: We have some people over on
5 this side who wanted to--

6 DR. LEIDERMAN: I just wanted to be clear
7 about the question that I think we were asking.
8 What was discussed internally within the agency was
9 the concern about off-label use. We all know that
10 drugs are used often more frequently for other than
11 their labeled indications. The question we wanted
12 to pose for this specific drug, does the committee
13 recommend restricting its prescription to the
14 labeled indication.

15 DR. KAWAS: So, actually, I think maybe,
16 put in that context, we could call the question and
17 try a vote here. In the opinion of this committee,
18 are we recommending that this drug needs to be
19 restricted in some fashion to on-label use? All in
20 favor?

21 [Show of hands.]

22 DR. KAWAS: Almost unanimously. Negative?

23 [One hand raised.]

24 DR. KAWAS: One negative vote from Dr.
25 Penn.

1 DR. VAN BELLE: I am going to abstain
2 because I was out of the room.

3 DR. KAWAS: Dr. Van Belle is abstaining.
4 Everyone else voted yes; am I correct? So, did we
5 give you a better answer this time?

6 DR. KATZ: Yes. All your answers are
7 good.

8 DR. PENN: Isn't this the first time
9 anybody has ever suggested that the FDA should be
10 restricting off-label use of drugs?

11 DR. KATZ: I doubt. I don't know.

12 DR. PENN: Isn't it stated in the FDA, all
13 of your regs, that you do not regulate medicine and
14 off-label use is up to the physician?

15 DR. KATZ: I don't know if it says we
16 don't regulate medicine but, certainly, I think we
17 have the authority to do, I think, plenty of things
18 that some people might consider practice of
19 medicine. So I don't think, as far as I know,
20 there is any--as far as I know, there is no legal
21 bar to this if that is the question you are asking.
22 I think we have done it in the past.

23 DR. KAWAS: I think that I want to make
24 the comment that even if it was the first time that
25 the FDA was doing this, it certainly is not new to

1 medicine. Now, insurance companies routinely make
2 us do this.

3 DR. FALKOWSKI: I have one question, I
4 guess, or one concern, and I just want
5 clarification. Did I not read this correctly? I
6 tried to read it all, but nowhere does it says
7 gammahydroxybuterate. Is this correct, sponsors,
8 that there is not the word gammahydroxybuterate in
9 any of these doctor or patient things.

10 In terms of issues here, I think it is
11 very important that the doctor information says
12 what this is.

13 MS. ENGEL: As we worked with our
14 colleagues in law enforcement, they urged us not to
15 put gammahydroxybuterate as the generic name of the
16 materials, et cetera, because they felt, for
17 example, if you are a patient, and you have
18 something in your home that says
19 gammahydroxybuterate, that might actually be an
20 attractant to a babysitter or someone else.

21 So the attempt, based on the advice of law
22 enforcement, was to separate that out.

23 DR. FALKOWSKI: I am not talking about
24 patient materials--to the doctors. Will the
25 doctors get to know? They don't have their

1 materials sitting around their home.

2 DR. KAWAS: Excuse me. Dr. Katz, is this
3 a question you would like the committee to discuss?

4 DR. KATZ: I think it is an interesting
5 question. I think we can work it out. The point
6 is well taken and, as the company says, they have
7 gotten conflicting advice for good reasons as well.
8 I think we can work it out.

9 DR. KAWAS: Great. Thanks.

10 DR. LEIDERMAN: I just wanted to respond
11 to Dr. Penn's comment about restrictions on
12 prescribing. Actually, there is some very recent
13 precedence in the non-CNS drug arena. The drug,
14 mifepristone, in fact, was approved under very
15 restricted distribution. It requires signed
16 documents by both physician and patient to be
17 returned to the distributor before--and only a
18 restricted group of physicians who certify to a
19 certain ability to handle the complications are, in
20 fact, allowed to prescribe the drug.

21 So that is a precedent in the non-CNS
22 arena.

23 DR. KAWAS: I am told that somebody on one
24 of our phone lines would like to make a comment?
25 Can you hear us?

1 DR. CHERWIN: Yes; I had wanted to make a
2 comment several comments ago, just to briefly
3 reiterate. I agree with Dr. Black said which may
4 be important that not all patients with cataplexy
5 have positive sleep studies. So, in addition to,
6 perhaps, in some cases, sleep studies not being
7 available, this is another concern.

8 DR. KAWAS: Thank you.

9 DR. CHERWIN: Another thing is that
10 cataplexy is not always a crystal-clear diagnosis.
11 Not too many people have talked about that, but
12 there can be cataplexy in the eye of one physician
13 that does not exist in the eyes of another
14 physician. That is a potential problem.

15 Finally, the International Classification
16 of Sleep Disorders, which is to the sleep field
17 similar to what the DSM is to psychiatrists, does
18 not specifically require a sleep study diagnose
19 narcolepsy.

20 I thought those three things might be
21 salient to the discussion especially--since we sort
22 of jumped to the appropriate prescribing section,
23 maybe we can run through the questions there and
24 see how many of them we can quickly comment on for
25 Dr. Katz and the agency.

1 Should physicians document that they read
2 the material sent to them before the pharmacy fills
3 the initial prescription? If we took a straw vote
4 right now, how many people would say yes? How many
5 people would say no? Since we have got a split
6 here, of the people who are on the yes side right
7 now, would some of you like to comment on what kind
8 of documentation you want?

9 I mean, are we talking a signature saying,
10 "I have read the materials that were sent to me,"
11 or are we talking about something more than that?.
12 Jerry?

13 DR. WOLINSKY: Again, it sort of depends
14 what we require or what might be expected for a
15 diagnosis rather than what would be required. I
16 think if a sleep specialist is comfortable with the
17 diagnosis in that patient, and refers the patient
18 back to treatment to that physician who is back in
19 North Dakota that you keep mentioning that can't
20 possibly have all of the diagnostic tests around,
21 then I think it is important that that physician in
22 North Dakota knows what they have signed on to.

23 If it is the sleep specialist who has got
24 150 patients on treatment because they are very
25 expert at this, if they have signed the document

1 once, that is probably enough for me.

2 But I think these are details that I am
3 not sure that we need to work out today. There are
4 plenty of things that can be worked out by Russ and
5 his people.

6 DR. KAWAS: Russ and his people gave us
7 this question.

8 DR. KATZ: And we didn't anticipate,
9 necessarily, a vote. But right now, as I
10 understand the program, the initial prescription is
11 filled and then the physician and the patient have
12 to send back a card that says, "Yes; I read this
13 stuff." It was just some sentiment internally for
14 all of that documentation that, "Yes; I have read
15 it. Yes; I understand it," that is to happen even
16 before the first prescription was filled.

17 We are going to get into major problems if
18 we try and apply a different standard to different
19 types of treating physicians, the expert versus the
20 non-expert. Actually, this was one of the issues
21 that I actually did want. A lot of them are not
22 necessarily that critical but this was one of the
23 few that I really wanted some discussion on. There
24 are a lot of other details I think we can take care
25 of.

1 DR. WOLINSKY: But I guess I was saying
2 that, that even the expert would sign it. He just
3 wouldn't have to sign it every time he gives out a
4 new dose.

5 DR. KATZ: No, no, no, no. We don't
6 anticipate that.

7 DR. KAWAS: Once.

8 DR. KATZ: I just meant the first time you
9 give a dose to a particular patient, you would sign
10 a card before the initial prescription was filled
11 for that patient. That is what I think we
12 anticipate.

13 DR. FALKOWSKI: On a patient by patient?

14 DR. KAWAS: I want to make the comment
15 that I am comfortable with the notion of physicians
16 having to sign for this potentially, but I am not
17 comfortable with what was suggested as a mechanism
18 to have it happen by the sponsor and that is
19 sending a drug representative to the physician's
20 office. I really feel very strongly that is not
21 the way this should be done.

22 Dr. Penix?

23 DR. PENIX: This is a question for Dr.
24 Katz. What is the purpose of the physician signing
25 such a document?

1 DR. KATZ: It is just to acknowledge that
2 they have read the material and that they are
3 familiar with its safe use and that they have
4 spoken to the patient about its safe use.

5 Actually, that is a separate question, but it is
6 all combined--that they know how the drug should be
7 used, what its risks are, what the penalties are
8 for inappropriate use.

9 DR. KAWAS: Doesn't it also sort of
10 acknowledge that this is a somewhat unusual drug in
11 some sense because every drug has all these risks
12 in prescribing and we don't ask any physician to
13 sign for all those drugs.

14 I sense on the committee a growing concern
15 that the more drugs we have to sign for, the more
16 uncomfortable they are becoming. But I think,
17 really, it points out to the physician who is
18 signing it that there is something different here.

19 DR. PENIX: I think, also, in that sense,
20 it is important for the physician-information
21 packet that they are aware that this drug is GHB
22 and so, therefore, they may understand why it is
23 required for them to sign this information.

24 I think that is really the bottom line.
25 So I think it would be useful for a treating

1 physician to know what type of drug this is.

2 DR. FALKOWSKI: I would say yes only if it
3 says it is GHB.

4 DR. DYER: Wouldn't CII make that implicit
5 to know that this is a drug that has illegal
6 implications and would be dangerous?

7 DR. KATZ: It is Schedule III.

8 DR. DYER: I am saying it belongs in
9 Schedule II.

10 DR. KATZ: I think that question has been
11 dealt with definitively. It has been legislated as
12 Schedule III by Congress.

13 DR. FALKOWSKI: Right. That was
14 legislated at another time.

15 DR. PENIX: Not to belabor this, but I
16 agree with that drug company's position not to let
17 the patient information--or not include GHB in the
18 patient information. But I think the treating
19 physician should be aware of that.

20 DR. KAWAS: I think that is a very
21 important point because physicians do have a
22 knowledge base of GHB even if it is from the
23 newspaper or whatever to insure that they
24 understand what it is.

25 DR. ROMAN: It also has the legal

1 implications of a physician somewhere who has been
2 prescribing this at a higher rate than expected for
3 that population. He may find his licensing--and a
4 problem if they find that he is prescribing more of
5 these, let's say more than a couple of patients in
6 a year, or whatever it is that delimits.

7 So we need to look into that because there
8 is potentially a risk for medical licensing.

9 DR. KAWAS: Can we see if we have shifted
10 the straw vote from about a 50:50 split to
11 something that is more consensuslike for the
12 agency? On the question, should physicians
13 document that they read the material sent to them
14 before the pharmacy fills the initial prescription,
15 presumably, some of those materials would
16 incorporate the fact that what this drug really is
17 is GHB whether or not it is on the bottle.

18 All in favor?

19 [Show of hands.]

20 DR. KAWAS: Nos?

21 [Show of hands.]

22 DR. KAWAS: And no abstentions. So let
23 the record show that nos were Dr. Richard Penn and
24 Dr. Gerald Van Belle. The remainder of the
25 committee voted yes. No abstentions.

1 Should physicians be required to
2 demonstrate safe use and appropriate dosage
3 preparation to patients before the first
4 prescription and be required to document that it
5 has been accomplished? Do we want to try a straw
6 vote and see if we can keep on going?

7 I think I will make the comment that
8 patient education is too important and sorely
9 underdone in this medical world that that is true
10 for everything. I think, personally, that it would
11 be the hope that, with all drugs, that the
12 healthcare team will insure these demonstrations.
13 I am going to suggest that we do not need to
14 require any specific demonstration or any specific
15 certification of this process.

16 I see some heads going in different
17 directions. Let me get a straw sense on this one.
18 Should physicians be required to demonstrate safe
19 use and dosage? How many people are going to say
20 yes? Straw vote.

21 DR. FALKOWSKI: Is the intent here that it
22 just be demonstrated regardless of who does it,
23 whether it is a nurse or a physician? What is your
24 intent?

25 DR. KATZ: The intent was that--I don't

1 think we necessarily meant the physician but
2 someone responsible in the physician's employ. It
3 shows them how to draw it up and how much your dose
4 is.

5 DR. FALKOWSKI: Should somebody
6 demonstrate how you administer this drug before the
7 patient takes it. So I think that is a good
8 question. Can we take a vote on that?

9 DR. KAWAS: You mean someone in the
10 physician's office should be required to
11 demonstrate it and, in some way, ascertain it. The
12 question is called on that. Who votes yes?

13 DR. VAN BELLE: Before we vote, there is a
14 further addition to that statement here, and it
15 says, "And be required to document that it has been
16 accomplished." Are you intending to have that
17 included as well?

18 DR. KAWAS: I think everything that
19 happens in a physician's office needs to be
20 documented. So, yes. That is why we are writing
21 twenty-seven page H&Ps right now.

22 So we have got one vote yes? Is that all?
23 Dr. Falkowski. No votes?

24 [Show of hands.]

25 DR. KAWAS: Abstentions.

1 [One hand raised.]

2 DR. KAWAS: We have got one abstention
3 with Dr. Simpson and the remainder of the committee
4 voted no.

5 DR. WOLINSKY: Having voted no on that in
6 terms of the office personnel and the physician, it
7 seems to me that it would be advantageous to the
8 company to have first doses shown in the home when
9 medication arrives. This is actually the effective
10 education.

11 What goes on in the physician's office, my
12 bias is, may not be as effective as with home nurse
13 agents.

14 DR. KAWAS: I think we are not going to
15 repeat the restricted prescribing for the drug
16 question. We have gone over that adequately, I
17 hope.

18 But the next one, does the risk-management
19 program assure appropriate prescribing or
20 sufficiently reduce the risks of misuse or
21 overdose. I am not quite sure where to start with
22 this one. Actually, Dr. Katz, which components of
23 the risk-management program are you asking us to
24 comment on?

25 DR. KATZ: That is a fair question. This

1 is sort of a global question, I think. To the
2 extent that you have seen the details of the
3 proposal, is there anything that leaps out at you
4 as being absolutely inappropriate, or is there
5 something that is not there that is a glaring
6 omission that you all believe absolutely should be
7 there?

8 I think that is sort of the sense of the
9 question.

10 DR. PENN: Yes. I don't think the
11 potential problems of the drug are explained to the
12 patient adequately. That is, the narcoleptic
13 patient won't necessarily know that this is an
14 abused drug or if they take it in the wrong way
15 that they can get into a lot of trouble and that
16 the real education has to be to the patient in some
17 manner.

18 I usually think that is the responsibility
19 of the physician to do that, but I don't see that--I mean,
20 we are protecting the patient from knowing
21 what the name of the drug is. We are protecting
22 them from knowing what the real side effects might
23 be.

24 It doesn't say that if you take double the
25 dose, it may have more than double the effect and

1 that you may go into coma and become incontinent
2 and have seizure--well, probably not seizure but
3 stop breathing or something unpleasant like that.

4 I think the emphasis should be on the
5 patient understanding the medication and how to use
6 it. The narcoleptic community suffers enough and
7 has pretty good ways of letting each other know
8 about the disease. Maybe you should use their
9 ability to instruct patients on the proper way to
10 do it and combine it in some way.

11 But that is where I think the glaring
12 error is. This is a drug with very little leeway
13 for dosing and people have to understand they
14 shouldn't use it during the day, for example,
15 because they won't have this period of time off.

16 So I think there is a huge amount to be
17 done. I just don't like to see it done in this
18 mandatory fashion because I don't think it will
19 work. You will get a lot of signed papers, but you
20 won't get the education you need done.

21 DR. KATZ: But I just want to clarify. I
22 understand your reservations about the entire
23 process but, given that there is a document that
24 goes to the patient that ostensibly tells them what
25 they need to know about using the drug safely, you

1 believe that that document that is currently
2 written really needs to be beefed up as far as
3 communicating to the patient what the risks are and
4 how to use it?

5 DR. PENN: Yes; I think that the patient
6 has to know what it is, that it is an abused
7 substance that potentially can be abused. It would
8 be like our not telling patients who use oxycodone
9 not to chop it in two and take it. That gets them
10 into trouble and they ought to know about that.

11 So there is a lot of education that has to
12 be done with this medication.

13 DR. FALKOWSKI: I think I already
14 addressed this question by saying I think the word
15 gammahydroxybutyrate should appear for patients and
16 particularly for the physicians, the prescribing
17 physicians. What is the secret? The way to have a
18 drug come into the market when it is already a
19 substance of abuse is not to pretend it doesn't
20 exist and not even call it what it is.

21 I don't think that is an informed approach
22 for physicians to know what it is.

23 DR. LACEY: Just as one presenter, and I
24 don't remember who, today gave us the common names,
25 the club names and everything. I think the patient

1 actually should be provided with as much of that
2 information as possible. To not want to put it on
3 the printed book or something because it is exposed
4 to someone else is one thing. But the patient
5 should be provided as much information as possible
6 to know what they are dealing with.

7 DR. KAWAS: Any other comments before we
8 move on to the next question? Jerry?

9 DR. VAN BELLE: Let me just make a
10 comment. I agree with that and, also, from the
11 practical point of view, we have already heard this
12 afternoon that the narcolepsy website network is
13 just far flung. If this is going to be approved by
14 the FDA, the word will be out in the next fifteen
15 minutes.

16 So to play coy and not put it on one set
17 of labels is just not going to work.

18 DR. ROMAN: I completely agree. The USA
19 Today had the title, "Company wants date-rape drug
20 approved for a sleep-disorder treatment." If that
21 is in the newspapers--

22 DR. FALKOWSKI: This question is--it is my
23 understanding, and I asked for clarification for
24 this prior to the beginning of this meeting today--that we
25 are voting here on specific questions. Is

1 the determination of approval made upon FDA's
2 consideration of what we talked about today?

3 DR. KATZ: Well, sure.

4 DR. FALKOWSKI: Is it made today?

5 DR. KATZ: Is the decision about what to
6 do with the application made today? Absolutely
7 not, no. Your opinions are all advisory. We take
8 them very seriously and then we go back and we
9 discuss it internally and we come to a decision, by
10 the PDUFA due date.

11 DR. KAWAS: Going to the next question,
12 can I ask, Dr. Katz--tell us what do you mean by
13 certification and certification of physicians for
14 prescribing?

15 DR. KATZ: There was some sense,
16 internally, on the part of some people that
17 physicians should--first of all, that it might be
18 restricted to use only by sleep experts or
19 physicians would have to somehow take a test to
20 show that they know about narcolepsy, that sort of
21 thing, that they are appropriate prescribers in
22 some sense.

23 DR. KAWAS: So we are not talking about
24 the same thing that we were talking about
25 previously, documenting that they have read

1 whatever materials with the first prescription that
2 they write?

3 DR. KATZ: It is something more than that.

4 DR. KAWAS: Okay. Let's take a straw vote
5 on that. I think we can get past that one
6 potentially fast, then. We are talking about more
7 than just documenting that you have seen materials.
8 Should certification of physicians, or some other
9 restrictions, for prescribing Xyrem be required?
10 Straw vote. How many people think yes? How many
11 people think no? How many people are abstaining?

12 Let the record show that Dr. Wolinsky
13 abstained. I am not sure, but I need to know why.

14 DR. WOLINSKY: Well, I am internally
15 conflicted on this. When I say conflicted, I don't
16 mean that I have some stockholdings anywhere but
17 that I am--

18 DR. KAWAS: Anyone knows when they use
19 that word they have time on the floor.

20 DR. WOLINSKY: I haven't come to a final
21 decision in my own mind, but I would lean towards,
22 I guess, certification of physicians when the
23 circumstances are special. That doesn't actually
24 keep patients from assessing care. It may mean
25 that they have to be diagnosed in an appropriate

1 situation and then can be cared for by a physician
2 who is willing to educate themselves about how to
3 best use the drug.

4 I know that most of my colleagues won't
5 like this but I think that this is where we have to
6 go if medicine is to maintain credibility with an
7 increasingly complex medical world that we live in.

8 DR. KAWAS: Now to go backwards to No. 5,
9 which the questions deal with safe use by the
10 patient. Should the patient sign an informed
11 consent form before receiving the initial shipment
12 of the drug? Straw vote. How many people think
13 yes? How many people think no?

14 I won't ask Dr. Penn.

15 DR. PENN: I am worried about the medical-legal
16 implications of informed consent in this
17 situation. What does informed consent mean? Who
18 signs it? All the things we get to in the
19 controlled trials and that we deal with daily in
20 the university setting.

21 It seems to me that, unless we work out
22 the details, I can't feel comfortable voting for
23 it.

24 DR. KAWAS: Actually, I abstained on the
25 straw vote. My concern, and maybe my question is,

1 informed consent about what? Presumably, we are
2 talking about some version of the education that we
3 have said they need to have. So is this just an
4 acknowledgment of that education? What is it we
5 want to make sure that they are informed about and
6 get a signature to verify that?

7 DR. KATZ: Usually, informed consent is--it mostly
8 emphasizes the potential risks. There
9 are drugs, of course, that have informed consent as
10 part of their approval. So that was the question.
11 Given the potential risks of this particular
12 treatment, do people think that patients need to
13 sign an informed consent.

14 It is unusual, but there certainly are
15 precedents for it.

16 DR. PENIX: I think informed consent does
17 imply a certain medical-legal situation but,
18 perhaps, a contract like they use in many pain-management
19 centers so that the patients acknowledge
20 the problems with the dispensing of the drug and
21 that type of thing. So maybe a contract would be a
22 better idea than an informed consent.

23 DR. KATZ: Again, we put it on the list
24 because it was raised internally at several
25 discussions that we had. It doesn't mean that we

1 necessarily, as a group, endorse it or most of us
2 think it is a good idea. It was an option. We
3 wanted to see what you thought about it.

4 DR. WOLINSKY: Call that question again.

5 DR. KAWAS: Does that mean you want to
6 change your vote?

7 DR. WOLINSKY: I would like to withdraw my
8 yes because this is much more complicated than
9 immediately meets the eye and goes beyond what we
10 really need, given all the other things that are
11 already in this package.

12 DR. KAWAS: Okay. Do we need any more
13 discussion before we call the question the second
14 time? Any other comments people want to make?
15 Should patients sign an informed-consent form
16 before receiving the initial shipment of the drug.
17 All who think yes, raise their hand.

18 [Show of hands.]

19 DR. KAWAS: Let's go around the table and
20 identify the yes votes.

21 DR. SIMPSON: Simpson.

22 DR. FALKOWSKI: Falkowski.

23 DR. ROMAN: Roman.

24 DR. LACEY: Lacey.

25 DR. VAN BELLE: Van Belle.

1 DR. KAWAS: All who think no.

2 DR. WOLINSKY: Wolinsky.

3 DR. KAWAS: Kawas.

4 DR. PENN: Penn.

5 DR. PENIX: Penix.

6 DR. KAWAS: Okay; we are set there.

7 Furthermore, should the patients be
8 required to return a registry form before receiving
9 the first shipment? Now, I assume that a registry
10 form that we are talking about is kept by the
11 sponsor?

12 DR. KATZ: Again, this analogous to what
13 we talked about with the physician. The idea here
14 was right now, the plan calls for such a form to be
15 submitted after the first prescription is filled,
16 that they have read the materials, they have
17 received them and they have read them.

18 The question here was just whether or not
19 you think that all has to happen before they even
20 get the first dose.

21 DR. KAWAS: To my mind, that simplifies it
22 considerably, then. Straw vote. How many people
23 think yes, it should be done before not after or
24 with the first dose.

25 DR. SIMPSON: Is this in addition to the

1 consent form?

2 DR. KAWAS: This is different than the
3 consent form; yes.

4 DR. SIMPSON: So, would it be in addition?
5 I mean, if they did the consent form, would they
6 need to fill out another form and send it in?

7 DR. KAWAS: I am not sure I am the right
8 person to answer that because I don't know whether
9 or not there is going to be a consent form. But
10 maybe Dr. Katz could--

11 DR. KATZ: We asked it separately. They
12 are two different things, although they are very
13 closely related, I suppose. If you sign a informed
14 consent that says, "I know what the risks are.
15 "The card--what do we call it--a registry card.
16 That presumably could be something that says, "I
17 have read the material. I assert that I know how
18 to draw the appropriate dose up. I know how to mix
19 it. I know that I have to mix both doses first."

20 They have a sense of how it is supposed to
21 be taken. So you would imagine it would have
22 different information, could have different
23 information, than an informed-consent form.

24 DR. KAWAS: So the registry, actually,
25 has--it is not just a name, address, serial number

1 of a person who is getting the drug. That is not
2 what we are talking about in the registry form? We
3 are talking about--

4 DR. KATZ: I think the idea here was, as I
5 said before, whether or not, analogous to the
6 question with regard to the physicians, that they
7 have read the materials, what I intended, anyway,
8 for this question was the exactly analogous
9 situation for the patient.

10 Should the patient have to send the form
11 back. It would be a registry form, I suppose, in
12 terms of who they are, but the pharmacist already
13 knows who they are so they get into the registry
14 that way, I suppose.

15 But whether or not they have read the
16 material and they understand what the risks are and
17 they understand how to take the appropriate dose,
18 just before the first dose.

19 DR. KAWAS: Okay. Now I think we can
20 better take a straw vote.

21 DR. SIMPSON: I just wanted to say I
22 thought the consent form was that.

23 DR. KAWAS: But, having rephrased it for
24 us, I think essentially what we are saying is now
25 we have said that we want the physicians to certify

1 that they have read, know and understand some of
2 the issues, the question is, should we ask the
3 patients to do the same thing.

4 All who think yes, raise your hand.

5 [Show of hands.]

6 DR. KAWAS: And nos?

7 [Show of hands.]

8 DR. KAWAS: I think we have got a bunch of
9 abstentions, mostly. Would you like to comment on
10 your thinking?

11 DR. PENIX: I think it is just pretty
12 complicated. I am not sure what a registry is
13 going to do, what the drug company is going to do,
14 with the information, who should keep the
15 information. There are a lot of different issues,
16 so I guess, in the late hour, I am going to
17 abstain.

18 DR. LACEY: I would think these two things
19 could be combined into one some way or the other.
20 If they can't, it is just getting to be too
21 complicated in terms of all the forms and whatever,
22 so they are losing interest in it.

23 DR. KAWAS: Are you talking about the
24 patient or the committee? No; I think that
25 something really important was just said here,

1 actually. I think that if we put too many layers
2 that nobody is going to pay attention to any single
3 layer here. The whole idea is to do exactly the
4 opposite, to have both the patients and the
5 physicians taking this seriously.

6 Anybody can write in a patient's chart, "I
7 have demonstrated how to do a safe dosage through
8 the patient," and signed their initials. That only
9 takes a few seconds. Getting them to spend the
10 time to do it in the office is quite a different
11 thing.

12 Obviously, what is more important is what
13 is actually done and not what is certified. But
14 let me see if I am getting the flavor from this
15 committee that, in general, they think there should
16 be one certification, registration, informed-consent process
17 or whatever for both physician and
18 for patient. Is that the gist of what we have been
19 saying?

20 All who agree with that statement, straw
21 vote, yes. All who think no.

22 DR. PENN: I abstain.

23 DR. KAWAS: Oh, gosh. And Dr. Penn
24 abstains and we are not going to even bother
25 finding out why.

1 Dr. Katz?

2 DR. KATZ: Given the late hour and the
3 list that still remains, I don't think we really
4 need much in the way of discussion or even a vote,
5 or a straw vote, on any of the other remaining
6 issues.

7 I would ask, though, the committee members
8 to just sort of quickly glance at it, or not, as
9 you wish. But, again, if there is anything that
10 strikes you as being a glaring omission in the
11 program as proposed and as amended by your previous
12 votes, just sing out. But I don't think we need
13 any detailed discussion of the rest. I think we
14 can sort of work it out.

15 DR. KAWAS: I would like to make the
16 comment that, at least on the postmarket
17 surveillance, I think there should be required
18 postmarketing reporting, surveillance, monitoring.

19 DR. PENIX: In addition to the usual
20 adverse effects, of course.

21 DR. KAWAS: Are there any other comments
22 or thoughts from the committee particularly on the
23 items we didn't specifically discuss like central
24 pharmacy, postmarketing surveillance or other
25 recommendations on protecting--

1 DR. SIMPSON: I guess there was just one
2 issue brought up about who would police the
3 policemen.

4 DR. KAWAS: You want to more specific in
5 which policemen we are talking about?

6 DR. SIMPSON: The issue was whether the
7 drug companies should be policing the correct usage
8 of the drug and then, if that were the case, who
9 would be policing that the drug company were doing
10 it right. And, if the physicians are supposed to
11 be making sure that the patients are doing it
12 right, and so on. That is what I mean. There is
13 layer on layer here.

14 DR. KAWAS: Let's start with the first
15 layer about if there is a surveillance or whatever
16 from the company.

17 DR. KATZ: Again, in some sense, we are
18 always in a position to oversee what the companies
19 do in terms of meeting their appropriate reporting
20 requirements and this sort of thing.

21 I think there is an understanding that
22 what comes out of this registry and the experience
23 will be reported to us. It will have to be
24 reported to us. We will be working in close
25 cooperation with the company to make sure that this

