

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE

Wednesday, June 6, 2001

8:15 a.m.

Holiday Inn
Bethesda, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting
Chairman
Sandra Titus, Ph.D., Executive Secretary

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Pippa Simpson, Ph.D.
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NON-VOTING:

Christine A. Sannerud, Ph.D.
Jerry Frankenhcim, Ph.D.
Jo-Ellen Dyer, Ph.D.

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Ronald Chervin, M.D.
Christian Guilleminault, M.D.

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.
John Feeney, M.D.
Deborah B. Leiderman, M.D.

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1 P R O C E E D I N G S

2 Call to Order and Introductions

3 DR. KAWAS: Good morning, everyone, and
4 welcome to the Wednesday, June 6, 2001 meeting of
5 the Peripheral and Central Nervous System Advisory
6 Committee. My name is Claudia Kawas, and I think
7 we can begin with introductions, please, perhaps
8 over by Dr. Temple's side.

9 DR. TEMPLE: Bob Temple, I am the Office
10 Director.

11 DR. KATZ: Russ Katz, Division of
12 Neuropharmacological Drug Products, FDA.

13 DR. FEENEY: John Feeney, neurology team
14 leader, FDA.

15 DR. MANI: Ranjit Mani, medical reviewer,
16 Neuropharm., FDA.

17 DR. LEIDERMAN: Deborah Leiderman,
18 Director, Controlled Substance Staff, FDA.

19 DR. SIMPSON: Pippa Simpson, University of
20 Arkansas Medical Sciences, biostatistician.

21 DR. FALKOWSKI: Carol Falkowski, drug
22 abuse researcher, Hazelden Foundation.

23 DR. ROMAN: Gustavo Roman, Professor of
24 Neurology at the University of Texas, San Antonio.

25 DR. WOLINSKY: Jerry Wolinsky, Professor

1 of Neurology, University of Texas, Houston.

2 DR. TITUS: Sandy Titus, FDA, the
3 administrator of the Peripheral and Central Nervous
4 System Committee.

5 DR. PENN: Richard Penn, neurosurgeon at
6 the University of Chicago.

7 DR. LACEY: Ella Lacey, professor emerita,
8 Illinois University, Carbondale, Illinois.

9 DR. VAN BELLE: Gerald Van Belle,
10 Department of Biostatistics, from the University of
11 Washington.

12 DR. PENIX: LaRoy Penix, Associate
13 Professor of Neurology at Moorehouse School of
14 Medicine.

15 DR. SANNERUD: Christina Sannerud, Drug
16 and Chemical Evaluation Section, Drug Enforcement
17 Administration.

18 DR. DYER: I am Jo Dyer, with the
19 University of California, San Francisco and the San
20 Francisco Poison Control System, California.

21 DR. FRANKENHEIM: Jerry Frankenheim,
22 pharmacologist, National Institute on Drug Abuse.

23 DR. KAWAS: Today we have met to discuss
24 the consideration of Xyrem, proposed to reduce the
25 incidence of cataplexy and to improve the symptom

1 of daytime sleepiness for persons with narcolepsy.
2 The main focus of the deliberations will also be on
3 risk management issues.

4 If we could ask Dr. Titus to begin with
5 the conflict of interest statement?

6 Conflict of Interest Statement

7 DR. TITUS: Before I begin the conflict of
8 interest statement, I just want to announce that we
9 have two people on line with us, Dr. Chervin and
10 Dr. Guilleminault. They are both in a room
11 listening to us and will participate with us on the
12 mikes.

13 The following announcement addresses the
14 issue of conflict of interest with regard to this
15 meeting and is made a part of the record to
16 preclude even the appearance of such at this
17 meeting.

18 The special government employees
19 participating in today's meeting have been screened
20 for interests in Orphan Medical's Xyrem and for
21 interests in the products and sponsors deemed by
22 the agency to be competing. Based on the agency's
23 review of each participant's response to the
24 conflict of interest screening, it has been
25 determined that there is no potential for a

1 conflict of interest with regard to this meeting.

2 With respect to FDA's invited guests,
3 there are reported affiliations which we believe
4 should be made public to allow the participants to
5 objectively evaluate their comments.

6 Dr. Ronald Chervin would like to disclose
7 for the record that he has a contract with Cephalon
8 to study Provigil, but not for use in narcolepsy.
9 He is the principal investigator, however, no funds
10 from Cephalon, present or past, have contributed to
11 his personal salary and none have been made
12 available for his non-research related use.
13 Further, in previous years Dr. Chervin was a
14 co-investigator with Cephalon in a narcolepsy
15 clinical trial.

16 Christian Guilleminault has been the
17 administrator of the Sleep Disorder Clinic in Palo
18 Alto, California, where the study of Xyrem was
19 performed by a team of researchers.

20 In the event that the discussions involve
21 any other products or firms not already on the
22 agenda for which an FDA participant has a financial
23 interest, the participants are aware of the need to
24 exclude themselves from such involvement and their
25 exclusion will be noted for the record.

1 With respect to all other participants, we
2 ask in the interest of fairness that they address
3 any current or previous involvement with any firm
4 whose products they may wish to comment upon.
5 Thank you.

6 DR. KAWAS: Thank you very much, Dr.
7 Titus. We will begin with Dr. Russell Katz, of the
8 FDA, who will give us the FDA overview of the
9 issues. I want to point out to the committee
10 members that they have much of the materials that
11 they will be seeing during this meeting in front of
12 them.

13 FDA Overview

14 DR. KATZ: Thanks, Claudia. First, I
15 would like to welcome the committee back. You were
16 here just a few months ago so I appreciate your
17 coming back so soon.

18 We have a number of invited guests who are
19 augmenting the committee today, and many of them
20 are experts in the evaluation of issues related to
21 drug abuse, and I would just like to welcome them,
22 in particular Drs. Simpson, Sannerud and
23 Frankenheim.

24 We have two other experts who will
25 actually be speakers later this morning. Dr. Dyer

1 will speak on her experience with GHB use and
2 misuse in cases she has seen, and Dr. Falkowski
3 will talk about the epidemiology of GHB abuse in
4 the United States.

5 Finally, as Dr. Titus mentioned, we have
6 two acknowledged experts in sleep disorders who are
7 attending the annual sleep meetings in Chicago, but
8 who have agreed to sit in a hotel room for however
9 long this takes and participate by phone. So, Drs.
10 Guilleminault and Chervin, wherever you are, thank
11 you. Thanks for being here.

12 As you know and as you have heard, today
13 we will ask you to discuss NDA 21-196, which was
14 submitted by Orphan Medical for the use of Xyrem,
15 gamma hydroxybutyrate or better known as GHB, for
16 the treatment of cataplexy and excessive daytime
17 sleepiness in patients with narcolepsy.

18 GHB is a simple molecule and it is
19 ubiquitous in mammalian tissues, its function
20 though is not really well known. Its relevant
21 regulatory history goes back to about 1990, and
22 prior to that date it was freely available in
23 health food stores. But in 1990 the agency began
24 to receive reports of widespread recreational use
25 in a number of different types of folks, for a

1 number of different types of reasons, or GHB and
2 began to get numerous reports of serious adverse
3 events associated with its misuse.

4 It was not entirely clear that all of
5 these events were necessarily related to GHB. It
6 was difficult to interpret some of these reports
7 because there were concomitant medications that
8 were unreported and it wasn't entirely clear
9 whether or how much GHB was in a particular
10 preparation that someone had taken. Those sorts of
11 issues made it difficult to completely interpret
12 the reports, but many of the reports were of events
13 that were known to be consistent with GHB's effect
14 as a potent CNS depressant, including things like
15 respiratory depression, coma and other decreased
16 levels of consciousness. So, it was reasonable to
17 believe that GHB was at least in part responsible
18 for some of these reports.

19 As a result of these reports, the agency
20 withdrew GHB from health food shelves and made it
21 illegal to use. However, illicit use continued and
22 continues to this day, not only with GHB but with
23 two related drugs which are precursors, GBL and
24 1,4-butanediol, and there have been similar reports
25 of serious adverse events associated with the use

1 of those products.

2 So, against this background of use, the
3 investigation of GHB as a treatment for cataplexy
4 began. Based on the results of a single trial
5 performed by the sponsor and their commitment to
6 perform additional trials, the sponsor was granted
7 a treatment IND in December of 1998. For those of
8 you unfamiliar with a treatment IND, it is
9 basically a mechanism to permit use of an
10 investigational drug outside the context of a
11 controlled trial for a serious disease for which
12 there aren't other available treatments. It is
13 usually granted relatively late in the development
14 of a drug so that by the time you grant it you have
15 some reasonable idea, based on controlled data,
16 that the drug is probably effective and reasonably
17 well tolerated.

18 Just another relevant piece of history, in
19 2000 Congress passed a law which placed GHB in
20 Schedule I and also placed it into Schedule III for
21 any approved uses that may be granted.

22 The NDA that we are discussing today was
23 submitted in September of 2000 by the company, and
24 it contains the results of four controlled trials
25 which the sponsor believes establish substantial

1 evidence of effectiveness for cataplexy and
2 excessive daytime sleepiness in patients with
3 narcolepsy. It also contains, obviously, safety
4 experience.

5 I just want to talk about the safety
6 experience for just a little bit. As you know from
7 the briefing documents, much of the safety data in
8 the application was not generated by the company
9 but by an individual investigator under his own
10 individual investigator IND. This is Dr. Scharf,
11 and he is an acknowledged expert in the use of GHB
12 and he has been treating patients under his IND for
13 about 16 years. His data comprise almost 30
14 percent of the patient safety database in the NDA.
15 If one looks at patient time, his experience
16 constitutes about 70 percent of the total patient
17 exposure.

18 As part of a routine investigation of the
19 NDA to look at source documents, the agency
20 investigators found that they were unable to locate
21 some critical source documents of Dr. Scharf's IND,
22 and it was difficult to confirm the sponsor's
23 submission of Dr. Scharf's data. However,
24 subsequent to that, Dr. Scharf has made extensive
25 efforts to provide the additional source documents

1 and agency investigators have reinspected that
2 data. I believe the conclusion of that
3 investigation is that we find that the records, for
4 the most part, do support the sponsor's
5 descriptions of Dr. Scharf's data. And, we believe
6 we can make certain statements about that data at
7 this point.

8 We were particularly interested in the 80
9 or so patients that Dr. Scharf treated that did not
10 move on into the company's treatment IND. He
11 treated a total of 143, or thereabouts, patients,
12 60 of whom went into the sponsor's treatment IND.
13 So, we had a good idea of what was happening to
14 those patients but there were about 80 that didn't
15 and who were basically discontinued from treatment
16 under Dr. Scharf's own IND.

17 So, except for a handful of patients, we
18 believe we know why those 80 patients discontinued
19 and their status. I believe we can say reasonably
20 comfortably say that nothing catastrophic that we
21 don't know about happened to those patients but,
22 unfortunately, we have relatively little
23 well-documented data regarding other less serious
24 adverse events in that cohort of 80. Other than
25 patient diaries, we have essentially no

1 documentation about exactly what dose those
2 patients took and for how long.

3 I have gone into this at some depth
4 because the safety experience in the NDA is
5 relatively small as compared to a typical NDA, and
6 that is by agreement. This is an orphan product.
7 Based on the sponsor's estimated prevalence of
8 cataplexy of about 25,000, it received orphan
9 designation and one wouldn't necessarily expect
10 that a safety database of a typical size, which is
11 somewhere in at least 10000 to 2000 patients in the
12 typical NDA, would be submitted in an orphan
13 application. So, we agreed with the sponsor that
14 about 500 patients treated for appropriate
15 durations, at appropriate doses would be
16 acceptable.

17 But, given the relatively small database
18 and some of these residual questions about a
19 reasonable proportion of it, that is to say Dr.
20 Scharf's data, that may take on some additional
21 meaning and we would like you to think about that
22 as the day goes on.

23 In addition to the safety and the
24 effectiveness data which is required in an NDA of
25 course, the sponsor has proposed a detailed risk

1 management program, and that has three goals: to
2 inform patients and physicians about the risks of
3 GHB; to minimize the risks to those patients; and
4 also to minimize the likelihood that subjects for
5 whom the drug has not been prescribed will be
6 exposed to it. This latter point not only refers
7 to diversion and its use illicitly by folks who
8 shouldn't be taking it, but also to the accidental
9 use of GHB in the home, perhaps by small children,
10 and you will hear how GHB is administered and what
11 form it is prepared in, and we think that is a
12 potential risk. So, we would like you to think
13 about that as the day goes on too.

14 As far as the risk management program, you
15 will hear about it in great detail from the company
16 but, in brief, it consists of a couple of sort of
17 major components. One is that the product will be
18 made available through a central pharmacy and will
19 be shipped directly to the patient at home.
20 Physicians and patients will also receive detailed
21 materials about the risks and the appropriate use
22 of the drug after the first prescription is filled.
23 Actually, they will receive those materials
24 initially and all subsequent refills of
25 prescriptions will be contingent upon patients and

1 physicians documenting that they have read these
2 materials, and they understand the risks and how to
3 take the drug appropriately. .

4 All patients and physicians will be
5 entered into a registry, and there will be close
6 surveillance instituted to ensure that untoward
7 events are minimized, for example, to ensure that
8 patients don't go from doctor to doctor trying to
9 get refills of prescriptions that are
10 inappropriate.

11 So, with these data and against the
12 background of misuse of GHB out in the population
13 at large, we bring you today's application and we
14 will ask you to formally vote on three questions.
15 One is whether or not you think that substantial
16 evidence of effectiveness has been submitted for
17 the indications that the sponsor has proposed, that
18 is to say, cataplexy and excessive daytime
19 sleepiness in patients with narcolepsy. If you
20 find that they haven't, we would be very interested
21 to know whether or not you feel that substantial
22 evidence has been submitted for either of those two
23 indications.

24 While you listen to the effectiveness
25 data, we would like you to pay particular attention

1 to the question of dose and for which dose you
2 think evidence of effectiveness has been submitted.
3 If you find there is substantial evidence of
4 effectiveness for a particular indication, we need
5 to ask you whether or not GHB can be considered
6 safe in use given appropriate labeling. Now, we
7 are not going to discuss necessarily the specifics
8 of proposed labeling but, nonetheless, we ask you
9 to think of it in that context.

10 Again, in assessing the safety of the
11 product, we ask you to concentrate on at least the
12 question of what dose you have found to be
13 effective and whether or not there is sufficient
14 safety experience at that dose for the drug to be
15 approved.

16 Finally, we want to take a formal vote on
17 the question of whether or not you think it is
18 required or should be required that the drug be
19 approved only with the risk management program of
20 some type, not necessarily the one specifically
21 proposed by the company. Obviously, the company
22 has proposed a risk management program but we need
23 to know whether or not you think it is mandatory
24 that it be approved with such a program in place.
25 If you do, we have a number of questions that we

1 would like you to discuss -- not necessarily take a
2 formal vote on but discuss with regard to a risk
3 management program and some of the provisions that
4 the sponsor has proposed.

5 There are some aspects of the program that
6 they have proposed that we would like you to pay
7 particular attention to and discuss. For example,
8 there is some considerable sympathy in the agency
9 for including a provision in the risk management
10 program that would restrict the use of the drug to
11 patients with whatever indication you believe has
12 been supported, that is to say, to restrict as much
13 as possible off-label prescribing. That is one
14 possibility.

15 There is also some enthusiasm internally
16 for physicians and patients to document that they
17 have reviewed the relevant materials before the
18 first prescription is filled. So, we would like
19 you to think about that as well as we talk about
20 the risk management program.

21 So, as you can see from the agenda, the
22 company is going to present the safety and
23 effectiveness data, after which Dr. Mani, from the
24 Division, will come up and present briefly some of
25 our views about the data you will have just heard.

1 Specifically, I believe we have some different
2 views about the evidence submitted for establishing
3 a claim for excessive daytime sleepiness in
4 narcolepsy, and there may be other additional
5 safety issues that we would like to bring up at
6 that time, in particular the question of an event
7 that has been called sleep walking.

8 I think with that as background, I will
9 turn it back to Dr. Kawas. Thank you.

10 DR. KAWAS: Thank you, Dr. Katz. Orphan
11 Medical presentation is to follow. Dr. David
12 Reardan, Orphan Medical?

13 Orphan Medical Presentation

14 DR. REARDAN: Hi. Good morning. Good
15 morning, ladies and gentlemen, members of the
16 committee and FDA.

17 [Slide]

18 My name is David Reardan, and I represent
19 Orphan Medical as head of regulatory affairs.
20 Orphan Medical is a small, 60-person firm,
21 dedicated to the development of orphan drugs. We
22 have obtained marketing approval for six orphan
23 products from FDA since we were founded, in 1994.

24 The firm became involved with Xyrem when
25 approached by FDA that same year, and Xyrem was

1 designated an orphan drug in 1994. Today we will
2 share with you the data that has been collected
3 with respect to the efficacy and safety since our
4 IND was submitted, in 1996.

5 [Slide]

6 Dr. Mignot, director of the Narcolepsy
7 Institute at Stanford University, will present a
8 picture of a narcoleptic patient and the serious
9 medical need such patients have for new therapeutic
10 treatments.

11 Dr. Houghton is the chief medical officer
12 and chief operating officer at Orphan Medical, and
13 he will present next on the efficacy that has been
14 collected. Dr. Houghton was chair of anesthesia
15 and critical care in Australia.

16 Dr. Black, director of the Stanford Sleep
17 Clinic and an investigator for several trials, will
18 share with you the EEG pharmacology of Xyrem. Dr.
19 Houghton will then present the safety data and
20 finish up with a benefit/risk assessment.

21 Following presentations by two FDA invited
22 speakers with respect to GHB abuse, Dr. Balster,
23 director of the Institute for Drug and Alcohol
24 Studies at the Medical College of Virginia, will
25 share with you his views on abuse liability.

1 Since there is public abuse of GHB and its
2 analogs, the company has developed a risk
3 management program for Xyrem that will be presented
4 by Patti Engel, our vice president of marketing and
5 sales.

6 [Slide]

7 In addition to those presenting today, the
8 following experts are available in the audience to
9 answer questions from the committee or FDA: Dr.
10 Emsellem, Dr. Hagaman and Dr. Ristanovic are all
11 directors of their respective sleep institutes, and
12 have been investigators in our clinical trials.
13 Dr. Okerholm is a consultant in the area of
14 pharmacokinetics and drug metabolism; Dr. Reno in
15 the area of toxicology; and Dr. Richard Trout, who
16 is a professor emeritus in statistics from Rutgers,
17 is here if there are any statistical questions.

18 [Slide]

19 This is the chemical structure of sodium
20 oxybate, more commonly known as gamma
21 hydroxybutyrate, or GHB. Notice that it is a
22 simple 4-carbon hydroxy fatty acid and, as such,
23 quite easy to synthesize. In fact, kits have been
24 illegally promoted on the Internet for its
25 manufacture. If an amino group were to replace

1 this alcohol functional group at position 4, you
2 would have GABA, gamma aminobutyric acid, another
3 CNS active chemical. Oxybate is a natural compound
4 in the human body.

5 [Slide]

6 Gamma hydroxybutyrate was first discovered
7 in the 1960's by Dr. Labore, in France, and was
8 investigated as an analog for GABA. It was found
9 to have hypnotic properties and was first approved
10 in France, and later a few other countries of
11 Europe, as an adjunct in anesthesia. It was used
12 in labor and delivery for quite a few years. The
13 injectable form is still available today in parts
14 of Europe.

15 In the 1970's initial work was begun in
16 Canada to test its properties in narcolepsy.
17 Following initial promise for use in patients with
18 narcolepsy two controlled trials were conducted by
19 independent investigators, one in the U.S. and one
20 in The Netherlands. In 1994, due to the promising
21 investigator trials, FDA Office of Orphan Products
22 approached Orphan Medical to consider the compound
23 for development.

24 Since there was no patent protection and
25 the market was very small, no other firms were

1 willing to consider the development of GHB for
2 narcolepsy at the time. Orphan Medical agreed to
3 sponsor this medication. Our new drug application
4 was submitted in October of 2000 and was designated
5 by FDA for priority review.

6 The clinical development has been fairly
7 straightforward and all controlled trials conducted
8 to date have shown sodium oxybate to be effective
9 and safe for the treatment of narcolepsy. This
10 project has been made more difficult because of the
11 abuse situation.

12 [Slide]

13 Let me explain why Xyrem is not going to
14 be a factor in the abuse of GHB and its precursors.
15 Orphan Medical was aware abuse existed at the time
16 the company agreed to sponsor development of Xyrem.
17 At this same time, Internet was burgeoning. Due to
18 its ease of synthesis and ready availability of
19 precursor chemicals, GHB was initially an easy
20 target for promoters of illegal drugs.

21 But GHB is not the only problem. GBI, and
22 1,4-butanediol are precursor chemicals that can be
23 easily converted to GHB and are, in fact, converted
24 to GHB in the human body. These precursors are
25 widely available as bulk chemicals and are being

1 illegally used in the United States, and the abuse
2 problem is growing.

3 Federal legislation, enacted in 2000,
4 helped to control the availability of GHB and GBL
5 but not 1,4-butanediol and other precursor
6 chemicals that can be used for the same purpose.
7 In many states, even with GHB schedules, GBL and
8 1,4-butanediol are not controlled.

9 We believe that approval of Xyrem for use
10 by patients with narcolepsy will not add to the
11 general abuse problem of GHB and its numerous
12 precursors.

13 [Slide]

14 The proposed indication for which we are
15 asking FDA for marketing approval is to reduce the
16 incidence of cataplexy and to improve the symptom
17 of daytime sleepiness in patients with narcolepsy.

18 [Slide]

19 Narcolepsy fits the definition of orphan
20 disease in the United States, with less than
21 200,000 patients. There are estimated to be about
22 135,000 patients, of which 55 percent are
23 diagnosed, with about 24,000 seeking treatment for
24 cataplexy.

25 [Slide]

1 I would now like to introduce you to Dr.
2 Emmanuel Mignot, from Stanford. Dr. Mignot has
3 been widely published in this area and is
4 considered one of the premiere international
5 experts on narcolepsy. He has not participated in
6 any of our clinical trials.

7 Medical Need

8 DR. MIGNOT: It is my privilege to talk to
9 you today about narcolepsy. I have been working on
10 narcolepsy for about 15 years, both at the level of
11 basic research as well as clinical care. I am a
12 medical doctor and I see patients with narcolepsy.

13 [Slide]

14 I am going to try to summarize in a few
15 minutes really a lot of data about narcolepsy and
16 how it impacts people.

17 [Slide]

18 First, I would like to start briefly by
19 reviewing the symptoms of narcolepsy. Narcolepsy
20 is usually associated with 5 different symptoms.
21 The most disabling and the most problematic in
22 patients with narcolepsy is sleepiness. Patients
23 with narcolepsy are sleepy all the time; tired;
24 they have sleep attacks; they cannot stay awake for
25 a long period of time, and it is usually why they

1 come to see the doctor. They just cannot live a
2 normal life. Especially in work conditions, as you
3 probably know, it is very difficult -- you have to
4 be awake all day long and it is a major problem in
5 narcolepsy.

6 Now, it is not enough to diagnose
7 narcolepsy. Narcolepsy is not just sleepiness and
8 there are a lot of other medical conditions that
9 are associated with sleepiness. Patients with
10 narcolepsy also have a series of symptoms that
11 correspond to the fact that they go very quickly
12 into rapid eye movement sleep. As probably many of
13 you know, rapid eye movement sleep is a stage of
14 sleep that only occurs 1.5 or 2 hours after you
15 fall asleep where you are actively dreaming but
16 your body is completely paralyzed and you have
17 these rapid eye movements.

18 Patients with narcolepsy go into REM sleep
19 extremely quickly, sometimes in a few minutes, and
20 that leads to a series of symptoms where patients
21 sometimes are half way through REM sleep, being
22 still awake. Consequently, they may experience odd
23 symptoms that we call the dissociated REM sleep
24 event, abnormal REM sleep event. Those are
25 cataplexy, hypnagogic hallucinations and sleep

1 paralysis.

2 An example is cataplexy. When a patient
3 gets emotionally excited, typically when they are
4 happy, they meet a good friend, sometimes when they
5 are angry but most often when they are joking, in a
6 nice environment and happy about something, they
7 may feel suddenly weak; they become paralyzed;
8 sometimes they fall down to the ground, completely
9 paralyzed and they cannot move. In very rare cases
10 they may even go into REM sleep. We believe
11 somehow being emotionally excited stimulates the
12 paralysis of rapid eye movement sleep that every
13 one of us experiences during sleep, except that in
14 patients with narcolepsy it may occur in the middle
15 of the day in response to emotion.

16 Also, when they fall asleep they sometimes
17 have hallucinations because they go so quickly into
18 REM that sometimes they dream while they are still
19 awake. I remember a patient, for example, who
20 every night would fall asleep and he would see
21 someone coming and strangling him. Or, they may
22 hear people talking; or see people walking in the
23 room. It can be very frightening and it can be a
24 very terrible experience for patients with
25 narcolepsy.

1 Another symptom of abnormal REM sleep that
2 patients with narcolepsy have as well is called
3 sleep paralysis. When they wake up from a nap or
4 when they fall asleep, sometimes they again go so
5 quickly into REM and disassociated REM sleep events
6 that sometimes they may be paralyzed from REM but
7 still be awake. Basically, they would wake up from
8 sleep and they cannot move, not even their little
9 finger. It can be very scary. It lasts a few
10 minutes and then finally they can move. Some
11 patients with narcolepsy have multiple episodes of
12 sleep paralysis when they nap during the day, and
13 so forth, and that is another very bothersome
14 symptom.

15 Finally, patients with narcolepsy,
16 contrary to what people say, don't sleep too much;
17 their main problem is that they just cannot stay
18 awake. They fall asleep very quickly in many
19 circumstances, but they are unable to stay asleep
20 for a long period of time. In fact, patients with
21 narcolepsy don't sleep 20 hours a day. What
22 happens is that at night they don't sleep well.
23 Often that is another symptom that is very
24 bothersome. They fall asleep very quickly at night
25 but after one hour they cannot sleep again. They

1 are just awake and cannot sleep.

2 Then, all these symptoms are quite severe
3 and, of course, affect the lives of patients. And,
4 since GHB is recommended in cataplexy, which is
5 muscle atonia triggered by emotion, I will just
6 show you a quick video of a patient with cataplexy.

7 This is a boy, a 9-year old. Narcolepsy
8 usually starts during adolescence and here the
9 clinicians are trying to make him laugh to just try
10 to elicit the symptom, and you see he is falling
11 down and he is completely paralyzed and he is
12 losing his muscle tone. Some of these patients
13 have that many time per day and it can be extremely
14 socially disabling. You can imagine being at a
15 party or being with some friends and having this
16 happen to you. In this kid it was particularly
17 severe.

18 Most cases of narcolepsy start during
19 adolescence but occasionally it starts as early as
20 5 years of age. It peaks around 15 years of age.
21 It is often extremely problematic because I am sure
22 you realize when you have this type of thing
23 happening to you and sleepiness at school,
24 especially when you are 15 years old, when you are
25 an adolescent, it really wrecks your life apart,

1 especially when it is not properly diagnosed.

2 [Slide]

3 There have been a number of studies, and I
4 won't have time to review them, that have shown
5 that the quality of life of patients with
6 narcolepsy is extremely impaired, as much as
7 depression, epilepsy or other reference conditions
8 in almost all the scales that you look at.
9 Clearly, it is a very socially disabling disorder.

10 [Slide]

11 It is also, of course, a disorder that
12 impacts just your daily life. For example, driving
13 -- patients with narcolepsy have a very increased
14 rate of accidents and sometimes many of them refuse
15 to drive just because of falling asleep or having
16 cataplexy while driving.

17 [Slide]

18 We have objective tests for diagnosing
19 narcolepsy. In fact, it is not just a
20 psychological disorder. You can actually use a
21 test like the Multiple Sleep Latency Test, where
22 you ask patients to come to the sleep lab. You
23 check that they sleep normally and the following
24 day you ask them to nap every two hours and you
25 measure how fast they fall asleep. You see,

1 normally people won't fall asleep or nap in the
2 middle of the day, or they would fall asleep with a
3 15-minute latency in the dark. A patient with
4 narcolepsy, as soon as you switch off the light,
5 they are sleeping. In a few minute latency, they
6 are asleep. So, we have objective ways to show
7 that these people have a problem.

8 [Slide]

9 Also, in this nap you see that they go
10 very quickly into REM sleep. Normal people won't
11 have REM sleep before one hour after falling
12 asleep, but patients with narcolepsy will go
13 straight into REM. You can actually demonstrate --
14 we call that sleep onset REM period -- that
15 patients with narcolepsy have all this sleep
16 abnormality and REM abnormality using sleep
17 testing.

18 [Slide]

19 Current treatment for narcolepsy is
20 completely symptomatic. We don't treat the cause
21 of the disease; we only treat the symptoms.
22 Typically, the treatment now uses two drugs, two
23 lines of drug. A patient with cataplexy will be
24 treated usually with two drugs. One is a stimulant
25 which would be a classical amphetamine-like

1 stimulant or this more recent drug that was just
2 approved that is called modafinil, Provigil, which
3 works on sleepiness. It will keep a patient awake
4 but will never normalize him; it only improves him.
5 And, they all have a lot of side effects. You
6 know, the stimulants can even produce psychosis in
7 some rare cases but, of course, they raise blood
8 pressure. They produce psychological changes.
9 They have a lot of other side effects.

10 We all know now that they all increase
11 dopamine in the brain. We have done a series of
12 studies which have shown that. Even modafinil, the
13 most recent drug -- we know now that it works by
14 increasing dopamine in the brain. And, they don't
15 have anything different from each other so some of
16 them are definitely safer than others.

17 For the antidepressants, for the treatment
18 of cataplexy -- this works well on sleepiness but
19 it doesn't work on cataplexy or nightmares, or
20 hallucination or sleep paralysis. For this you use
21 antidepressants. Why? Because antidepressants
22 depress REM sleep and they also suppress cataplexy
23 and all the other abnormal dreaming that patients
24 with narcolepsy have. The problem is they also
25 have a lot of side effects. Actually, the new

1 SSRI, they don't work as well as the old
2 tricyclines. Often you even have to use the old
3 tricycline antidepressants because norepinephrine
4 uptake inhibition seems to be the mode of action of
5 these drugs, more than serotonin. They don't
6 really work that well and, of course, they have a
7 lot of side effects and a lot of different
8 problems.

9 [Slide]

10 Finally, I want to stress again that we
11 need new treatments for narcolepsy just because all
12 the treatments we have now just don't make people
13 normal. They just help them to be better. You can
14 best illustrate that using the MSLT/MWT, which is a
15 slightly different test where, instead of measuring
16 how fast people fall asleep in the dark, you ask
17 people to try to stay away in the dark and you see
18 that normal people can stay awake. They don't fall
19 asleep in 20 minutes, whereas patients with
20 narcolepsy fall asleep very dramatically after a
21 few minutes in the dark.

22 Even if you treat them with modafinil
23 which is a very good treatment for narcolepsy,
24 which was recently approved, you improve them but
25 they never become normal. Then, it is clear that

1 what we have is not enough. We just need better,
2 and this would be the same for amphetamines. Even
3 high dose amphetamines don't normalize these
4 patients. That has been shown by multiple studies.

5 [Slide]

6 We have worked for more than 15 years
7 trying to find the cause of narcolepsy, and
8 recently we have isolated the gene for narcolepsy
9 in a canine model where the disease is genetically
10 determined, and we found that it was a receptor for
11 a neuropeptide that is called hypocretin. We found
12 that in humans with narcolepsy it is not like dogs
13 with narcolepsy; it is not the receptor but a
14 peptide called hypocretin which is expressed in
15 about 10,000 cells in the brain, here in the
16 hypothalamus, which is missing in patients with
17 narcolepsy.

18 This is brain tissue of a patient with
19 narcolepsy. You see here is the normal; everything
20 is gone. If you measure in the cerebrospinal
21 fluid, this is a normal level in a normal person,
22 or in patients with MS or other neurological
23 symptoms, and you see in all patients with
24 narcolepsy that this hypocretin molecule is gone.
25 We know now that the cause of narcolepsy is not

1 dopamine or norepinephrine, which is the current
2 treatment for narcolepsy, which are stimulants and
3 antidepressants acting through these
4 neurotransmitters, and probably replacing this
5 hypocretin would be an ideal treatment for
6 narcolepsy. But this finding was only made one
7 year ago and it is going to take probably 10 years
8 or many years before we actually have a treatment
9 based on this new discovery.

10 [Slide]

11 To summarize the medical need, I think I
12 have convinced you that narcolepsy is a serious and
13 disabling condition that needs treatment, and these
14 patients are in desperate need of better treatment.
15 As you will see from the presentation afterwards,
16 GHB is one of the effective treatments which helps
17 a lot of people. So, current treatments like
18 amphetamines and antidepressants don't work well in
19 terms of efficacy. They have a lot of side
20 effects. They all work the same way but they don't
21 act on the cause of the disease and, clearly, we
22 know that GHB, even though it probably doesn't act
23 on hypocretin, acts differently from other drugs.
24 And, it is one more drug that would be available to
25 help a lot of patients with narcolepsy.

1 Finally, even though there have been
2 numerous, very recent developments that are very
3 exciting in the hypocretin area, unfortunately, you
4 all know it takes a long time until drugs are
5 available and it is going to take probably many
6 years until this available.

7 This is a very quick summary of what we
8 know about narcolepsy to date. Thank you.

9 DR. REARDAN: Thank you, Dr. Mignot. Dr.
10 Houghton will now present the data which has been
11 assembled in support of the efficacy of Xyrem. Dr.
12 Houghton is a qualified anesthesiologist, with 18
13 years of clinical experience in critical care
14 medicine and numerous years experience in
15 pharmaceutical drug development. Bill?

16 Efficacy

17 DR. HOUGHTON: Good morning.

18 [Slide]

19 I am sorry to start with such a complex
20 diagram but this just outlines the pattern of
21 studies that we will be talking about this morning.
22 On the left-hand side here are the 4 controlled
23 studies on which the assessment of efficacy will be
24 based, but what is unusual about this program is
25 that patients, in an uncommon way, move to

1 extension protocols. So, as Dr. Katz pointed out,
2 even though the total database may be small, the
3 total duration of exposure of patients is quite
4 promising.

5 The first study that I will talk about is
6 entitled OMC-GHB-3, and the patients, at the
7 completion of this short-term treatment study did
8 progress to a long-term, open label study and then
9 had the opportunity to move into one of the
10 treatment IND protocols, with some of them still
11 participating in that study.

12 A second contributor to that protocol was
13 the patients who completed the first 6-month safety
14 treatment IND protocol, and the significance of all
15 of that is that it was from this protocol that the
16 patients are represented in the long-term pivotal
17 blinded efficacy study that supports the long-term
18 efficacy of Xyrem.

19 [Slide]

20 The first and pivotal study is a
21 randomized, double-blind, placebo-controlled,
22 parallel group, multi-center trial comparing the
23 effects of three doses, 3 g, 6 g and 9 g of orally
24 administered Xyrem with placebo for the treatment
25 of narcolepsy. As I mentioned, this was a study

1 conducted in 136 patients in 16 centers.

2 [Slide]

3 The primary efficacy parameter was the
4 change in the number of total cataplexy attacks in
5 the last two weeks of the treatment period compared
6 to the two weeks of the baseline period.

7 Secondary efficacy parameters that were
8 considered included complete and partial cataplexy
9 attacks; daytime sleepiness; inadvertent sleep
10 attacks during the day; hypnagogic hallucinations;
11 sleep paralysis; and a clinical global impression
12 of change.

13 [Slide]

14 Patients naive to sodium oxybate therapy
15 were chosen with a bona fide diagnosis of
16 narcolepsy for at least 6 months. They were
17 required to have a record of a polysomnograph or
18 Multiple Sleep Latency Test within the last 5 years
19 to exclude other causes of daytime sleepiness, and
20 particularly sleep apnea.

21 They were required to have a history of
22 daytime sleepiness and cataplexy for at least 6
23 months, and recurrent daytime naps that occurred
24 almost daily in the preceding 3 months.

25 [Slide]

1 The overall study design was divided into
2 5 stages. Firstly, there was a screening period in
3 which the patients were required to qualify for
4 entry criteria and then withdrawn from their
5 existing anti-cataplectic medications over a 4-week
6 period to avoid rebound phenomena which were
7 considered a safety consideration. At the end of
8 this withdrawal period they entered a washout
9 period, which was determined by at least 5 times
10 the half-life of their preceding drug to remove any
11 effects of those drugs. However, if patients
12 weren't on any cataplectic medications, they were
13 still required to remain 5 days in that washout
14 period to familiarize themselves with the use of
15 diaries.

16 They then proceeded to a baseline period
17 of 2 to 3 weeks, using daily diary recording to
18 establish the severity of their disease and to
19 confirm that they had reached a stable stage in
20 their disease. They then entered a 4-week blinded,
21 randomized treatment period, with a visit at 2
22 weeks, a telephone call the day after commencing
23 treatment, and then safety telephone calls 3 times
24 a week during the treatment period, at the end of
25 which they were abruptly withdrawn from drug and

1 followed up 3 to 5 days later to assess any rebound
2 phenomena and any adverse experiences that may have
3 ensued.

4 [Slide]

5 As is shown here, the patient groups were
6 very evenly balanced at baseline. They represented
7 a fairly severe group of narcoleptics, with an
8 average incidence of cataplexy of around 34 per
9 week at baseline.

10 There was a dose-response relationship
11 across the doses based on median change in the
12 total number of cataplexy attacks that, when
13 compared to placebo, approached significance at the
14 9 g dose, with a p value of 0.0529, and achieved
15 highly significant change at the 9 g dose.

16 [Slide]

17 This dose relationship is clearly shown in
18 the plot of median change from baseline in the
19 number of cataplexy attacks per week, and the
20 spread of the data is demonstrated as the quartile
21 lines around these median values.

22 [Slide]

23 A more clinically relevant presentation of
24 the data is the percentage change in the number of
25 cataplexy attacks from baseline. This was

1 calculated as the distribution of percentage change
2 values for each individual patient and is again
3 presented as the medians. This representation
4 clearly shows that the major change in cataplexy
5 occurs in the first 2 weeks, but with ongoing
6 change in the subsequent 2 weeks, as represented in
7 2 of the dose groups.

8 [Slide]

9 Secondary efficacy variables included
10 assessment of excessive daytime sleepiness using
11 the validated Epworth Sleepiness Scale which rates
12 the patient's feeling of daytime somnolence by
13 scoring on a scale of 0-3 the probability of
14 falling asleep in the circumstances of 8 common
15 life scenarios. This results in a potential
16 maximum score of 24.

17 [Slide]

18 This slide demonstrates a clear
19 dose-related reduction in the Epworth Sleepiness
20 Scale, reaching a significant level of 0.0001 in
21 the 9 g group compared to placebo. This change was
22 incremental beyond the effects of stable dosing of
23 stimulants because stimulant medications were
24 maintained constant throughout the study. In all
25 Xyrem-treated groups some patients improved beyond

1 the defined narcolepsy range, with some patients in
2 the 6 g and 9 g groups actually improving into the
3 normal range as rated by the Epworth Sleepiness
4 Scale.

5 The second component of daytime
6 sleepiness, the number of inadvertent naps during
7 the day, was also significantly reduced compared to
8 placebo in the 6 g group and 9 g dosing.

9 [Slide]

10 The severity of the disease at baseline
11 was rated by the principal investigator according
12 to the following validated scale. Then, at the end
13 of the treatment period a blinded global impression
14 of change according to the rating shown here was
15 made, rating from very much improved through no
16 change to very much worse.

17 [Slide]

18 Assignment of these modal values indicated
19 a primary distribution of the placebo patients
20 mainly to no change or minimally improved, but
21 there is an obvious predominance of assignment in
22 the 9 g dose to very much improved and much
23 improved.

24 [Slide]

25 Because of the complexity of presenting

1 these assigned categories, a post hoc
2 simplification was applied to group the patients
3 that showed clear clinical improvement into a
4 responder group, and all others were called
5 non-responders. This again displays the
6 dose-response trend in the categorical data, with a
7 clear statistical difference between the 9 g group
8 and the placebo group.

9 [Slide]

10 Other secondary measures that achieved
11 significant change included the number of
12 awakenings at night, subjective sleep quality,
13 morning alertness, the ability to concentrate.
14 Hypnagogic hallucinations and sleep paralysis,
15 which had a much lower incidence at baseline,
16 showed a non-significant trend towards improvement.

17 [Slide]

18 The next study that I would like to
19 present is the study that was suggested by the FDA
20 to provide evidence of long-term efficacy of Xyrem
21 based on the return of cataplexy following the
22 cessation of long-term treatment with the active
23 drug.

24 [Slide]

25 Patients entered this blinded, randomized

1 study from the long-term open-label study I showed
2 you initially having completed the GHB-2 protocol
3 and proceeded into the GHB-3 protocol for periods
4 up to 2 years, or from the initial treatment IND
5 protocol. This provided assessment of potential
6 adverse consequences of the abrupt withdrawal of
7 long-term therapeutic doses of Xyrem as well.

8 Patients having taken the drug for 6
9 months to 3.5 years were screened, and after
10 blinded randomization entered a single blind
11 baseline period in which daily diaries were used to
12 record the severity of their cataplexy. They then
13 entered a double-blind phase of 2 weeks wherein
14 they were randomized in a 50 percent ratio to
15 either continued, unchanged dose of Xyrem in a
16 blinded fashion or to placebo. Randomization was
17 performed in a centralized manner to ensure equal
18 representation of dosing in the comparative groups.

19 [Slide]

20 The primary efficacy variable was the
21 change in the number of cataplexy attacks in the
22 double-blind period compared to baseline. There
23 was a median change of zero in the Xyrem group but,
24 as seen, there was a marked increase in the
25 incidence of cataplexy in those randomized to

1 placebo. This was highly significant.

2 [Slide]

3 When the median change from baseline by
4 week was calculated, you can see that there was a
5 step-wise increase in cataplexy which supported the
6 long-term efficacy of the drug in a statistically
7 significant manner, but they represent a gradual
8 return of cataplexy rather than an acute rebound
9 phenomenon.

10 [Slide]

11 I will now present very briefly some
12 supportive data from 2 early controlled, crossover
13 design studies that have been published, and for
14 which Orphan Medical purchased the databases and
15 included in the NDA submission.

16 [Slide]

17 The first was a study conducted by Dr.
18 Lawrence Scrima, then of the University of
19 Arkansas, in 20 patients, 10 males and 10 females,
20 using a dose of 50 mg/kg, much lower than some of
21 those in the previous studies and equivalent to
22 about 3.5 g per day in a 70 kg man.

23 Following the withdrawal of
24 anticataplectic medications, he recorded a baseline
25 period during which the patients were required to

1 have a minimum of 10 cataplexy attacks, then were
2 randomized into an initial treatment period of 29
3 days, followed by a washout period of 6 days, and
4 then crossed over to the alternate treatment, again
5 followed by a washout of 6 days. Stimulants were
6 continued throughout this study and all patients
7 were actually transferred to methylphenidate as
8 their stimulant.

9 [Slide]

10 The primary efficacy measures are
11 identified, with the average number of cataplexy
12 attacks compared to baseline and objective
13 sleepiness index as determined by the Multiple
14 Sleep Latency Test. This was to represent a
15 measure of daytime sleepiness.

16 Because of logistic issues in the study
17 conduct and methodologic issues in design and
18 definition, this is presented as supporting data
19 only to represent cataplexy response at a lower
20 dose. As can be seen, this patient group again
21 represented a reasonably severe narcoleptic
22 population. They had a baseline measure of 20
23 cataplexy attacks per week. There was an initial
24 fairly significant placebo response, as was shown
25 in the previous studies, but by week 3 and week 4

1 statistically significant differentiation between
2 placebo and active treatment was shown, and there
3 was a statistically significant overall response in
4 the study. There was no significant change in the
5 sleepiness index as the measure of daytime
6 sleepiness, however, in this study.

7 [Slide]

8 The second study that I will present very
9 briefly was conducted by Dr. Lammers, in The
10 Netherlands. It is, again, a randomized, blinded,
11 crossover design study in 24 narcoleptics. The
12 other significant difference in this study was that
13 concomitant medications for both cataplexy and
14 excessive daytime sleepiness were continued
15 throughout the study.

16 Following a 1-week baseline to establish
17 disease severity, the patients were randomized to a
18 4-week treatment period at a dose of 60 mg/kg in
19 divided nightly doses, followed by a washout period
20 of about 3 weeks, and then a baseline period of 1
21 week again preceding a second treatment period of 4
22 weeks.

23 [Slide]

24 As is obvious here, the severity of
25 cataplexy during the baseline period was much lower

1 in this study, potentially the consequence of
2 continued anticataplectic medication in some
3 patients. But, again, there is a significant
4 response. According to the statistical plan which
5 was very scant that was represented in the
6 published study, and agreed to by the FDA, there
7 was an incorrect or unsatisfactory statistical
8 management of this study. The change in cataplexy
9 was not statistically significant. When the
10 results of this study were submitted by Orphan,
11 they were reanalyzed with an ANCOVA analysis as had
12 been applied in the GHB-2 study, and this change
13 was significant according to the ANCOVA analysis.

14 [Slide]

15 Other measures that showed significant
16 improvement included hypnagogic hallucinations and
17 daytime sleep attacks again.

18 [Slide]

19 Although not eligible for determination of
20 efficacy since it is an open-label study, I would
21 like to briefly mention three aspects of the
22 follow-on study to the pivotal GHB-2 study. And,
23 117 patients chose to participate entering the
24 study at the 6 g per day dose and then slowly
25 titrating to clinical efficacy between the doses of

1 3 g and 9 g. This study, therefore, represents the
2 proposed clinical use of the drug and, although
3 primarily a safety study, represents some important
4 dynamic information.

5 [Slide]

6 This slide shows the response in cataplexy
7 over the 12-month period. What is surprising is
8 that the maximum nadir occurred at about 8 weeks,
9 and then the sustained efficacy was maintained
10 across the 12 months in all dose groups.

11 [Slide]

12 A similar pattern was seen in the Epworth
13 Sleepiness Scale, which shows the same time frame
14 with maximum response at about 8 weeks, and then
15 maintained efficacy over the course of 12 months in
16 this open-label study. What is also interesting to
17 note is that most of the patients in most dose
18 groups were maintained beyond the defined
19 narcolepsy range.

20 [Slide]

21 When the distribution of doses to which
22 the patients were titrated is shown, it is seen
23 that 6 g per day is the most common dose, followed
24 by the 9 g dose group.

25 [Slide]

1 This represents the pattern of dosing seen
2 in other open-label studies where doses were
3 titrated to clinical response. What is important
4 to note is that there is not a change in dosing
5 between the 6-month and the 12-month dosing groups,
6 suggesting no tolerance development to maintain the
7 dynamic effects shown.

8 [Slide]

9 This slide represents the cohort of
10 patients that entered the SXB-21 protocol via the
11 GHB-2 and then GHB-3 protocol. Represented here is
12 the incidence of cataplexy for each individual
13 patient at the baseline in GHB-2. They were then
14 maintained in the study I have just shown you over
15 the course of up to 2 years, and this is the
16 incidence of cataplexy of each of the individual
17 patients in the single-blinded baseline in the
18 SXB-21 protocol. When the paradigm of random
19 assignment to placebo is shown, then there is
20 certainly a demonstration of efficacy between those
21 who were randomized to the placebo group in SXB-21
22 versus those that maintained their Xyrem treatment,
23 which certainly helps to support the efficacy
24 statement in the GHB-3 protocol.

25 [Slide]

1 Finally and to summarize, we have
2 presented data to show efficacy of sodium oxybate
3 to reduce cataplexy in 4-week treatment periods in
4 a dose related manner that is highly statistically
5 significant at the 9 g dose, and approaching
6 statistical significance at the 6 g dose.

7 We have presented supportive data
8 demonstrating statistically significant efficacy of
9 the lower doses, and demonstrated statistically
10 significant efficacy in terms of daytime
11 sleepiness, using the Epworth Sleepiness Scale,
12 again at 9 g. In a scale used in the Lammers study
13 at 60 mg/kg daytime sleep attacks were
14 statistically significantly reduced in all 3
15 studies. We supported the long-term efficacy of
16 Xyrem with return of cataplexy when blindly
17 assigned to placebo in the SXB-21 protocol.

18 [Slide]

19 I would now like to very briefly summarize
20 the pharmacokinetics studies that were conducted by
21 Orphan Medical.

22 [Slide]

23 In total, we conducted 8 clinical
24 pharmacokinetic studies, including 2 studies in
25 narcoleptic patients and 6 in healthy human

1 volunteers. This slide lists the 8 pharmacokinetic
2 studies by their primary objective.

3 The studies included a single dose pilot
4 study in 6 narcoleptics, and a second study in
5 narcoleptic patients comparing acute and chronic
6 dosing over an 8-week period. Normal volunteer
7 studies were conducted to examine the kinetics of
8 Xyrem with respect to gender differences, dose
9 proportionality and the effects of food. Also, 3
10 drug interaction studies were performed with
11 Zolpiden, protriptyline and modafinil as
12 representatives of the 3 classes of drugs used
13 commonly to treat the symptoms of narcolepsy.
14 Lastly, an in vitro study, using human hepatic
15 microzymes, was conducted to assess the effects of
16 oxybate.

17 [Slide]

18 I will only present the studies that have
19 a significant message, and in very brief summary
20 form. This slide displays the results of the dose
21 proportionality study that compared nightly dose of
22 4.5 and 9 g given in 2 equally divided doses at
23 bedtime and 4 hours later. A randomized, 2-day
24 crossover design was utilized, and doubling the
25 dose from 4.5 to 9 g resulted in a nearly 4-fold

1 increase in the area under the time concentration
2 curve. The peak plasma concentration and the time
3 to peak concentration changed significantly with
4 doubling the dose, the latter suggesting
5 capacity-limited absorption. C_{max} was higher after
6 the second dose than with the first nightly dose,
7 as has been seen in other studies with divided
8 dosing.

9 These findings indicate non-linear
10 kinetics and capacity-limited elimination and
11 absorption, as reported in previously published
12 studies.

13 [Slide]

14 The results of the effect of food study
15 are displayed graphically on this slide. In this
16 randomized, crossover study 34 healthy subjects
17 were dosed with 4.5 g of Xyrem on 2 occasions 1
18 week apart, either after an overnight 10.5 hour
19 fast or immediately following a high fat
20 standardized breakfast. After the high fat meal
21 the peak plasma concentration decreased by almost
22 60 percent. The median time to achieve peak levels
23 increased from 45 minutes to around 2 hours, and
24 the AUC decreased by 37 percent. All of these
25 differences were statistically significant. The

1 apparent half-life was not significantly altered.
2 Thus, the presence of food significantly reduces
3 systemic exposure to GHB, a finding not previously
4 reported.

5 In the 3 volunteer kinetic studies the
6 urinary excretion of Xyrem was measured, and renal
7 excretion was shown to be a minor pathway of
8 elimination, accounting for less than 5 percent of
9 the administered drug.

10 [Slide]

11 As an example of the drug interaction
12 studies, on this slide we present the modafinil
13 results. The upper graph indicates that
14 co-administration of 200 mg of modafinil had no
15 impact on the kinetics of Xyrem. The lower graph
16 demonstrates that 4.5 g of Xyrem had no clinically
17 significant effect on the kinetics of a standard
18 dose of modafinil.

19 Likewise, in the Zolpiden protriptyline
20 interaction studies, no significant kinetic
21 interactions were found. In the separate in vitro
22 study using human hepatic microzymes, sodium
23 oxybate was found to have no effect on 6 cytochrome
24 p450 enzymes either to inhibit or induce their
25 activity.

1 [Slide]

2 So in summary, Xyrem oral solution is
3 rapidly absorbed and eliminated with a half-life
4 of about one hour. The drug displays non-linear,
5 dose-dependent kinetics, indicative of
6 capacity-limited absorption and elimination. Xyrem
7 kinetics are similar in men and women and do not
8 change with chronic administration at therapeutic
9 doses.

10 [Slide]

11 Chronic dosing did not change the kinetics
12 of Xyrem in a patient population, and a high fat
13 meal appreciably delayed absorption and reduced
14 total systemic exposure to the drug. Three
15 separate in vivo drug interaction studies, as well
16 as the in vitro p450 enzyme study, would suggest
17 the probability of significant drug-drug
18 interaction with Xyrem is minimal. Thank you very
19 much.

20 DR. REARDAN: Thank you. I would now like
21 to introduce Dr. Jed Black, from Stanford
22 University Sleep Center, and he will present on the
23 polysomnographic effects of Xyrem and GHB.

24 Polysomnographic Effects of Xyrem

25 DR. BLACK: Good morning, ladies and

1 gentlemen. I would like to summarize the body of
2 data that has been collected over the past 25 years
3 which characterizes the effects of gamma
4 hydroxybutyrate or sodium oxybate on sleep
5 parameters. I will then speculate briefly on a
6 possible mechanism whereby these effects on sleep
7 result in a robust improvement in daytime
8 narcolepsy symptoms seen with this agent.

9 This has been a particular focus of my
10 research in sleep over the past years. That is,
11 how does what happens in the brain at night affect
12 various aspects on daytime function and alertness?

13 It is unexpected that a medication that
14 objectively markedly improves sleep quality also
15 improves measures of daytime alertness as this
16 finding has never been observed with traditional
17 hypnotics or sleep aids. To pursue an
18 understanding of this possible interaction, 6
19 investigations have been conducted in humans.
20 These studies explored the effect of sodium oxybate
21 on a variety of nocturnal sleep parameters, using
22 electroencephalography during sleep and a
23 laboratory test known as polysomnography.

24 The first 3 studies found an increase in
25 slow wave sleep. Slow wave sleep, also known as

1 stages 3 and 4 sleep, is the deepest portion of
2 sleep and correlates positively with functions of
3 daytime concentration, attention and alertness in
4 normal subjects. These studies also reveal a
5 reduction in nocturnal awakenings with GHB.

6 The more recent studies of Scrima, Lammers
7 and Orphan Medical explored both measures of
8 nocturnal sleep as measured by polysomnography, or
9 PSG, and measures of daytime sleepiness with the
10 Multiple Sleep Latency Test, or daytime alertness
11 with the Maintenance of Wakefulness Test.

12 [Slide]

13 These 2 studies, the design of which has
14 been reviewed by Dr. Houghton, again found
15 significant reductions in slow wave sleep, that is
16 to say stage 3-4 sleep or slow wave sleep, and
17 reductions in nocturnal awakenings. Additionally,
18 the Scrima group reported a reduction in stage 1
19 sleep, a very light stage of sleep, and the Lammers
20 group noted significant reduction in the percentage
21 of time patients spent awake during nocturnal
22 polysomnography.

23 [Slide]

24 The most recent study, a multi-center
25 trial performed at 4 sites with an enrollment of 25

1 patients, was designed to further explore the
2 effects of sodium oxybate on nocturnal sleep
3 parameters and daytime measures of sleepiness and
4 alertness. In this open-label study patients were
5 kept at a stable stimulant dose throughout the
6 protocol. Cataplexy medications were tapered,
7 followed by a 2-week washout and baseline period.
8 Sodium oxybate was initiated at 4.5 g in a divided
9 nightly dose for 4 weeks, then increased to 6, then
10 7.5, then 9 g for 2 weeks each. Nocturnal
11 polysomnography and the Maintenance of Wakefulness
12 Test, or MWT, were obtained at the time points
13 noted here.

14 [Slide]

15 This study revealed the expected increase
16 in slow wave, or stages 3-4 sleep, and increase in
17 delta power. Delta power is the measure of the
18 depth of sleep. It incorporates the combination of
19 the amplitude of the slow frequency waves and the
20 prevalence of those waves through the night to
21 produce a single number called delta power. Delta
22 power is another measure found in a variety of
23 animal and human studies to correlate positively
24 with sleep quality. The calculation of this value
25 requires sophisticated processing which was

1 unavailable for the prior studies. The increments
2 in slow wave sleep and delta power were found to be
3 dose related. Dose-related improvements in daytime
4 alertness and subjective sleepiness were also
5 observed.

6 [Slide]

7 The dose-response increase in the number
8 of minutes of slow wave sleep is illustrated in
9 this slide, with an increase from 6 g up to the 9 g
10 dose. The total duration of slow wave sleep
11 increased to over 5-fold that of baseline at the 9
12 g dose.

13 It is important to note that while these
14 results are predicted to be dose related, time on
15 medication cannot be factored out as a potential
16 contributor to these increments.

17 [Slide]

18 Delta power, which characterizes slow wave
19 activity throughout the entire sleep period, not
20 just during stages 3 and 4, was also found to
21 increase in a dose response fashion with a 50
22 percent increase noted at the 9 g dose over
23 baseline.

24 [Slide]

25 The Maintenance of Wakefulness Test, or

1 MWT, is a daytime evaluation which places the
2 patient in a dimly lit room in a semi-recumbent
3 position, with nothing to do and with the
4 instruction to remain awake. The duration of
5 sustained wakefulness was measured in this study
6 over 40-minute intervals across 4 periods, spaced 2
7 hours apart during the day. Substantial
8 dose-related increases in the ability to remain
9 awake were observed at both the 4.5 g and 9 g
10 doses.

11 [Slide]

12 As previously noted, the MWT was not
13 performed at the 6 g nor 7.5 g doses in this
14 protocol. Similar marked reductions were found in
15 the Epworth Sleepiness Scale scores. In this
16 measure the individual rates their own potential to
17 fall asleep in a variety of more sedentary daytime
18 activities.

19 [Slide]

20 A post hoc analysis of the possible
21 correlations between sodium oxybate-related changes
22 in nocturnal parameters with changes in daytime
23 measures revealed the strongest correlation
24 occurring with delta power and Epworth Sleepiness
25 Scale scores. This was a negative correlation,

1 such that the greater the delta power, the lower
2 the daytime sleepiness. In addition, trends toward
3 significant correlations between delta sleep and
4 MWT scores, and between slow wave sleep and Epworth
5 and MWT scores were observed.

6 [Slide]

7 In conclusion, studies of sodium oxybate's
8 effects on sleep demonstrate increases in measures
9 of restorative sleep, including dose-related
10 increments in slow wave and delta sleep, coupled
11 with and correlated with improvements in measures
12 of daytime alertness and sleepiness.

13 It is postulated that sodium oxybate works
14 directly to enhance brain neurochemical activity
15 critical to the restorative mechanisms of slow wave
16 sleep and of slow wave activity during the total
17 sleep period. Such enhanced activity may be the
18 cause of substantial improvement in both subjective
19 and objective measures of sleepiness and alertness
20 observed with sodium oxybate in narcolepsy.

21 DR. REARDAN: Thank you, Dr. Black. Dr.
22 Houghton will now present the safety summary
23 overview of Xyrem and finish up with a benefit/risk
24 assessment.

25 Safety Overview and Summary of

1 Risk/Benefit Assessment

2 DR. HOUGHTON: Thank you.

3 [Slide]

4 I am sorry to horrify you with this
5 complex diagram again but it is just to outline the
6 15 studies that will be referred to today as the
7 updated safety database. The Lammers study was
8 excluded because adverse events were not recorded
9 in the classical way and, as Dr. Katz explained,
10 the Scharf study was separated and will be
11 explained again later.

12 [Slide]

13 The safety profile was reported based on
14 exposure of 479 narcoleptic patients and 125
15 healthy volunteers from the pharmacokinetic
16 studies. This represents an exposure of greater
17 than 6 months in 360 patients in total, and greater
18 than 12 months in 296 patients, which represents a
19 total patient-year exposure of 1328 years with the
20 Scharf database included.

21 [Slide]

22 When exposures were restricted to the
23 studies other than the Scharf database, 399
24 narcoleptics and 125 subjects represent exposure in
25 524 persons. This represents exposure of greater

1 than 6 months in 296 patients and greater than 12
2 months in 223 patients, for a total exposure of 330
3 patient-years.

4 [Slide]

5 In the open-label studies patients were
6 titrated between the doses of 3-9 g in divided dose
7 at night. This slide represents the distribution
8 of patients across this defined dose range and,
9 again, identifies the 6 g dose as the most commonly
10 used, followed again by the 9 g dose. In fact,
11 approximately 80 percent of patients were titrated
12 within the 6-9 g range.

13 [Slide]

14 In the updated integrated safety database,
15 composed of 402 patients, 399 of whom were treated
16 with active drug and 3 patients received placebo
17 only, it can be seen that 65 percent of patients
18 completed therapy or were ongoing in the treatment
19 IND study. Thirty-five percent have discontinued
20 treatment for the reasons noted here, with 13
21 percent discontinuing due to adverse events; 2
22 percent discontinuing because of lack of efficacy;
23 and there were 2 deaths that occurred in the
24 treatment IND studies, both due to suicide.

25 [Slide]

1 Across all of these studies, 82 percent of
2 treated patients reported any adverse event, as did
3 70 percent of patients exposed to placebo. It is
4 important to note that the placebo exposure
5 represents 4 weeks as compared to active drug
6 treatment over a much longer period of up to 4
7 years. Hence, severe adverse event
8 discontinuations and serious adverse events are
9 significantly greater in the active treatment
10 groups.

11 [Slide]

12 When considered in terms of dose at onset,
13 there seemed to be a slight preponderance of
14 incidence in the 9 g group.

15 [Slide]

16 This slide represents the most frequent
17 adverse events reported across the integrated
18 database. There was a consistent pattern of events
19 across the study. Nausea, dizziness, sleep
20 walking, are represented here as a partial
21 representation of the term sleep disorder, enuresis
22 and confusion were most frequently considered dose
23 related, while others represent intercurrent
24 illness.

25 [Slide]

1 This profile is reinforced by
2 consideration of the controlled trials in which
3 there is represented a balanced exposure to placebo
4 and active medication. Again, dizziness, nausea,
5 pain, sleep disorder, confusion, infection,
6 vomiting and urinary incontinence separate. A dose
7 relationship was shown introduction eh GHB-2 trial
8 for confusion, nausea, dizziness and urinary
9 incontinence.

10 [Slide]

11 In the SXB-21 trial the most common
12 adverse events that were reported are shown here.
13 The incidence was very low in this study of
14 patients on long-term treatment, but what is
15 relevant is the data that looks at the possible
16 presentation of a withdrawal syndrome with the
17 abrupt cessation of long-term therapy.

18 [Slide]

19 This is in marked contrast to a severe
20 syndrome that is being described in the abuser
21 population who have significantly escalated both
22 dose and frequency of dosing. When we looked at
23 symptoms that could relate to a withdrawal
24 phenomenon, we saw only 2 patients with anxiety in
25 a circumstance of escalating cataplexy, 1 patient

1 with dizziness, 1 insomnia, 1 sleep disorder that
2 actually in verbatim terms, was increased
3 awakenings, and 1 patient with somnolence as their
4 narcolepsy worsened.

5 [Slide]

6 I would like to now address the Scharf
7 database. This was conducted under an investigator
8 IND commencing about 10 years before Orphan's
9 involvement, without any of the rigors of external
10 monitoring, and really represents over 16 years
11 experience in the use of the drug rather than drug
12 development clinical research with regulatory
13 disciplines.

14 Patients were scattered all over the
15 country and, hence, the data is based primarily on
16 diary recordings without medical review and
17 interpretation, leading to a significant
18 discontinuation rate for lack of compliance. Dose
19 accountability and titration were less clearly
20 defined and less controlled. Patients had less
21 defined entry criteria and represent a broader
22 profile of associated pathologies. On this basis,
23 the study data has been reported separately to the
24 integrated database, as Dr. Katz had suggested.

25 [Slide]

1 We will address the Scharf open-label
2 experience in terms of dosing exposure, patient
3 disposition, adverse event incidence over 16 years,
4 and then to try and establish some parity with the
5 integrated database. We have considered the
6 adverse event experience reporting in just the
7 first 6 months of the study.

8 [Slide]

9 Patient disposition in the Scharf database
10 is represented in this slide. At the time of
11 database closure 63 patients transferred into the
12 SXB 7 protocol. The FDA expressed concern
13 regarding the accountability of the 80 patients
14 that did not continue. We provided a narrative
15 account for each individual patient, with updated
16 status where possible, in the form of a major
17 amendment. In addition, FDA requested further
18 clarification of adverse events initially deemed
19 unevaluable, which we have also provided.

20 Of these 80 patients, 8 continued in the
21 Scharf trial under his treatment IND. The 71
22 patients who withdrew had received oxybate for from
23 5 days to 10 years, and the reasons for early
24 withdrawal of the 71 patients were primarily
25 classified into non-compliance, adverse event and

1 cost.

2 [Slide]

3 The adverse event profile reflects the
4 length of the study. The relatively large numbers
5 of viral infection, flu syndrome, pharyngitis, etc.
6 shouldn't be worrisome considering the 16 years
7 duration of the study. However, of particular
8 interest is the unusual incidence of sleepwalking
9 and urinary incontinence and these will be
10 discussed in some detail later.

11 [Slide]

12 The most frequent adverse events in the
13 first 6 months of the Scharf trial are shown here.
14 When compared to the integrated safety database,
15 few adverse events separate in incidence. Most
16 notable are somnolence, infection, viral infection
17 and malaise. There were few new adverse events
18 reported after the first 6 months.

19 The FDA requested further information
20 regarding the following adverse events of
21 particular interest. They were represented by
22 incontinence and convulsions, confusion,
23 neuropsychiatric events and sleepwalking.

24 [Slide]

25 I will address incontinence first. In

1 their review of the GHB-2 trial, submitted in
2 October, 1998, the FDA requested an analysis of
3 adverse event terms for incontinence in association
4 with central nervous system adverse events
5 suggestive of seizure.

6 [Slide]

7 We responded by initiating the following:
8 a questionnaire to all investigators to review the
9 history of abnormal nocturnal observations that
10 could be suggestive of seizures; a detailed
11 urologic history preceding oxybate therapy and any
12 new neurologic symptoms.

13 Examination of the databases for potential
14 correlation between central nervous adverse events
15 that could be related to seizures and incontinence,
16 either urinary or fecal, was undertaken. Review of
17 both preclinical and clinical data in the
18 literature was performed and an overnight EEG
19 recording after a 9 g dose was conducted in 6
20 patients who had reported incontinence during their
21 oxybate therapy. An expert opinion was provided by
22 Dr. Nathan Chrone, a neurologist of Johns Hopkins
23 University.

24 [Slide]

25 The issue as represented is shown here.

1 Urinary incontinence was presented by 8 patients
2 reporting 15 events in the GHB-2 study, by 13
3 patients reporting 51 events over the 2-year period
4 of GHB-3, and in the Scharf study by 33 patients
5 reporting 140 events.

6 When central nervous system events were
7 analyzed for contemporaneous reporting, 2 patients
8 in each of the GHB-2 and -3 trials recorded such
9 events corresponding to episodes of incontinence,
10 as did 7 patients in the Scharf database.
11 Relatively few incontinence events were temporally
12 associated with the CNS adverse events suggestive
13 of seizure. No potential seizure genesis was
14 reported by bed partners in response to specific
15 questions, and many of the partners reported
16 relevant urinary symptoms such as frequent nocturia
17 preceding the Xyrem treatment.

18 [Slide]

19 Single events of fecal incontinence
20 occurred in 4 patients in 4 different trials.
21 Association between these incontinence events and
22 central nervous system adverse experiences were
23 present only in 1 patient in the Scharf trial and 1
24 in the pharmacokinetic SXB-11 trial. In this
25 patient the event of fecal incontinence was

1 definitely associated with a seizure in a patient
2 with a known pre-study history of seizures. The
3 subject in the SXB-11 effect of food study was a
4 patient who, while significantly obtunded and with
5 respiratory obstructive symptoms, had a brief
6 episode of fecal incontinence.

7 [Slide]

8 In conclusion, there was limited support
9 for a relationship between incontinence and
10 seizures from the clinical trials, the prospective
11 EEGs or from the literature.

12 [Slide]

13 The vast majority of events that could
14 have been coded as convulsions were actually
15 recorded under the COSTART dictionary as cataplexy
16 events. One patient in the integrated trial
17 database did not represent this classification and
18 he has been investigated by a neurologist for
19 seizure genesis. His fugue state and automatic
20 behavior episodes have been deemed part of his
21 narcolepsy syndrome.

22 In the Scharf database two patients with
23 definite seizures recorded history of preexisting
24 disease, and two other patients recorded seizure
25 events without definitive diagnosis but with

1 complicated polypharmacy.

2 [Slide]

3 To now address confusion, in the
4 integrated safety database 30 patients or 70
5 percent reported 48 events recorded as confusion,
6 leading to discontinuation from study in 3
7 patients. A possible dose relationship was
8 suggested by a review of the entire database. In
9 the Scharf database, again 7 percent of patients
10 reported 15 such events, with no discontinuations
11 and no dose relationship pattern observed.

12 [Slide]

13 The coding of confusion embodied a wide
14 range of verbatim terms, as shown here. These do
15 not represent confusion based on a standard medical
16 status examination. They do not differentiate
17 between nighttime events from those of awakening or
18 arousal parasomnias. These events led to no dosage
19 adjustment in 37 instances, but dose was reduced in
20 4 events, led to temporary discontinuation
21 following 4 events, and 3 patients discontinued
22 permanently because of a side effect of confusion.

23 [Slide]

24 When the GHB-2 controlled trial was
25 considered with respect to confusion, the highest

1 incidence in the databases is represented in this
2 4-week study by 10 patients. The highest incidence
3 was seen in the 9 g dose, and 6 of the 10 developed
4 during the first week of treatment. Seven of these
5 10 events were in patients over the age of 50. The
6 difference in this study, of course, was the
7 assigned doses rather than dose titration. It is
8 important to note that 1 event was reported in a
9 placebo patient.

10 [Slide]

11 In conclusion, the term represents a
12 symptom report rather than confusion defined in a
13 medical sense by formal mental status examination,
14 and all resolved usually without interruption of
15 therapy or dose modification. Confusion and other
16 associated symptoms are not unexpected with
17 sedating medications. The blinded, controlled
18 trial results suggest that a higher incidence may
19 result without dose titration.

20 [Slide]

21 Neuropsychiatric events will now be
22 reviewed. The adverse event database was searched
23 for terms that could represent neuropsychiatric
24 symptoms, and this led to the classification shown
25 in this slide. Fifty-two patients reported 57 such

1 events in the integrated safety database, of whom
2 12 discontinued as a result of these events. In
3 the Scharf database 41 patients reported 84 such
4 events, leading to 2 patient discontinuations.

5 [Slide]

6 Of these 57 events, 1 occurred while a
7 patient was on placebo. This slide lists the terms
8 examined and some, such as stupor and coma, failed
9 to represent neuropsychiatric events. Many
10 represented symptoms of narcolepsy such as
11 hypnagogic hallucinations COSTART-coded to the term
12 hallucinations. The most frequent was clinical
13 depression, and this represents a symptom rather
14 than a diagnosis of major depressive disorder.
15 Depressive symptoms are frequent accompaniments in
16 narcolepsy, and this is well recorded in the
17 literature. Suicide was attempted in 4 patients
18 with major preexisting psychiatric history, and
19 resulted in death in 2 of these patients. The
20 other representations of psychotic disorders and
21 the patient with manic depressive disorder also
22 occurred in patients with preexisting major
23 psychiatric disease. As is shown, a similar
24 profile of reported symptoms is found in the Scharf
25 database.

1 [Slide]

2 In conclusion, most patients with major
3 events had a preexisting psychiatric disorder.
4 Many events do not qualify as neuropsychiatric
5 disorders, as was represented by the terms pointed
6 out. Assignment of causality is very difficult
7 because narcolepsy is associated with depression
8 and even mechanistically there has been an
9 association between psychosis and the central
10 processes in narcolepsy. As Dr. Mignot mentioned,
11 stimulant medications are associated with central
12 nervous system side effects that are represented by
13 neuropsychiatric symptoms. And, it is true to say
14 that in many patients, particularly in the Scharf
15 database, pre-study screenings were deficient.

16 [Slide]

17 To lastly address sleepwalking, in the
18 integrated safety database 7 percent of patients
19 reported such events, whereas in the Scharf
20 database 32 percent of patients reported events
21 that were listed as sleepwalking. In the Scharf
22 trial, however, these reports were primarily data
23 listings in patient diaries in response to a
24 specific leading question, listed as a line item in
25 the diary.

1 [Slide]

2 The listing of this term did not receive
3 the benefit of medical consideration of a
4 differential diagnosis of somnambulism, and since
5 most patients were not seen by the investigator no
6 clarification was provided. Post hoc consideration
7 was rendered impossible given the lack of
8 information regarding sleep stage, time of night,
9 relationship to drug dosing, and could be
10 representative of any of the differential diagnoses
11 listed on this slide.

12 [Slide]

13 In the controlled trials only 3
14 sleepwalking events were reported, 2 of which
15 occurred on active treatment and 1 occurred in a
16 patient during placebo treatment.

17 [Slide]

18 Hence, in conclusion, the incidence in the
19 integrated safety database of 7 percent is not
20 particularly dissimilar to the range reported in
21 the literature for normal patients. This was
22 reported by Dr. Mahowald, of Minneapolis, as
23 between 4-10 percent in a publication in 1998, and
24 between 1-7 percent by Dr. Roger Broughton of
25 Canada.

1 Diary recording without medical
2 classification represents a potential increased
3 reporting in the Scharf trial. The slight increase
4 in incidence over the general population may
5 certainly be representative of Xyrem effects with
6 increase in slow wave sleep, but REM behavior
7 disorder, common in narcolepsy, may be a separate
8 consideration.

9 [Slide]

10 To summarize the safety profile of this
11 drug, we based our assessment to date on 604
12 patients, which represents 524 patients excluding
13 the Scharf database. Dosing was between 3-9 g per
14 day in divided nightly dosing. The common adverse
15 events were certainly headache, unspecified pain,
16 nausea, dizziness, and less common but important
17 adverse events were vomiting, confusion,
18 restlessness, agitation, sleepwalking and enuresis.

19 [Slide]

20 All events have been reversible. There
21 were no significant changes in lab values or vital
22 signs identified across the studies. There was no
23 evidence of organ toxicity outside the
24 pharmacologic effects in the central nervous
25 system. There was no diversion or consumption of

1 clinical trial supplies by any family members
2 during the trials, and there was certainly no
3 evidence of Xyrem diversion in our database.

4 [Slide]

5 I would like to conclude with the
6 statement that Xyrem was generally well tolerated.

7 [Slide]

8 To commence a risk/benefit assessment, I
9 would like to remind you of the indication proposed
10 by Orphan Medical for the use of Xyrem. That is,
11 to reduce the incidence of cataplexy and to improve
12 the symptom of daytime sleepiness in patients with
13 narcolepsy.

14 [Slide]

15 As has been pointed out, narcolepsy is an
16 uncommon disease, with an incidence of around 0.05
17 percent and, as such, has been qualified for orphan
18 designation. There are no therapies approved for
19 the treatment of cataplexy. Because of this, the
20 FDA were very kind to apply a priority review to
21 our submission and we are very appreciative of that
22 recognition. Current off-label therapies, so well
23 described by Dr. Mignot, are unsatisfactory.
24 Excessive daytime sleepiness has approved therapies
25 but these do not address cataplexy. There is

1 clearly a medical need existing beyond the
2 therapies available.

3 [Slide]

4 The benefits of Xyrem in the trials
5 presented were based on patient diary recordings,
6 investigator ratings of overall clinical
7 improvement in overall disease severity, and
8 objective measures of changes in sleep architecture
9 and daytime response.

10 [Slide]

11 Clinical benefit in the short-term
12 reduction in cataplexy was shown by the
13 dose-related reduction in cataplexy in the GHB-2
14 and Scrima studies and in the long-term efficacy in
15 the SXB-21. Subjective changes in the Epworth
16 Sleepiness Scale have been well demonstrated, and
17 reduction in daytime sleep attacks have accompanied
18 this change. Early objective Maintenance of
19 Wakefulness Test data supported these changes in
20 daytime sleepiness. The global impression of the
21 investigators for overall changes in disease
22 severity also showed a significant dose
23 relationship.

24 [Slide]

25 Xyrem was generally well tolerated when

1 used in the proposed dose range, with the most
2 common side effects reported including nausea,
3 dizziness, headaches, pain and confusion. Less
4 common but important associated effects include
5 enuresis and sleepwalking, with a possible dose
6 relationship suggested. Although there were 11
7 deaths in the Scharf trial over 16 years and 2
8 deaths by suicide in the integrated database, no
9 deaths were associated with Xyrem.

10 [Slide]

11 In relation to the specific FDA inquiries,
12 there is a possible relationship between Xyrem
13 therapy and somnambulism but further definition is
14 required. There is a marked discrepancy between
15 the reported incidence in the Scharf study of the
16 32 percent, recorded solely by diary entry in
17 response to a leading question, and the 7 percent
18 in the integrated database, which is really in the
19 range in public literature for the normal
20 population. In the controlled trials there were
21 only 3 such reports in total, 2 recorded in active
22 treatment and 1 during placebo treatment.

23 [Slide]

24 Confusion is also an adverse accompaniment
25 of sedative hypnotic drugs and has been identified

1 as an occasional side effect of Xyrem. Dose
2 titration may assist in limiting this side effect
3 but it remains an important component of patient
4 and physician education.

5 [Slide]

6 The incidence of enuresis with Xyrem
7 treatment supports an association that may be dose
8 related, but any association of these events with
9 seizure activity is very weak. In terms of Xyrem
10 causing seizures at the therapeutic doses, there
11 was no reliable support for such causality. In
12 this regard, the coding to the COSTART dictionary
13 terms of cataplexy as convulsion was confusing.
14 However, there were 2 patients recording seizures
15 with preexisting causes. Two further patients in
16 the Scharf database reported seizures where
17 confounding contributions rendered assignment very
18 difficult. One patient in the Orphar studies
19 represented a complex history of symptoms
20 characterized by fugue state and these symptoms
21 have been attributed to his narcolepsy syndrome.

22 [Slide]

23 No significant measures were seen in
24 laboratory measures, vital signs or ECG measures
25 and these changes were comparable across the

1 treatment groups. There was no evidence of organ
2 toxicity at therapeutic doses that were not part of
3 the central nervous system pharmacology of the
4 drug.

5 [Slide]

6 We did not identify any evidence of
7 kinetic or dynamic tolerance in the narcoleptic
8 populations studied and the absence of drug-drug
9 interactions in the 3 classes of drugs commonly
10 used in narcolepsy, along with the absence of
11 either induction or inhibition of the oxybate p450
12 enzyme system make it possible to predict that
13 drug-drug interactions should be minimal.

14 [Slide]

15 Although a serious withdrawal syndrome has
16 been described in the abuser population that
17 relates to escalation in both dose and frequency of
18 dosing, no evidence of withdrawal has been
19 demonstrated in patients maintained on long-term
20 therapeutic doses in narcolepsy. Following abrupt
21 discontinuation of long-term dosing in the blinded
22 study, only 2 patients reported anxiety but in the
23 presence of worsening cataplexy, with 1 patient
24 reporting mild dizziness and 1 report of insomnia.

25 [Slide]

1 We have not attempted in any way to
2 minimize the issue of abuse with GHB or its
3 precursors. We recognize that this is a serious
4 problem, but stress the fact that this has been
5 peripheral to the development program in
6 narcolepsy. We have detected no evidence of abuse,
7 diversion or self-escalation of dosing in patients
8 in clinical trials. Great efforts have been
9 applied to working with the appropriate expert
10 bodies to plan a restricted distribution system to
11 support in every way the unique bifurcated
12 scheduling legislated by Congress and to plan
13 physician and patient education to minimize the
14 possibility of diversion. This will be greatly
15 facilitated by the documentation centrally of
16 prescribing and patient use. This will be
17 described in detail to you later.

18 {Slide}

19 In conclusion, I would propose that we
20 have established statistically and clinically
21 significant evidence for the reduction in
22 cataplexy, and for improvement in daytime
23 sleepiness when used concomitantly with stimulant
24 medications.

25 Xyrem is generally well tolerated, with a

1 safety profile well characterized in this orphan
2 population by long-term exposure. The medical
3 benefits clearly outweigh the risks for a
4 therapeutic agent that may be the first single
5 agent to address the multiple symptoms of
6 narcolepsy. Thank you very much.

7 DR. REARDAN: I would just like to thank
8 the committee and FDA for your attention. I
9 believe Dr. Mani has some comments, or we are now
10 happy to take questions from the committee.

11 DR. KAWAS: The FDA will give us a
12 response to the presentation, and then we will
13 probably take a break before we have questions,
14 unless the committee has anything burning they need
15 to ask now. Dr. Ranjit Mani will present for the
16 FDA.

17 FDA Response to the Presentation

18 DR. MANI: What I propose to do in the
19 next few minutes is address two issues where our
20 views diverge somewhat from those of the sponsor.

21 [Slide]

22 The first is the effect of GHB on measures
23 of daytime sleepiness in narcolepsy.

24 [Slide]

25 This overhead illustrates how many

1 measures of daytime sleepiness there were in the
2 GHB efficacy trials. As you can see, GHB-2 had 3
3 measures of daytime sleepiness; the Scrima study
4 had 2, of which 1 was primary; and the Lammers
5 study had 2. I will draw your attention to the
6 fact that, with the exception of the Scrima study,
7 the remaining measures were all designated as being
8 secondary.

9 [Slide]

10 Because what is considered statistically
11 significant does depend or could depend on the
12 number of comparisons made, I think it is also
13 important to illustrate how many secondary efficacy
14 measures there were in each trial. In the GHB-2
15 trial I was able to count a total of 10; in the
16 Scrima study 17; and in the Lammers study 7.

17 [Slide]

18 This is based on data provided by Orphan.
19 As you can see, in the GHB-2 trial the Epworth
20 Sleepiness Scale measure did reveal a fairly
21 clear-but efficacy for GHB but only at the 9 g
22 dose. The p value of 0.001 probably remains
23 statistically significant even when adjustment is
24 made for multiple comparisons.

25 On the other hand, the frequency of

1 daytime sleep attacks and duration of daytime sleep
2 attacks should probably be considered negative
3 evidence of efficacy if adjustment is made for
4 multiple comparisons.

5 [Slide]

6 Again, in the Scrima study one primary
7 efficacy measure was sleepiness index of the
8 Multiple Sleep Latency Test. Here, the results
9 must be considered negative whether adjusted for
10 multiple comparisons or not.

11 [Slide]

12 The other measure was the frequency of
13 daytime sleep attacks, again negative whether
14 adjusted for multiple comparisons or not.

15 [Slide]

16 In the Lammers study the severity of
17 daytime sleepiness was 1 of 7 secondary efficacy
18 measures which is probably negative when adjusted
19 for multiple comparisons. On the other hand, the
20 frequency of daytime sleep attacks was positive,
21 but using an ANCOVA which was not a protocol
22 specified analysis.

23 [Slide]

24 So, here are the problems as we see them
25 with the proposed claim for excessive daytime

1 sleepiness. Most measures were secondary. The
2 only measure that was primary was negative. The
3 majority of measures were negative after adjustment
4 of the Type 1 error for multiple comparisons. The
5 effects were inconsistent across studies, and the
6 clearly positive results on the GHB-2 trial on the
7 Epworth Sleepiness Scale were not replicated. As
8 mentioned, the approval of modafinil for the
9 treatment of excessive daytime sleepiness was based
10 on replicated results in 2 efficacy studies. And a
11 minor point, the results on the GHB-2 study were,
12 to some extent, confounded by concurrent stimulant
13 use, raising the question, among other questions,
14 of whether Xyrem is effective as monotherapy for
15 the treatment of excessive daytime sleepiness.

16 [Slide]

17 The second issue that I want to address
18 briefly is that of sleepwalking. As you can see, I
19 have put it in quotes. As Bill Houghton has
20 already emphasized, we do not know what these
21 episodes represent. They have not been clinically
22 characterized.

23 [Slide]

24 The term sleepwalking does not correspond
25 to the medical entity of somnambulism. The term is

1 based entirely on patient diary entries, and there
2 has been no attempt to characterize the episodes
3 further and define what clinical entity they
4 correspond to.

5 The incidence of these episodes, whatever
6 they may represent, was approximately 32 percent.
7 The majority of patients did list as having more
8 than one episode. A single patient had a total of
9 346 episodes over a 5-year period. As already
10 said, an adequate clinical description is lacking,
11 and the episodes cannot be said to be completely
12 benign.

13 There was one patient who is reported to
14 have overdosed twice during two consecutive
15 episodes of sleepwalking. During one episode the
16 patient became comatose and needed to be
17 hospitalized, needed to be on a ventilator for some
18 hours but completely recovered. A second pat had
19 multiple episodes of sleepwalking. She was found
20 by her husband to be smoking, apparently
21 inadvertently. During one such episode her clothes
22 were set on fire. The fire was put out. She was
23 taken off GHB and did not have any further such
24 episodes. A third patient is reported to have
25 swallowed nail polish remover during an episode,

1 without any serious consequences.

2 I would also like to add one minor point
3 in response to Dr. Houghton's presentation. That
4 is, I believe that in the Scharf study there was
5 one patient who was withdrawn from the study
6 because he felt that he had benefitted from Xyrem
7 and decided that these benefits could be extended
8 to a circle of friends who also received part of
9 his own supply, again apparently without serious
10 consequences. Thank you. That is really all I
11 have to say.

12 DR. KAWAS: Thank you, Dr. Mani. Does the
13 committee have any questions they would like to ask
14 before the break? If not, we will reconvene this
15 meeting at 10:30 sharp.

16 [Brief recess]

17 Committee Discussion

18 DR. KAWAS: Will you please have a seat so
19 we can reconvene this session? This meeting of the
20 Peripheral and Central Nervous System Advisory
21 Committee is now reconvened. We appreciate the
22 presentations from the sponsor and the FDA, and the
23 floor is open for questions. The first question is
24 going to come from someone who has been patiently
25 sitting on the phone. Dr. Chervin, can you hear

1 me?

2 DR. CHERVIN: Yes, thank you.

3 DR. KAWAS: Dr. Chervin, we can't year you
4 yet, if you will give us a moment to do whatever it
5 is we have to do?

6 DR. CHERVIN: Can you hear me now?

7 DR. KAWAS: Give it a shot.

8 DR. CHERVIN: I have a question perhaps
9 for Dr. Houghton. In regard to the safety
10 experience with the 1328 patient years, were there
11 any reports that alcohol was taken in the evening
12 in combination with GHB? If so, what was the
13 outcome?

14 DR. HOUGHTON: It was certainly
15 recommended as a contraindication in our protocols.
16 The advice to the patient was that they not consume
17 alcohol during the studies. I can't vouch for the
18 fact that it was entirely complied with, but we
19 don't have protocol or database record of
20 consumption of alcohol during the trials. There
21 certainly is record of patients having imbibed
22 during the Scharf study and I am not in a position
23 to clarify that.

24 DR. GUILLEMINAULT: This is Dr.
25 Guilleminault. I have also a question, and it is

1 for Dr. Mani, about the sleepiness data. Was there
2 the slow wave sleep information looked at for
3 sleepiness? As you know, delta power greatly
4 improves alertness and there are many studies,
5 sleep deprivation studies and investigation into
6 sleep disorders such as obstructive sleep apnea,
7 where it is very clear that decrease in delta power
8 and in slow wave sleep has a big impact on the
9 alertness, and the more delta power you have and
10 the more slow wave sleep you have, the better
11 alertness the next day.

12 So, one of my understandings is that this
13 drug has an impact on slow wave sleep and delta
14 power. Was there any analysis of that in data
15 looking at alertness?

16 DR. MANI: To the best of my knowledge, it
17 was not listed as an efficacy measure in any of the
18 controlled studies that I looked at.

19 DR. GUILLEMINAULT: Okay. The second
20 question is maybe a question about my ignorance. I
21 did not understand exactly the statistic about the
22 ESS because in the investigation of the results of
23 the ESS there was an investigation with negative
24 studies. All the results, when you look at
25 everything there, was there a positive p value?

1 Was there a statistical difference? Because I
2 don't understand the manipulation which was done.
3 Maybe through poor knowledge, I have never seen
4 this type of manipulation.

5 DR. REARDAN: Dr. Guilleminault, which
6 study are you referring to when you ask about the
7 Epworth Sleepiness score?

8 DR. GUILLEMINAULT: I think OMS-2.

9 DR. REARDAN: Is that for Dr. Mani, or do
10 you want to pose that to the company?

11 DR. GUILLEMINAULT: No, I was asking that
12 because Dr. Mani reported that he looked at that
13 study and classified the results, and my
14 understanding, and it may be a wrong understanding,
15 is that he made a subdivision in looking at the
16 results and I did not see completely the
17 statistical rationale for that approach.

18 DR. MANI: Are you referring to the
19 statistical adjustments for multiple comparisons?
20 Is that what you mean?

21 DR. GUILLEMINAULT: No, the Epworth
22 Sleepiness Scale study in GH3 2, secondary efficacy
23 daytime sleepiness on your slide, and I did not
24 understand exactly how that was analyzed, the type
25 of analysis that was done or redone.

1 DR. MANI: Perhaps I should ask the Orphan
2 statisticians to explain that in greater detail,
3 but the analysis was an ANCOVA.

4 DR. GUILLEMINAULT: The microphone must be
5 poorly placed because we cannot hear the response.

6 DR. MANI: Can you hear me now?

7 DR. GUILLEMINAULT: Yes.

8 DR. MANI: The analysis was an ANCOVA. I
9 mean, perhaps I should get the Orphan study
10 statistician to explain the analysis to you in
11 greater detail.

12 DR. REARDAN: I am just asking Dr. Richard
13 Trout, the statistician, to comment on how the
14 Epworth Sleepiness score was statistically
15 analyzed.

16 DR. TROUT: Hi. My name is Dick Trout.
17 First of all, the analysis was just as you
18 described, that is to say it was an analysis of
19 covariance which was preplanned. I think the
20 concern that you expressed was the fact that it was
21 listed as a secondary efficacy measure --

22 DR. GUILLEMINAULT: Right.

23 DR. TROUT: -- as compared to a primary,
24 and there was a number of secondary efficacy
25 measures, but even if one adjusted for the multiple

1 testing which I think you were concerned about, the
2 9 g separation from the placebo group would still
3 be significant. We already adjusted for the
4 multiple testing with regard to the dosing issue,
5 using Dunnett's test, but your concern was with
6 regard to the fact that there were a number of
7 secondary efficacy measures which would then
8 diminish the effect.

9 DR. GUILLEMINAULT: Okay, thank you.

10 DR. PENN: I can see that the claim for
11 helping daytime sleepiness is going to be one that
12 we will want to look into very carefully, and I
13 want to ask our FDA statistician a question about
14 that in a general sort of way. If you were a
15 gambling person, which I assume a statistician
16 would not be --

17 [Laughter]

18 -- from the data that you have looked at
19 for 9 g, would you say that in a good controlled
20 trial you would bet on it working to decrease
21 daytime sleepiness? It looks like the strongest
22 data is at 9 g and that is what the company is
23 suggesting. I am going to ask you to bet on that,
24 and then I am going to make a point.

25 DR. MANI: You addressed the question to a

1 statistician; I am not a statistician.

2 DR. PENN: Oh, I am sorry. Anybody else
3 want to gamble with this?

4 DR. REARDAN: Coming up to the podium is
5 Dr. Sharon Yan, who is the FDA statistician that
6 has been working on the Xyrem program.

7 DR. YAN: Basically we rely on the results
8 that were prespecified, and a lot of results that
9 we looked at -- and you want me to bet -- after
10 looking at those results, most people would bet
11 that the data shown, for example, the 9 g it seems
12 that it is highly positive; it is highly
13 significant, but we rely on the analysis which is
14 prespecified. Without that, the data information
15 -- it is hard to bet on anything.

16 DR. PENN: But I am asking you how you
17 would bet on that if you had to make a bet now in
18 Las Vegas, and the point I am trying to make is
19 that it seems to me a reasonable bet that it does
20 help daytime sleepiness but that they haven't
21 presented two clean studies that show at 9 g that
22 that is the case. And, is there going to be some
23 middle ground to this where that claim can be put
24 in language that would be acceptable later on? So,
25 I wanted to see if you agree that that analysis

1 then presenting of the problem is the correct one,
2 that is, that there is very strong suggestive
3 evidence, not as strong as we often want for a
4 claim, that it helps daytime sleepiness. When you
5 sit back and you look at all the data, would you
6 bet on that helping daytime sleepiness?

7 DR. KAWAS: Perhaps Dr. Katz could help
8 with this response.

9 DR. KATZ: Yes, again, I will just sort of
10 reiterate something that Dr. Yan has already said,
11 which is that whether or not we personally believe
12 something is true or what we would bet on is not
13 really the standard. The standard which we apply
14 is what the law requires, which is substantial
15 evidence of effectiveness, ordinarily defined,
16 unless there is some compelling reason to do
17 otherwise, as data from at least two adequate and
18 well-controlled trials demonstrating effect. We
19 have adopted by tradition a usual sort of
20 statistical rule by which we decide whether or not
21 a study is "positive" for a particular indication.
22 So, I think that is the standard. Unless there is
23 some, as I say, very compelling reason to apply
24 some different standard, like what would I bet on
25 or what my personal belief is, that is the standard

1 we need to apply. Again, unless there is a view
2 that there is some compelling reason to apply some
3 different standard, we would ask you as a committee
4 whether you think that the evidence for that
5 particular claim meets that standard.

6 DR. PENN: So, once again the question
7 should go then to Orphan, whether or not they feel
8 they have met that standard on two separate
9 occasions using their 9 g amount, and I haven't
10 gotten a clear-cut idea in my mind whether they are
11 really claiming that or just showing us data that
12 would be for a good bet.

13 DR. YAN: May I clarify one thing? For
14 the analysis for daytime sleepiness for GHB-2 the
15 sponsor showed it was highly significant, with a p
16 value of 0.001, and I analyzed the data with the
17 original scale and, as I analyzed it, it shows that
18 the normal assumption was validated and then the
19 log transformation to then improve the data, and I
20 used nonparametric analysis to analyze the p value,
21 and it is not that small. As I remember, the p
22 value is 0.03 or something.

23 DR. RFARDAN: I can comment on the trials.
24 We have GHB-2, obviously, where the trial was very
25 effective. I don't think there is a dispute with

1 FDA on that. The question is do we meet the
2 standard of two well-controlled trials for that
3 indication. The data in support of that comes from
4 the Lammers study. The sleepiness scale used there
5 was something he developed, not a validated scale
6 but it was statistically significant for daytime
7 sleepiness, albeit in a very small, 24-patient
8 crossover trial.

9 So, we have a small supportive study. We
10 have the large controlled study, GHB-2. That is
11 the evidence basically. Bill, do you want to
12 comment?

13 DR. HOUGHTON: Yes. We are not trying to
14 make this something that it is not in any way, and
15 if you apply the absolute, most rigorous standards
16 of normal drug development to our database, we have
17 a small database. We did have the two components
18 that were statistically significant. This was
19 supported by the reduction in daytime sleep attacks
20 which are very clinically significant to the
21 patient, and we had two components of statistical
22 significance there.

23 The other issue, and I know that this from
24 a pure mathematical sense is problematic, is the
25 evidence of long-term support in daytime sleepiness

1 claim with the GHB-3 protocol, which showed the
2 Epworth Sleepiness Scale and the daytime sleepiness
3 reduced and maintained over the long period of
4 time. The fact then that the objective data in
5 SXB-20 was so strongly supportive and the change in
6 Maintenance of Wakefulness Test is an objective
7 measure and was clearly positive was very
8 important.

9 The part that concerns me from a clinical
10 point of view is if you look at the patient
11 profiles as they enter the studies, they are on
12 stable doses of stimulants and, yet, their ratings
13 are very low. The real issue is that daytime
14 sleepiness with current medications isn't well
15 addressed. So, the question is not only have we
16 shown absolute irrevocable evidence of long-term
17 efficacy for daytime sleepiness with the existence
18 of the present treatments for long-term
19 effectiveness, what we didn't do is ask for a claim
20 in daytime sleepiness.

21 [Slide]

22 Our proposed indication was to improve the
23 symptom. We didn't attempt to do studies that
24 displaced the stimulant therapies. What we are
25 really looking at is a hand-in-glove approach that

1 actually makes patients better as an incremental
2 change, and all therapies up to now have been very
3 separate. The symptoms of daytime sleepiness and
4 those of the associated REM phenomena have been
5 treated by entirely separate medications. If there
6 is a component of Xyrem that assists in daytime
7 sleepiness as an incremental change, we think it is
8 very clinically important and that is what we
9 sought to present today. I want to stress very
10 clearly that we are not looking for the claim of
11 daytime sleepiness; we are looking at an
12 improvement in the symptom thereof.

13 DR. KAWAS: Dr. Houghton, can I ask you
14 then, to my reading, that indication is actually
15 two indications, I mean, cataplexy and sleepiness
16 being a separate one. When I was reading the
17 materials that you very carefully provided us,
18 obviously for cataplexy the GHB 2 and the SXB-21
19 study speak to that issue as pivotal trials. I was
20 going to ask you which were the two that speak to
21 the issue of daytime sleepiness. Now I understand
22 them to be the GHB-2 and the Lammers small trial
23 with the questionnaire that was developed there.
24 In both of those cases, however, we are talking
25 about subjective sleepiness from the Epworth scale

1 and the other question. Since there are factors
2 that can influence someone's subjective feelings of
3 sleepiness, do you have any objective measures that
4 support the indication of daytime sleepiness?

5 Specifically, the one trial that I am aware of that
6 had an MSLT and did daytime sleepiness as a primary
7 outcome measure, in fact, appears to be not
8 supportive of the indication.

9 DR. HOUGHTON: Yes, in the Scrima trial he
10 used the MSLT measure and that was not
11 statistically significant, as shown. The objective
12 data that we propose supports very strongly the
13 effect of adequate dosing of GHB was the SXB-20
14 trial that Dr. Black discussed. That is not only a
15 profound improvement in the MWT at the 9 g dose but
16 a defined dose response across all doses. That is
17 very positive data.

18 DR. KAWAS: In ten patients, it appears.

19 DR. HOUGHTON: Twenty-one.

20 DR. MANI: May I also add that that was an
21 open-label, non-randomized study?

22 DR. HOUGHTON: Sure, but using an
23 objective measure.

24 DR. RISTANOVIC: I am I am Ruzica
25 Ristanovic, medical director of Sleep Disorders

1 Center, in Evanston, Illinois. I would like to
2 comment on add-on Xyrem in the presence of other
3 stimulants. Other studies attempt to try to
4 document the effectiveness of other stimulants in
5 narcolepsy-related sleepiness documents, including
6 the most rigorous trial of modafinil in
7 double-blind, placebo-controlled studies. They
8 document that these drugs improve sleepiness but
9 very seldom outside of the range of pathological
10 sleepiness as measured by Multiple Sleep Latency
11 Test and Maintenance Wakefulness Test. So, the
12 patients remain sleepy. That is the message.
13 Add-on treatments are approved for other
14 indications in other neurological diseases, such as
15 epilepsy. So, I assume that this application for
16 that particular indication is not for monotherapy
17 but as an add-on to concurrent use of stimulants.
18 I would like to bring this to your attention. So,
19 patients do remain sleepy on stimulants and they
20 need additional treatments.

21 DR. KAWAS: Dr. Temple?

22 DR. TEMPLE: Dr. Houghton also seemed to
23 be distinguishing between monotherapy and add-on
24 therapy. That is not the problem. The problem is
25 whether there is adequate support for use as an

1 addition for whatever else the patient is on, and
2 whether there are well-controlled studies that
3 support that. So, add-on would be perfectly fine.
4 That is usually true in a lot of conditions, not
5 just neurological ones, where you continue to give
6 standard therapy and try to improve it.

7 I just want to make one observation about
8 the evidence. We do expect to see replicated or
9 reproduced findings. Some of the issues here are
10 whether the fact that the endpoints are secondary
11 and need some correction means that there isn't
12 adequate support. A lot of these things are
13 matters of judgment that the committee can weigh in
14 on. Not everything is, you know, a yes/no. Some
15 of the things are moderately subtle and that is why
16 this is being brought to you for judgment. There
17 is one study that is obviously stronger than the
18 rest but the others can be considered, and you sort
19 of have to think about how many real endpoints
20 there really are; how much of a correction is
21 needed. Those are difficult discussions but worth
22 considering.

23 DR. KAWAS: Dr. Katz?

24 DR. KATZ: I agree, but I think we would
25 still have to have the application meet the

1 standard of independent replication, in other words
2 two trials. You can decide that one of the other
3 trials actually does meet the usual standard,
4 again, taking into consideration the multiplicity
5 and that sort of thing. All I am saying is that I
6 don't think we can say we have one study that looks
7 good. If you believe that GHB looks good and the
8 others sort of contribute to a feeling that it
9 probably is okay, I mean, we really need two
10 independent sources that you believe demonstrate
11 the effectiveness.

12 The only other point I wanted to add is to
13 something, Claudia, you said which has to do with
14 Dr. Houghton's view that they are not going for a
15 claim of daytime sleepiness; they just want, I
16 guess, to have language in the labeling that says
17 that it improves that symptom. Most of the drugs
18 we approve are for symptomatic claims, so there is
19 no question that the inclusion of this language in
20 the indication is a claim as we always understand
21 that term.

22 DR. KAWAS: Dr. Guilleminault, followed by
23 Dr. Wolinsky, please.

24 DR. GUILLEMINAULT: If you look at all the
25 published data on modafinil, on amphetamine, on

1 methylphenidate, none of these drugs ever
2 normalized all the objective tests on alertness and
3 daytime sleepiness. None of them, including the
4 modafinil data which were approved by the FDA. The
5 MSLT and MWT for all these drugs are pitiful. The
6 only data which shows significance was the Epworth
7 Sleepiness Scale, which is a subjective scale, in
8 all these trials. So, we cannot expect to have any
9 positive result with subjective tests in any of
10 these drugs. We will always have to rely on
11 subjective tests even if the subjective test is not
12 great. Everybody in the field agrees that the
13 Epworth Sleepiness Scale is the most used scale
14 despite the fact that it has a lot of downfall, and
15 we have to remember that when we look at what has
16 been approved and what is being used.

17 DR. KAWAS: Thank you, Dr. Guilleminault.
18 I think that many people would agree with those
19 comments, but my question to you would be not
20 whether or not the Epworth Scale subjective
21 measurements are good but do we have two
22 randomized, controlled trials that show an
23 improvement in subjective sleepiness.

24 DR. GUILLEMINAULT: That was my initial
25 question because my understanding is, when the

1 statistician from the FDA responded, she said that
2 when she did a nonparametric analysis she found out
3 that she had a p value of 0.03. So, my
4 understanding is that she had a significant finding
5 even when she did the reanalysis. That was my
6 understanding of her response.

7 DR. KAWAS: Would you like to comment, Dr.
8 Yan?

9 DR. YAN: I am sorry, the previous number
10 is not right. I checked. The number for the
11 nonparametric analysis, the p value was 0.0109.

12 DR. WOLINSKY: I have a couple of
13 questions first for some information before I ask
14 the real question. For the informational questions
15 perhaps Dr. Mignot could help with. So, the first
16 question I have is if you could enlighten us or
17 re-enlighten us about how many patients that have
18 narcolepsy have had cataplexy as a component
19 symptom. What proportion?

20 DR. MIGNOT: In most case series it is
21 about 70 percent.

22 DR. WOLINSKY: The second question is that
23 at least for most of these studies which were done
24 and presented to us since cataplexy was being
25 measured, as is appropriate, the number of

1 cataplectic attacks was relatively high. I think
2 in these studies it was around 20 cataplectic
3 attacks per week. So, how many of the 70, 75
4 percent of patients with narcolepsy who have
5 cataplexy have cataplectic attacks at that level?

6 DR. MIGNOT: I would guess 20 percent.

7 DR. WOLINSKY: Thank you very much.

8 DR. MIGNOT: Yes, roughly.

9 DR. WOLINSKY: And then they would fall
10 down below that level for the remainder of the 55
11 percent of narcoleptics with cataplectic attacks.

12 DR. MIGNOT: If you analyze the spread of
13 the number of cataplexy episodes per week, but you
14 have to balance that also with the efficacy of
15 current treatments. A lot of people that currently
16 have cataplexy that is relatively mild just don't
17 want to take the antidepressants because they have
18 so many side effects, especially sexual side
19 effects, dry mouth, all these problems --

20 DR. WOLINSKY: This is not the question
21 though. So, now the question to Orphan which has
22 really, truly become an orphan drug question, is
23 since all of the studies that have been done have
24 enriched for cataplexy, do we have any data that
25 would suggest that if cataplexy is adequately

1 controlled or if there is no cataplexy so we don't
2 have to worry about the control of cataplexy there
3 would be any effect of the drug on daytime
4 sleepiness in non-cataplectic narcoleptics?

5 DR. REARDAN: I think Jed Black wants to
6 make a comment on that.

7 DR. BLACK: Just a comment on the
8 prevalence of cataplexy in the 70-75 percent of
9 folks with narcolepsy that had cataplexy, the
10 frequency of events -- this is something that Dr.
11 Mignot is not aware of, the cataplexy was
12 subdivided into major events and minor events.
13 About 20 percent or so would have the major events
14 to that level, but when we look at the minor events
15 a far greater percentage of that 70 percent, which
16 may be up to 80, 90 percent of that 70 percent,
17 will have that number of minor effects. Those are
18 not complete attacks where they fall down. In
19 fact, with most narcoleptic patients, they
20 distinguish between the two and they will often
21 only report to the physician the major events. But
22 in the diaries that Orphan had set up all the
23 events are characterized.

24 DR. WOLINSKY: So, the second question --

25 DR. BLACK: We have no idea. That is an

1 excellent question that I think needs to be
2 determined, but in the studies that have been
3 completed that question cannot be answered.

4 DR. REARDAN: Jed, the only study I can
5 think of maybe is SXB-20 where cataplexy was not an
6 entry criterion and I don't know what the cataplexy
7 incidence in that trial was. Bill is shaking his
8 head -- we didn't record it and we didn't
9 quantitate it.

10 DR. BLACK: We can't comment on that.

11 DR. REARDAN: It is true that in most of
12 our studies patients were selected because at entry
13 criteria they had to have a baseline cataplexy.

14 DR. KAWAS: Dr. Penix?

15 DR. PENIX: Before we address the two
16 separate indications issue -- and I guess, Dr.
17 Black, I could direct this question to you -- in
18 the GHB-2 study you did look at all cataplexy
19 events, I guess, and then total and partial
20 cataplexy. In the background material, in the
21 separation of the two it appeared that there was no
22 significant difference in any of the three doses of
23 GHB on total or complete cataplexy but your effect
24 was primarily in partial cataplexy. Is that
25 correct?

1 [No verbal response]

2 So, my question in that regard is what is
3 the clinical significance of partial cataplexy, and
4 you mentioned that patients frequently do not want
5 treatment for partial cataplexy. So, is this a big
6 problem? I presume that the patients that would
7 perceive a problem would be the ones with the
8 complete cataplexy but there we see no significant
9 difference. So, is there a problem there with
10 that?

11 DR. BLACK: I think this is a good point,
12 and the difficulty comes in trying to separate the
13 two because it is not sort of a box of partial and
14 a box of complete; it is a gradation, you know,
15 ranging from small partials to large partials and
16 the completes. So, I think this analysis is
17 difficult to perform. Clinically the degree of
18 improvement with traditional anticataplectic
19 medications that we use is similar. So, the
20 reduction in partial -- if that is all that is
21 being seen here and I am not convinced that
22 clinically that is the case -- while the
23 statistical analysis didn't demonstrate a
24 significant difference in the complete cataplexy
25 attacks, clinically there is an improvement in all

1 the different categories, and it is very
2 substantial in traditional antiepileptic
3 medications as well as with GHB.

4 DR. PENIX: Could Dr. Mignot comment on
5 the clinical significance of partial cataplexy? Is
6 it a big problem?

7 DR. MIGNOT: Yes, it is a big problem. In
8 fact, the problem is especially the social aspect
9 of cataplexy, when you have to realize that you are
10 just in the middle of a crowd and are meeting some
11 friends, and you can never tell when it is going to
12 happen. It may happen in very odd circumstances.
13 So, often even the doctors don't know what it is
14 and they just look at it and they wonder why this
15 person is kind of losing slight control and has to
16 sit down. There is also almost a social aspect
17 with fear of cataplexy that can occur at any time,
18 any moment and, yes, it is a very significant
19 problem.

20 Again, it is a balancing act because the
21 drugs that we use are somewhat effective but they
22 have all these side effects and you just have to
23 choose between two evils. I am pretty sure that,
24 for example, GHB, based on my relatively limited
25 experience, has less side effects than

1 anticataplectic classical tricyclic
2 antidepressants, and that a lot of patients would
3 prefer to take GHB even for partial cataplexy.

4 DR. PENIX: The case that you showed of
5 the nine-year child I assume is complete cataplexy
6 --

7 DR. MIGNOT: Yes.

8 DR. PENIX: -- but you are also saying
9 that patients with partial cataplexy have a
10 significant impairment of their life.

11 DR. MIGNOT: Absolutely. But, as Dr.
12 Black mentioned, it is not an "all or none." I
13 mean, most patients, the ones that are complete,
14 have a lot of partial cataplexy. You never know
15 how bad it is going to be. Most of them are small,
16 little attacks, and sometimes they may even be
17 perceived only by the patient. Sometimes the face
18 may melt; the head drops. Sometimes they just have
19 to sit down; sometimes they don't have to sit down.
20 I showed a young kid because it is more dramatic,
21 but you would see the same thing in some of the
22 patients with partial cataplexy occasionally.

23 DR. BLACK: I am realizing that a
24 definition may be useful here. In general when we
25 were describing patients who documented the partial

1 versus complete, we told them to think about
2 complete as an episode where they fall to the
3 ground with complete paralysis or where, if they
4 weren't sitting, they would have fallen to the
5 ground with complete paralysis. Otherwise,
6 anything else is partial -- so, slurred speech,
7 head drops, dropping things are the partials, and
8 those become very important for quality of life and
9 daytime performance. Driving, those kinds of
10 things can become a very significant event for
11 partials.

12 DR. MIGNOT: Yes, one thing I should also
13 emphasize is that in a very large number of series
14 that, for example, have analyzed several hundred
15 patients with narcolepsy and cataploxy, as a mean
16 the large majority of patients have several attacks
17 per day, several attacks per week. Between several
18 attacks per day and several attacks per week, that
19 is generally partial or complete attacks and it is
20 not something that appears just once, you know,
21 every ten years. It is really something that
22 occurs regularly and sometimes totally
23 unexpectedly.

24 DR. KAWAS: Dr. Falkowski?

25 DR. FALKOWSKI: That leads me to a

1 question just for clarification. For the purposes
2 of these clinical trials, were the cataplectic
3 events something that was just perceived by the
4 patient and recorded in a diary, or were they
5 verified by some third party?

6 DR. REARDAN: These were taken from
7 patient diaries. So, it is patient recorded
8 episodes.

9 DR. HAGAMAN: I am Dr. Hagaman and I just
10 wanted to address the partial versus the complete
11 cataplectic events. I think that you have to take
12 it on an individual basis. We have patients that
13 come in that are teenagers that have tests in front
14 of them and they have a partial cataplectic event
15 and they drop their pencil; people that cut hair
16 that have scissors in their hands and they drop
17 their scissors. So, even though they have not had
18 a complete event, this has been a very debilitating
19 event in their lives. So, it is a continuum and I
20 think you just have to really look at each person
21 as an individual and what they are doing.

22 DR. KAWAS: Dr. Dyer?

23 DR. DYER: How variable in the same
24 patients are the number of cataplectic attacks per
25 week? What is the variance in that?

1 DR. MIGNOT: We have looked at that quite
2 a bit.
3 Actually, I did some diaries in a large number of
4 patients with cataplexy. It is really totally
5 unpredictable and that is one of the most scary
6 parts about cataplexy when you have narcolepsy. Of
7 course, if something emotional is going to happen,
8 say a patient is going to go to a wedding, often
9 they will kind of fear that event much more because
10 they think it is very likely that they are going to
11 have cataplexy in front of everyone and, indeed,
12 they may actually have a lot more cataplexy because
13 it is an emotional event.

14 Still, I have followed, for example,
15 patients and sometimes they may have like 80 for
16 one week and then the following week they may have
17 only three or four. I mean, it can really vary
18 quite a bit. And, one of the main reasons is
19 really that emotion is something that is very
20 variable. In fact, someone mentioned how easy it
21 is to observe cataplexy. It is very difficult to
22 get it on tape because typically the patient come
23 to your office; he really wants to show you what it
24 is but, you know, he is tense and it just will not
25 occur but as soon as he leaves the office and

1 something happens -- boom, he is going to collapse.
2 So, it is very difficult to predict and it is quite
3 variable.

4 DR. ROMAN: For Dr. Mignot also, you
5 mentioned that cataplexy probably is the result of
6 what you called dissociated REM. However, if I
7 recall correctly, the polysomnographic analysis has
8 shown that Xyrem actually decreases the amount of
9 REM sleep and increases delta sleep. Would you
10 like to speculate on what could be the mechanism of
11 action to improve the cataleptic component?

12 DR. MIGNOT: That is a very, very
13 difficult question. One of the difficult
14 questions, of course, is the mode of action of GHB.
15 I have looked into it myself for quite a while
16 because I was trained as a pharmacologist, and it
17 is not clear. There are two camps. Some people
18 think it acts on GHB receptors, specific receptors;
19 others think that it acts through the GABA-B
20 receptors. We know that it has some strong effect
21 on dopamine transmission. If you inject GHB in
22 animals the rate of activity of dopaminergic cells
23 shuts down and dopamine can increase in the brain
24 proportionally to the dose. We have done quite a
25 bit of studies that have shown that the

1 dopaminergic system is very important to regulate
2 both wakefulness and also cataplexy and the
3 regulation of emotion. I believe it is by changing
4 the balance of the dopaminergic system, that
5 improves cataplexy the following day maybe by
6 increasing dopamine in the brain during the night,
7 but this is highly speculative and a lot more
8 research needs to be done.

9 The fact that it does not increase REM --
10 first, it is quite variable because some studies
11 have shown that it does increase REM and this
12 contrasts dramatically with what all hypnotics do.
13 If you take MVN or all the other
14 benzodiazepine-like hypnotics, what they do is
15 actually, rather, reduce slow wave sleep and reduce
16 REM sleep. Xyrem doesn't do that. It actually
17 promotes slow wave sleep and, if anything, would
18 promote REM sleep or doesn't change it. That is
19 still, you know, much more in the right direction
20 of promoting normal sleep, including REM sleep.

21 The last comment I want to mention is that
22 it is not sufficient -- if you know a lot about
23 narcolepsy, it is not sufficient to just explain
24 narcolepsy as a disorder of REM sleep. Indeed,
25 they have all this transition to REM sleep but they

1 also have impaired wakefulness per se. For
2 example, if you do MSLTs they don't always go into
3 REM. They will often just fall asleep into normal
4 sleep. So, it is not only REM sleep that is
5 disregulated in narcolepsy, it is also wakefulness
6 and by improving slow wave sleep you presumably
7 also can improve the wake aspect of narcolepsy. My
8 answer may be a little complicated but I would be
9 happy to discuss it in more detail.

10 DR. KAWAS: Dr. Van Belle?

11 DR. BLACK: Just another comment on that,
12 the Broughton study showed an increase in REM at a
13 lower dose. The first dose of the SXB-20 that I
14 participated in showed at 4.5 g the first night an
15 increase in REM, which was then followed by a
16 dose-related decrease in REM over time, which is
17 very different from REM suppressant agents where
18 there is a robust, or in fact the largest effect
19 that can often be seen on the first night of
20 administration.

21 So, we don't know exactly why it is that
22 over time the REM with higher doses is reduced, and
23 why with the first dose, and with the lower doses,
24 as has been demonstrated here with Roger
25 Broughton's work, why the REM is increased. There

1 has been established sort of a competitive reaction
2 between slow wave sleep and REM sleep. It appears
3 that there may be factors that regulate slow wave
4 sleep that also are important in regulating the
5 appearance, or lack thereof, of REM sleep. It may
6 be that gama hydroxybutyrate is sort of normalizing
7 slow wave activity which then results in a more
8 normal control or regulation of the REM or
9 REM-related events.

10 DR. KAWAS: Can I ask for my
11 clarification, what dose the company is proposing?

12 DR. REARDAN: Bill, can you take that
13 question?

14 DR. HOUGHTON: Yes, the dosage regimen
15 that we are proposing is that patients be started
16 at 4.5 g and then titrated between the range of 3-9
17 g to clinical efficacy. Although in the strictest
18 mathematical sense the only statistical efficacy in
19 the GHB-2 study was clearly defined at 9 g, that
20 may well represent that the study was too short
21 because in the open-label study that followed, as I
22 showed, the maximum nadir occurred at 8 weeks, and
23 when those patients were followed over the course
24 of 12 months they maintained efficacy across the
25 dose range. Certainly, there is an advantage in

1 terms of the important side effects to dose
2 titration. In all of the treatment IND protocols
3 and the safety studies the data was generated at
4 between 3-9 g. Now, 80 percent of the patients
5 were maintained between 6 g and 9 g, but there was
6 certainly facility for down-titration from the 4.5
7 or maintenance there as well.

8 DR. KAWAS: Thank you. Dr. Van Belle?

9 DR. VAN BELLE: It seems to me that there
10 is reasonable agreement with respect to efficacy
11 for cataplexy at least between the FDA and the
12 sponsor. So, I would like to get back to the
13 secondary endpoints. I would like to ask a
14 question to the sponsor's statistician, Dr. Trout,
15 as to whether he thinks that multiple comparisons
16 is a problem. Secondly, if multiple comparisons
17 are a problem, how he would adjust.

18 DR. REARDAN: Do you want to put this in
19 relation to a specific trial or all the trials in
20 general?

21 DR. VAN BELLE: Well, I bring it up in
22 connection with the analysis of Dr. Mani where he
23 clearly comes to conclusions that differ from yours
24 with respect to the efficacy of some of these
25 secondary endpoints.

1 DR. TROUT: You know, it is hard to answer
2 that question. I think the way I would answer that
3 is as follows: The GHB-2 analysis, the results
4 that we found and also that were expressed earlier
5 were very strong. So, even with the fact that
6 there is some multiplicity, we also have, remember,
7 some other outcome measures which were related to
8 this particular general area in terms of daytime
9 sleep attacks. So, there were at least two
10 measures that suggested improvement with respect to
11 that particular outcome.

12 The other second study that has been
13 discussed is the Lammers study, and that study is
14 obviously much smaller. It is obviously a weaker
15 study, and there is some issue with regard to
16 whether the appropriate method of analysis was
17 there. So, I think that is a harder one to
18 address.

19 Now, there are two kinds of multiplicity
20 going on here, which you are well aware of. One is
21 the multiplicity with regard to the multiple dosing
22 levels and that was accounted for in our analyses.
23 The question that was brought up by Dr. Mani with
24 regard to the multiplicity of secondary endpoints,
25 and I am not a betting man but I think there is

1 certainly evidence to suggest that daytime
2 sleepiness is being affected possibly. But I don't
3 go to Las Vegas nor Atlantic City.

4 DR. KAWAS: Actually, while we have Dr.
5 Trout up, I would ask him with regard to excessive
6 sleepiness on the Epworth Scale in the GHB-2 study,
7 while there certainly was a difference in the two
8 groups, there were also major baseline differences
9 in sleepiness for the responders and the
10 non-responders. In fact, those that appeared to
11 respond had a baseline that was better than the
12 improvement in the other group. There was a
13 significant difference. Are you concerned about
14 these and how these might affect the results?

15 DR. TROUT: There is always concern about
16 baseline differences, and that was attempted to be
17 accounted for in two mechanisms, one, we looked at
18 change from baseline and we also did a covariate
19 adjustment to try to account for that.

20 DR. KAWAS: Dr. Katz?

21 DR. KATZ: I would like to ask Dr. Trout a
22 question also. Dr. Yan mentioned that we didn't
23 believe that the data were normally distributed,
24 and when you transformed the data it didn't really
25 help very much. I don't want to get bogged down in

1 a hyper-arcane discussion about normally
2 distributed data, but when we did that we got a p
3 value for that comparison -- I guess it was the
4 Epworth, of about 0.01 --

5 DR. MANI: I am sorry, it wasn't the
6 Epworth. You are talking about the Lammers study
7 where you are talking about the frequency --

8 DR. KATZ: I thought we were talking about
9 GHB-2.

10 DR. MANI: Oh, sorry, fine.

11 DR. KATZ: So, if we are right, it takes
12 the p value which was 0.0001 or something like that
13 to 0.01, and then when you get to the multiple
14 comparisons issue it makes it less weak. I agree if
15 you take a p value of 0.001 or 0.0001, no matter
16 what you do to it as far as a multiple comparison,
17 it is still going to be significant. But if it is
18 0.01 it is a little different story. So, I am just
19 wondering, again without getting into excruciating
20 details, what about this question of the data being
21 normally distributed and not necessarily being
22 improved very much by transforming it? Is there
23 common agreement about that or not?

24 DR. TROUT: My recollection, and it has
25 been sometime since I have seen the results of the

1 analysis, is that it suggested that we didn't see a
2 particular problem with the normal distribution as,
3 for example, was the case with cataplexy which was
4 clear. I am not sure if Dr. Yan did a
5 nonparametric covariance analysis or not. I
6 haven't seen those analyses. And, I think the
7 point was made earlier that that would be, I think,
8 an appropriate thing to do in order to account for
9 some potential baseline differences. If she did,
10 then whether it is a reflection of a decreased
11 sensitivity of a nonparametric analysis or whether
12 it is a normal distribution -- I can't answer that
13 without seeing the data. Maybe it was just a
14 standard, nonparametric analysis which might help
15 account for the difference.

16 [Comment away from microphone; inaudible]

17 DR. TROUT: No, I know that but Dr. Yan
18 did a nonparametric analysis because she was
19 concerned about the normality, and did look at the
20 log transformation and it didn't have any impact on
21 that, which doesn't surprise me at all.

22 DR. KAWAS: I would like to ask the
23 sponsor, I mean, there clearly was a dose
24 relationship in terms of the adverse events. Were
25 any other factors looked at that may be related to

1 the adverse event profile, things like age, even
2 previous psychiatric history, other medications?
3 Whether or not they drank alcohol? Anything?

4 DR. HOUGHTON: No, we didn't go as far as
5 an alcohol history. Certainly for the major
6 psychiatric, a preexisting history of major
7 psychiatric disease emerged. Major psychiatric
8 disease was actually a protocol exclusionary
9 criterion, but in those that, for instance
10 attempted suicide, post-study it was discovered
11 that they had a previous psychiatric history and in
12 actual fact in one of the patients a previous
13 suicide attempt had been made. There was major
14 depressive disease reported in those, but for those
15 who developed psychosis there was definite recorded
16 preexisting psychiatric history.

17 In terms of age, we haven't done a
18 breakdown of the database, and in most instances
19 there was not a dose relationship. There were just
20 instances that were mentioned in the presentation.
21 Confusion and sleepwalking suggested a dose
22 relationship. In the GHB-2 protocol which was
23 obviously blinded, there was the association with
24 nausea, vomiting, confusion and enuresis that was
25 definite, but that didn't extend across the whole

1 study database. So, the relationship with dose is
2 not well defined.

3 DR. KAWAS: But how about relationship
4 with anything else? For example, were the patients
5 who had confusion more likely to be the elder
6 patients? You might be able to tell I am in aging.

7 DR. HOUGHTON: I can identify well. Do we
8 have a breakdown of confusion by age? A range
9 would be still useful.

10 [Slide]

11 Here is a slide that shows that the
12 distribution of age was between 25 and 73 years,
13 with 67 percent over 50 years of age, but the range
14 is still wide. There is the distribution across
15 doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8
16 events at 7.5, and 13 events at 9 g.

17 DR. KAWAS: Thank you. Do we have any
18 other questions from the committee? If not, we
19 will move on. Dr. Katz?

20 DR. KATZ: A quick question, if I heard
21 you correctly, there were 14 events reported as
22 convulsions, but when you went back and looked at
23 that, 13 of them were actually cataplexy. So,
24 presumably cataplexy was a verbatim term. How is
25 it that cataplexy got coded as convulsions?

1 DR. REARDAN: The COSTART dictionary puts
2 cataplexy in as a convulsion. It is a definition.
3 Convulsion has ten different terminologies,
4 verbatim events, and they all code up to
5 convulsion.

6 DR. WOLINSKY: Along those lines, how come
7 there were only that few number of convulsions when
8 we were studying cataplexy in the trial? I mean, I
9 don't know that it is easy to explain this in both
10 sides of one's mouth.

11 DR. HOUGHTON: No, and we are not trying
12 to. If there was a cataplexy event that occurred
13 of a severity to be seen as unusual for that
14 patient, and the patient volunteered it as an
15 event, then it was recorded as an adverse event.
16 Or, there may have been injury related to the
17 cataplexy events. We do have representation in the
18 database. I can recall absolutely a fractured
19 ankle in the washout study. So, there were
20 traumatic events associated with a major cataplexy
21 event that would have been of sufficient impression
22 on the patient to report as a separate event.

23 DR. WOLINSKY: But then the event would
24 not have been withdrawal from the primary measure
25 of efficacy even though it was also registered as

1 an adverse event?

2 DR. HOUGHTON: I am sorry?

3 DR. WOLINSKY: Was it still counted as an
4 event in the measure of efficacy if it was also
5 shifted to be counted as an adverse event?

6 DR. REARDAN: Yes, the patient diaries
7 recorded cataplexy. If they record cataplexy as an
8 event itself, that was part of the efficacy
9 outcome. It wasn't necessarily an adverse event.
10 If they had an adverse event -- fall and break an
11 ankle, cataplexy is coded as part of that adverse
12 event. It is the cause of the adverse event and so
13 it shows up in the database.

14 DR. KAWAS: Dr. Simpson?

15 DR. SIMPSON: I have two questions. One
16 really was just a clarification of this business
17 about the sleepiness. I think we have all agreed
18 that there has to be some adjustment for multiple
19 comparisons on the sleepiness index, and the GHB-2
20 study, even if you make an adjustment, there are
21 certainly some of the indices about sleepiness
22 which seem to be significant. But coming back to
23 the Lammers study, have we established whether or
24 not, once we have made an adjustment, we have any
25 significance there or not? Because that is the

1 pivotal trial, isn't it, because we need two?

2 DR. REARDAN: Remember that the Lammers
3 study was a very small trial, 24 patients. Daytime
4 sleepiness was a secondary endpoint in that study,
5 and I forget the p value. Maybe Dr. Yan or Dr.
6 Katz could comment. I don't think any formal study
7 of multiple analysis was done, except maybe by Dr.
8 Yan --

9 DR. YAN: No.

10 DR. REARDAN: -- and I think she needs to
11 comment on that.

12 DR. YAN: For Lammers study there was no
13 prespecified analysis, except the Wilcoxon assigned
14 rank test. It was across the study and we
15 considered it not very appropriate, and for a
16 secondary analysis none of the statistical analyses
17 were specified. The problem with this Lammers
18 study is that if you use different statistical
19 analyses which are considered appropriate, you get
20 a very different result. Some could be less than
21 0.05 and some ranged to something like 0.2. So,
22 the results are not consistent and we don't have a
23 reliable method to see which one we could consider.

24 DR. REARDAN: We don't disagree with that.
25 I mean, the problem with Lammers is that it was a

1 one-sentence statement about how he was going to
2 analyze it, and it was an inappropriate statistical
3 analysis for a crossover study. So, that creates
4 issues about not having a prospective statistical
5 plan appropriate for the study. But even in that
6 initial Wilcoxon analysis the daytime sleepiness
7 was statistically significant. It was not
8 corrected for multiple analyses.

9 DR. KAWAS: Dr. Simpson?

10 DR. STIMPSON: I just have another question
11 that I wondered if you could clarify. In a lot of
12 these studies you talk about an intent-to-treat
13 analysis, but when I read it I wasn't clear whether
14 or not that meant the patients that were randomized
15 were actually included always in the analysis or
16 not.

17 DR. REARDAN: Yes, the intent-to-treat
18 would include every patient who received drug. Is
19 that correct?

20 DR. TROUT: Yes, every patient who
21 received at least one dose.

22 DR. SIMPSON: So, how did you then deal
23 with the patients who dropped out?

24 DR. TROUT: In the GHB-2 analysis we
25 selected an endpoint. So, in order for the patient

1 to be included in that analysis there had to be at
2 least one post-baseline measure of cataplexy or
3 sleepiness, or whichever outcome you want. So, it
4 was an endpoint analysis that was done in order to
5 accommodate that.

6 DR. KAWAS: It looks like we are
7 completely behind schedule and we will have a very
8 late lunch, I will warn everyone. The FDA's
9 invited speakers on risk management issues is the
10 next component of this discussion. The first
11 speaker is going to be Dr. Carol Falkowski, of the
12 Hazelden Foundation, in Minnesota, who will be
13 speaking on the epidemiology of GHB abuse issues.

14 FDA Invited Speakers on Risk Management Issues
15 Epidemiology of GHB Abuse Issues

16 DR. FALKOWSKI: Hello. Good morning,
17 almost afternoon.

18 [Slide]

19 This is the title of my talk, GHB Abuse in
20 the United States. I am Director of Research
21 Communications at the Hazelden Foundation. I have
22 been a member of the National Institute on Drug
23 Abuse's Community Epidemiology Work Group since
24 1986. I am author of a book, called, "Dangerous
25 Drugs: An Easy-to-Use Reference for Parents and

1 Professionals." What is missing from this overhead
2 is that I served on the Drug Abuse Advisory
3 Committee for the FDA from 1995 through 1999.

4 [Slide]

5 In the very short time that I have, I am
6 going to try and just hit the big points about what
7 we know about the abuse of GHB in the United
8 States, starting off with measuring drug abuse.
9 There are a number of things that are thought to
10 bear when we talk about measuring something as
11 complex and multi-dimensional as drug abuse. This
12 includes population surveys. It includes hospital
13 emergency room episodes; medical examiner data;
14 addiction treatment data; law enforcement data, as
15 well as ethnographic studies that look at specific
16 populations of users that are more anthropological
17 and ethnographic in nature.

18 [Slide]

19 I also want to make the point that all
20 data systems have limitations, and this is
21 particularly true in the case of new drugs of
22 abuse. For example, if we are talking about GHB
23 and trying to measure the number of patients who
24 have presented to addiction treatment centers
25 across the country with GHB as their primary drug

1 of abuse, it is now the case that it is often
2 grouped in a category of drugs called sedative
3 hypnotics. It is not its own line item. So, in
4 preparation for a meeting like this it is very hard
5 to get an accurate count of the extent to which GHB
6 itself is the presenting drug of abuse.

7 Similarly, surveys that are conducted --
8 we have not added GHB to the National Household
9 Survey or the Monitoring the Future Survey,
10 although to the Monitoring the Future Survey that
11 looks at drug use among 8th, 10th and 12th graders
12 ecstasy, another club drug, has been added.

13 Also, in terms of law enforcement
14 indicators, there is no field test for GHB so it is
15 hard to also get that indication of it as well.

16 In addition, new methods of abuse are hard
17 to track. I recall, in 1986, when we started at
18 the national level wanting to track crack cocaine,
19 we knew about how to track cocaine but, all of a
20 sudden, we were looking at it by a different route
21 of administration. So, it was a challenge to all
22 of us to start switching our data systems just to
23 measure crack instead of cocaine, to make that
24 distinction.

25 Existing data systems are slow to respond,

1 and there is a system-wide learning curve when a
2 new drug of abuse appears on the scene. That means
3 it is a learning curve in terms of emergency room
4 personnel, treatment providers, law enforcement, as
5 well as prevention agencies, and that is why we
6 rely on a lot of the scientific literature put out,
7 particularly in emergency medicine, to inform the
8 field about emerging drugs of abuse and how people
9 present with those problems.

10 [Slide]

11 My background in this has been as part of
12 the Community Epidemiology Work Group. This is a
13 group of drug abuse researchers from twenty cities
14 in the country that has been convened by the
15 National Institute on Drug Abuse since 1976. This
16 model of drug abuse epidemiology has also been
17 adapted in different parts of the world. There is
18 a similar group in Europe, in Canada, Mexico and
19 Asian cities.

20 [Slide]

21 The Community Epidemiology Work Group is
22 an early warning epidemiological surveillance
23 network that detects new drugs of abuse, patterns
24 of use and populations at risk.

25 [Slide]

1 It involves researchers looking at the
2 same data from different geographic areas and in
3 this case, as I mentioned, there are people like me
4 in twenty cities in the country who write
5 quantitative reports on drug abuse twice annually,
6 and we are convened by the National Institute on
7 Drug Abuse twice a year.

8 [Slide]

9 Having done this and written over twenty
10 reports on drug abuse trends in my city and met
11 with my colleagues, it has given me a sort of
12 broad-based perspective on how emerging drugs are
13 measured and how we get a handle on them. But
14 everyone looks at medical examiner data. We look
15 at the data from the Drug Abuse Warning Network,
16 which is data from a representative sample of nine
17 federal short-stay hospitals with 24-hour emergency
18 rooms, and that is conducted in 21 cities, as well
19 as some other areas of the country.

20 We also look at treatment data, law
21 enforcement data and price, purity, trafficking and
22 the sale of drugs, as well as supplemental research
23 data and information from multiple sources.

24 [Slide]

25 I want to start my introduction to GHB by

1 telling you about the abuse of a group of drugs
2 that are called club drugs. That is really the
3 first time in a long time we have had a name like
4 club drugs applied to drugs because they are used
5 in a particular setting. That is why they came to
6 be called club drugs. It is a mixed category of
7 drugs. It includes stimulant drugs as well as
8 depressant drugs that are used in nightclub
9 settings. GHB is also known in these settings as
10 liquid X, gamma, G, easy lay, Georgia Home Boy or
11 great hormones at bedtime. MDMA or 3,4 methylene
12 dioxide methamphetamine is ecstacy, e or x.
13 Ketamine is known as special K. It is a veterinary
14 anesthetic, a dissociative drug similar in effects
15 to PCP. Flunitrazepam, Rohypnol is a long-acting
16 benzodiazepine, which was dubbed the original date
17 rape drug which is a drug not approved for medical
18 use in this country; methamphetamine and LSD.

19 If there is one point to make about club
20 drugs as a term, one thing that has emerged is the
21 fact that clearly these drugs are not limited to
22 club settings and I will be talking to that in a
23 moment. It is not just clubs where they are used.

24 [Slide]

25 To give you a little slice of the

1 progression of GHB and how it came on the CEWG
2 radar screen, it was first mentioned in 1990
3 through a poison information center from my
4 colleague in Miami. Then, from 1990 to 1994 it
5 appeared in the Miami and the New York city
6 reports. In 1996 it appeared in 6 other cities,
7 and by the year 2000 most cities in this 21-city
8 work group were reporting GHB. It reports 23
9 deaths in the 20 CEWG cities, and I refer you to a
10 handout that I prepared that sort of gives the
11 chronology of how my colleagues describe the
12 growing abuse of GHB in their cities.

13 [Slide]

14 Now, in terms of user typologies, they
15 tend to be young adolescents through adulthood.
16 There is really no age group but when we look at
17 population surveys in this country of who are drug
18 abusers, by and large the biggest bulk of drug
19 abusers are people who are under the age of 35.

20 The motive for use is multiple. It
21 includes not only intoxication, but also people
22 seeking intoxication effects in the absence of
23 alcohol. I have had people describe it to me as it
24 gives them the effects of alcohol without having to
25 waste that time drinking alcohol. This is by young

1 people who haven't developed the taste.

2 It is also used by weight lifters and body
3 builders for its alleged anabolic effects. It is
4 also marketed in nutritional supplements to promote
5 better sex, better sleep and some people take it to
6 counter the effects of other club drugs. One of
7 the characteristics of drug abuse in nightclubs
8 that has come up over the past year is the fact
9 that people seem to have the impression that if you
10 take just a little bit of this and a little bit of
11 that nothing can really hurt you in a club setting.
12 So, you might take a little bit of ecstasy to get
13 you going, with a little bit of cocaine to keep you
14 there, and maybe a little bit of heroin to take the
15 edge off. This sort of mixing and matching is also
16 part of the user typology.

17 The settings it is used in are nightclubs,
18 raves, parties, but also in homes, in health clubs,
19 gyms and other settings. The sources of it come
20 from health food stores, mail order kits, the
21 Internet or at these clubs where it is being used
22 by the capful. Sometimes at these clubs, because
23 ecstasy dehydrates you, people have a lot of water
24 bottles and it is not unusual to have a water
25 bottle that may have GHB mixed in it, and for ten

1 bucks someone can get a swig of it. This makes it
2 very imprecise dosing, as you can imagine.

3 [Slide]

4 In terms of deaths, in terms of the
5 consequences of use -- there is a huge bullet
6 missing from this slide, which I will get to. So,
7 if everybody wants to find their slides and write a
8 bullet in it, I would appreciate it. Deaths --
9 there have been 71 documented deaths, according to
10 the Drug Enforcement Administration, through
11 November of last year. Again, the problem is that
12 because it is a new drug of abuse people don't
13 know. You know, you have to know what you are
14 looking for to be able to find something and this
15 has clearly been the case in trying to document GHB
16 deaths. It is a huge issue and I hope we get
17 enlightened on that this afternoon.

18 Also, there have been adverse medical
19 reactions, not only people who come into emergency
20 rooms, but the countless people, which is quite
21 hard to quantify, who have episodes but never get
22 emergency room treatment for it. But there have
23 been medical reactions, adverse ones.

24 Dependence -- there has been a reported
25 increase in people presenting to addiction

1 treatment centers with GHB as their primary
2 substance of abuse, and an increase in the reported
3 addiction to GHB by those who may not make it to
4 treatment programs.

5 I work at the Hazelden Foundation. We are
6 based in Center City, Minnesota, with campuses in
7 Chicago, New York City and West Palm Beach. There
8 were 5 patients in 1999 who had a history of GHB
9 abuse, and that had grown to 39 in the year 2000
10 and we are just one treatment center.

11 Finally, the missing bullet on here is
12 drug rape. One thing we have seen in this country
13 since the early 1990's is the use of drugs, this
14 predatory use of drugs where you administer drugs
15 to people without their knowledge for the purpose
16 of disabling them to commit crime on them. The
17 first drug that came to this sort of notoriety was
18 Rohypnol, but now we are in a situation where GHB
19 is often used in drug-induced rape. In fact,
20 several years ago when President Clinton signed the
21 federal date-rape law, the Samantha Reid and Hilary
22 Farris Date Rape Act, that was in response to two
23 cases of drug rape that were not related to
24 Rohypnol but to GHB. So, that bullet should be up
25 there, drug rape.

1 Also, another bullet would include the
2 trafficking, sale and manufacture, the law
3 enforcement consequences.

4 [Slide]

5 Let's look at hospital emergency room
6 episodes of GHB. This looks at them from 1994
7 through 1999. You can see the increase in hospital
8 emergency department mentions of GHB. Mentions is
9 sort of unusual term for people who aren't familiar
10 with the Drug Abuse Warning Network, and it quite
11 literally means, in a retrospective review of
12 patient records, that they find a mention of GHB.
13 Sometimes it is the sole drug that precipitated the
14 medical emergency and sometimes it is used in
15 combination with other drugs. For every drug abuse
16 episode in the Drug Abuse Warning Network there can
17 be the mention of 4 drugs and alcohol, but when
18 alcohol is used in combination with other drugs; it
19 is not an alcohol tracking system.

20 [Slide]

21 So, this is what it looks like through
22 1999. This looks at it by half year increments.
23 You can see this takes us into the year 2000 and we
24 have the first half of the year 2000.

25 I want to go back to just my opening

1 remarks about club drug abuse. I think in the
2 general population when we think of club drugs, you
3 know, what we hear about, what everybody is talking
4 about, what seems to be in U.S. News and World
5 Report, in Newsweek and Time Magazine is ecstasy.

6 [Slide]

7 This is from exactly one year ago. This
8 is Time Magazine from June 5, 2000. It talks about
9 ecstasy. For many folks, club drugs -- you think
10 ecstasy.

11 [Slide]

12 This was, I believe, from Time magazine as
13 well. You see the water bottle there. If you
14 didn't see Time magazine, you may have seen The New
15 York Times Sunday magazine insert. This is from
16 January of this year, talking again about ecstasy.
17 This is from January 2001.

18 So, since it is in the same category of
19 drug, I think it is relevant to look at how GHB
20 emergency room episodes compare with those of
21 ecstasy.

22 [Slide]

23 Ecstasy, or MDMA, is in the pink and GHB
24 is in blue. You can see in the first half of the
25 year 2000 that GHB hospital emergency episodes have

1 surpassed those of ecstasy.

2 [Slide]

3 Efforts to control GHB -- a number of
4 states have done things to try to control GHB abuse
5 in their states. This is sort of a listing of the
6 scheduling of it in various different states. It
7 was added, as you know from the materials the
8 committee received, to the Federal Control
9 Substance Act.

10 [Slide]

11 Finally in conclusion, GHB is a
12 significant, growing drug of abuse. We have seen
13 rapid growth in the adverse medical consequences
14 related to GHB since 1999 and, in fact, hospital
15 emergency mentions of GHB now surpass those of
16 ecstasy or MDMA. We have seen rapid growth in
17 adverse medical reactions despite not only federal
18 scheduling but the scheduling in numerous states.
19 We have multiple user typologies. This is not a
20 substance that is sought after simply by people at
21 parties and raves. These products that contain GHB
22 as well as its precursor drugs, GBL and 1,4-BD, are
23 sought after by people who believe the claims on
24 these nutritional supplements and take them for
25 promoting muscle growth, for sleep; and take them

1 for better sex, as well, and as I said, use it in
2 sort of predatory way. Dependence is clearly
3 possible.

4 So in closing, here we have a drug with an
5 established widespread abuse record. With GHB we
6 needn't talk about abuse potential. With GHB we
7 have abuse reality. We have a decade of GHB abuse
8 in this country; a decade of deaths and hospital
9 emergency room episodes and dependence. We have
10 escalating abuse of GHB in spite of recent efforts
11 to control it and, yes, people acquire this drug
12 and its precursors in many ways. But make no
13 mistake, the effects being sought are the GHB
14 effects. The chemical agent in the body that is
15 producing these effects is GHB, and this
16 undisputable fact is entirely relevant to our
17 discussions today.

18 I have to take issue with the statement
19 from the sponsor that says Xyrem is not the
20 problem. If Xyrem equals GHB, then I believe it is
21 a problem. This drug, if approved, will exist
22 outside the confines of this room. Patients will
23 use it outside the confines of clinical trials. In
24 America, in 2001 we have a serious, significant and
25 growing problem with GHB abuse in this country, and

1 it just so happens that this coincides with Orphan
2 Medical seeking approval for this drug.

3 This drug already has avid followers, and
4 there is no reason to assume that another source of
5 GHB would not be sought after by these folks, and I
6 think we need to bear that in mind throughout our
7 discussions. Thank you.

8 DR. KAWAS: Dr. Falkowski, can I ask you
9 one question? With regards to the emergency
10 department data for GHB, I recognize the
11 difficulties of all of this kind of data but, for
12 example, MDMA is not infrequently the only drug and
13 when they go to the emergency room that is clearly
14 because of the MDMA. Can you give us any kind of
15 quantification or semi-quantification? You
16 mentioned that sometimes GHB is the only drug.

17 DR. FALKOWSKI: The question was how often
18 is GHB used in combination, and let me find that.

19 DR. KAWAS: For the emergency room data.

20 DR. FALKOWSKI: Yes, that is what I am
21 looking for. I have it right here. It is 70
22 percent of the time. Like many other drugs, GHB
23 episodes involve drugs other than GHB as well.

24 I would also like to add that I believe
25 these hospital emergency room episodes

1 underestimate GHB because drugs that are used in a
2 predatory way, that are administered to people
3 without their knowledge are not DAWN reportable.
4 So, if someone comes to the emergency room and says
5 I believe somebody gave me something and it is
6 making me sick, that is not a DAWN reportable
7 thing. That is being addressed by the Substance
8 Abuse and Mental Health Services Administration.
9 But what that means is that people who are drugged
10 with any sort of drug are not picked up by this
11 particular reporting system.

12 DR. KAWAS: And, what are the most common
13 drugs or classes of drugs that go along with GHB
14 when people take them in combination? What are the
15 favorites?

16 DR. FALKOWSKI: It is probably ecstasy,
17 MDMA, and to a lesser extent ketamine and also
18 alcohol.

19 DR. SANNERUD: I have some data on the
20 DAWN statistics too. When drugs are used in
21 combination, 50 percent alcohol, 11 percent
22 stimulants, 8 percent marijuana, poly drugs,
23 hallucinogens and sedatives and all these are at
24 least at 3 and 2 percent each.

25 DR. KAWAS: Dr. Dyer, I believe you are

1 our next speaker.

2 DR. KATZ: Claudia, if I could just ask a
3 question, and I don't know who best to direct it,
4 but you said 70 percent of the time the reports are
5 of GHB in association with something else. So,
6 presumably 30 percent of the time it is the sole
7 drug. I have a sort of methodologic question. How
8 reliable would you say that information is, just in
9 general? What is sort of the nature of the
10 information that is recorded and from whom that
11 allows us to conclude that, in fact, GHB is the
12 only drug that was taken? Who reports that, and
13 how reliable are those reports, just as a general
14 rule? Number one.

15 Number two, how many of the deaths and
16 very serious adverse events were associated with
17 GHB use alone?

18 DR. FALKOWSKI: I believe you could
19 address the reliability of DAWN. You are a DAWN
20 reporter. Again, regarding the deaths, you know,
21 the Drug Abuse Warning Network also collects data
22 from medical examiners, but the people in the
23 20-city work group of mine rely more often on
24 getting data directly from the medical examiners,
25 first because it is more timely and also because it

1 casts a better net. It captures situations that
2 are not only due to drug-related toxicity but also
3 ones where the use of drugs were considered by the
4 medical examiner to be significant contributing
5 factors to the death. So, that is what I can say
6 about deaths.

7 Also, I have a table, if you are
8 interested, that I could make available that shows
9 exactly DAWN emergency room data for 1999 and what
10 were the co-ingestants.

11 DR. KAWAS: Our next speaker is Dr. Jo
12 Ellen Dyer, from the California Poison Control
13 System at UCSF, speaking on adverse medical effects
14 with GHB.

15 Adverse Medical Effects with GHB

16 DR. DYER: Thank you and good afternoon.

17 [Slide]

18 In 1990 I identified and made the first
19 reports on GHB abuse from over-the-counter sales of
20 GHB. Over the next 11 years I have been following
21 GHB. I have an interest in it and I have been
22 reporting on the progress, the adverse effects and
23 the trends in use.

24 [Slide]

25 This is a description of the California

1 Poison Control System data of GHB reports to our
2 center. We logged these reports over 10 years.
3 The first years are when the San Francisco center
4 stood alone so it is a population base of 7 or 8
5 million. We became a system in '97 so we have 4
6 years of data for the entire state.

7 We are a medical toxicology consult
8 service, so we are not a required or mandatory
9 reporting center. So, this reflects just the tip
10 of the iceberg of use and abuse and adverse effects
11 that are out there.

12 [Slide]

13 In our experience GHB produces a profound
14 coma. This has been known for over 40 years,
15 starting out in surgical anesthetic studies where
16 it was evaluated as an anesthetic and now through
17 numerous occurrences of coma in users through this
18 widespread public use, where accidental overdoses
19 are occurring because of the narrow and variable
20 therapeutic index for this drug.

21 [Slide]

22 Looking at 5 studies, anesthetic studies
23 that cover over 700 patients -- there are many
24 other studies; I just picked a small set of them --
25 you see the effects of GHB in a controlled

1 situation. GHB causes unconsciousness and a
2 profound coma. This is what is intended with an
3 anesthetic. The respiratory effects that are seen
4 are Cheyne-stokes respiration. There were
5 aspirations. There was a case of unexplained
6 pulmonary edema. In many of these cases the
7 patients are intubated and the airway is attended
8 to. If their airway was left to chance in these
9 situations, it would be compromised. They lose
10 their airway protective reflexes. They have no
11 gag. So, with the high incidence of vomiting,
12 about 30 percent in these studies, combined with
13 the loss of gag, it is not difficult to see how
14 aspiration is going to occur.

15 There are cardiovascular effects, like
16 bradycardia, and then there are isolated incidences
17 where blood pressure rose up to 30-60 mmHg for
18 unexplained reasons really. There is myoclonus
19 that we see. There is an emergence delirium,
20 confusion. There are also secretions like
21 salivation, vomiting, incontinence and diaphoresis.

22 [Slide]

23 If I look at 16 reports that cover 175
24 cases of adverse events where GHB was in public
25 use, you see these same physiologic responses to

1 GHB. You have profound coma. They develop a mild
2 respiratory acidosis; bradycardia; myoclonus;
3 confusion; emergence delirium; and then the
4 secretions. This raises doubts for safety of use
5 among a generalized public population.

6 [Slide]

7 If we look at a closer group where we did
8 a study in our emergency department, and this is
9 the San Francisco County emergency room that sees
10 over 200 patients a day -- we looked at GHB
11 overdoses that we had over 3 years. This is just a
12 retrospective descriptive study where we were
13 trying to get a handle on what is going on. We
14 found that of those cases, about 33 percent had no
15 co-ingestion. This was documented by either
16 toxicology or patient report. Those patients came
17 in, a quarter of them, with Glasgow Coma Score of
18 3. So, they were profoundly comatose and 33
19 percent of them had coma scores between 4-8. The
20 coma lasted 15 minutes to 6 hours.

21 Again, a third of the patients had these
22 same symptoms, bradycardia, respiratory acidosis,
23 hypothermia, vomiting. We saw hypotension in about
24 11 percent. Those cases were primarily cases where
25 alcohol was co-ingested. Then, on emergence these

1 patients are difficult to manage. They can have an
2 emergence delirium which includes combative,
3 agitated behavior.

4 [Slide]

5 Because of that evidence and wanting to
6 focus in closer and get some GHB levels to find out
7 if that is truly what we were looking at, we did a
8 prospective study over 6 months, looking at 15
9 cases of GHB overdose, and 73 percent of those came
10 in with a Glasgow Coma Score of 3. Our intent was
11 to document the presence of GHB, to detect the
12 co-ingestants and what they were or if there were
13 none, and then to verify that our ability to
14 predict an overdose is truly GHB by the toxidrome
15 that we are using, whether or not that was
16 effective.

17 So, all of these 15 cases did have GHB
18 that was measurable. They were young, ages 20-39;
19 73 percent were male. The study inclusion criteria
20 were patients presenting with Glasgow Coma Scores
21 less than 8 and 73 percent of these patients had a
22 Glasgow Coma Score less than 3.

23 In 5 of the cases there were no other
24 drugs or alcohol detected. The GCS was 3 in 80
25 percent of those cases. So, profound coma from

1 accidental overdose; no other obvious cause.

2 [Slide]

3 It is clear to us that there is really
4 substantial evidence that GHB causes coma. Coma is
5 life-threatening, and these deaths are occurring
6 from accident or injury and from respiratory
7 compromise. We are seeing that through aspiration;
8 through apnea; through positional asphyxia -- these
9 are profoundly comatose people, they can't even
10 move to open their airway -- and through pulmonary
11 edema.

12 [Slide]

13 So, I have reviewed 20 GHB related
14 fatalities where I had autopsy reports. I just
15 sent letters to medical examiners asking for their
16 reports. In these cases, the ages ranged from 15
17 to 46 years. Three-quarters of them were male; 20
18 percent of them had no concurrent ingestions. If
19 we look at those that had co-ingestants, the 80
20 percent. We will see that many of these substances
21 are legal commonly ingested things. Tylenol was
22 one of them; caffeine; alcohol. The levels of
23 alcohol went up to 0.17 percent. The legal limit
24 for driving ranges from 0.08 to 0.1. So, most of
25 these cases were in the lower range, right around

1 the legal limit of driving, saying that they had
2 maybe one or two drinks and none of these would
3 reach an alcohol level that would cause coma.

4 [Slide]

5 The societal costs that were seen from GHB
6 abuse, there are many driving under the influence
7 arrests that have occurred with GHB. There were a
8 whole lot that were not recognized until GHB
9 testing became available and now they are being
10 recognized. I don't go out really and collect this
11 data but there are two vehicular manslaughter, I
12 guess they would call it, cases where a person
13 driving under the influence of GHB has hit and
14 killed another individual. One of those was in '96
15 and one was in 2000.

16 Another societal cost is the assaults
17 where the victim is under the influence of GHB
18 given to them or slipped to them by the assailant.
19 It is common enough that they have a term for it.
20 It is called being "scooped" by GHB. The assailant
21 then attacks the victim while they are unconscious
22 or amnesic to the effects of the drug, making
23 prosecution and even reporting of these very, very
24 difficult.

25 These are 4 cases. There are others. But

1 in these GHB was clearly documented as the cause.
2 The first was a woman who was drugged and assaulted
3 by her boss as they went out with a group of
4 colleagues after work. She had GHB in her urine.
5 There were 10 victims of some DJs in Los Angeles
6 that were slipping GHB into drinks and then
7 assaulting them. There was a 24-year old that was
8 eventually prosecuted more for trafficking drugs
9 after a woman had reported an assault to them and,
10 in kind of the bargaining, he admitted, yes, he had
11 drugged her twice with GHB and she has no memory of
12 the first event at all. Nothing. The last is two
13 15-year old females who were unconscious at a
14 party. One was hospitalized and one of these girls
15 died.

16 [Slide]

17 We also see addiction as another burden
18 from GHB abuse. We are currently seeing one to two
19 cases a month at our poison center, and this is
20 eight cases that I collected. The age range is
21 young, 22-38, again three-quarters male. The
22 pattern just continues through all these of the
23 demographics of who is using. Of these, 63 percent
24 started taking GHB for body building. They had
25 what they thought was kind of a legitimate use of

1 this dietary supplement. In this group, 88 percent
2 of them were employed or students. These were
3 functional members of society that have had trouble
4 now because of this drug. These are not people
5 that really had drug-seeking behavior. The onset
6 of symptoms we see within 1-6 hours. It progresses
7 over a couple of days. The duration is 5-15 days.

8 Now, these are often unrecognized by
9 healthcare professionals when they present for
10 treatment. GHB abuse addiction is not really very
11 well known out there. These are severe
12 neuropsychiatric symptoms with autonomic
13 instability that we see. I have had physicians who
14 have treated many, many cases of severe alcohol
15 withdrawal that have called me up and said, my
16 gosh, I am impressed; I am so impressed by this
17 withdrawal symptom. The patients become agitated,
18 combative, delirious. They are hallucinating.
19 They require sedation, a milligram a minute of IV
20 Ativan has been used over a few hours to gain
21 control. They require four-point leather
22 restraints and intensive care. One of the
23 patients in this series died while being
24 hospitalized for GHB withdrawal.

25 [Slide]

1 Substantial and compelling evidence from
2 case reports of accidental poisoning and from
3 toxicology supported adverse events really shows us
4 that these effects are due to GHB. It is not some
5 contaminant or something else that is causing
6 these. And, there is an insufficient or no safety
7 margin between the effective level of the
8 therapeutic dose of these drugs that these people
9 are taking and the dose that causes these effects.
10 As you can see from the sponsor's study, the
11 adverse effects that they are reporting are very
12 similar. The confusion, the nausea, the vomiting
13 are very similar to the things that we are seeing.

14 One physician, Dr. Gallamberti from Italy,
15 who is doing therapeutic use of GHB withdrawal
16 states talks about a 15 percent problematic GHB use
17 among his population. This can be dose escalation.
18 This can be GHB overdoses up to 10 times a year, or
19 GHB dependence.

20 [Slide]

21 This slide just looks at the kinetics to
22 illustrate that there is really a very narrow
23 therapeutic index with this drug and there is a lot
24 of variability. The pharmacokinetics of GHB are
25 capacity-limited absorption, capacity-limited

1 elimination. The coefficient of variation of some
2 of these parameters is 50 percent. There is a lot
3 of variation and we don't really know what the
4 consequence in different populations and different
5 people of these really variable kinetics is going
6 to be, or why they are so variable. You are used
7 to using phenytoin. It has capacity-limited
8 elimination. We know that when you are bumping the
9 dose of a patient on phenytoin you have to be
10 really careful because they can exponentially
11 increase their level. Well, the same thing happens
12 with GHB and we don't know where that is yet.
13 There is not enough experience. And, with
14 phenytoin the absorption is pretty good. We know
15 the bioavailability of IV phenytoin and oral
16 phenytoin. Here, I don't think it is so constant.
17 It really changes with food and there is a
18 capacity-limited absorption that is going to vary
19 between patients. So, this is a really difficult
20 drug to control, particularly orally on an
21 outpatient basis.

22 [Slide]

23 So, what is the current level of GHB abuse
24 that is out there? We really don't know. If we
25 wanted to project from one survey that was done,

1 Dr. Miotto, a UCLA physician that works addiction
2 medicine did a 45-minute structured interview with
3 42 GHB users. Among that group, 69 percent had
4 admitted that they had lost consciousness, had
5 periods of consciousness laps from minutes to
6 hours. There was variability in the amnesia
7 dependent upon how often people used. Twenty-eight
8 percent admitted having an overdose; 9 percent had
9 been to the emergency department for an overdose.

10 Now, there is an interesting misconception
11 here where they don't consider the loss of
12 consciousness to be an overdose, and people
13 overdose and when they are in a profound coma are
14 not taken to the emergency department. So, there
15 are really some problems there, and this gives us
16 an example of the kind of under-reporting that is
17 out there.

18 If we try and extrapolate from the amount
19 of drug that we are seeing marketed illicitly, this
20 is just one arrest in Marin County, a small county
21 north of San Francisco, where they had 207 L of
22 butanediol. The average street dose varies around
23 2 g. If you look at that, that is 103,500 doses in
24 one capture at one house, and there are many, many
25 of these. There are lists of different amounts

1 that have been busted all over.

2 Then there is the problem that Carol has
3 already talked about, surveying and policing the
4 issues of this type of new drug abuse. There is no
5 systematic method in place for data collection on
6 this.

7 There is rapid metabolism of the drug. It
8 clears from the blood in within about 6 hours; it
9 clears from the urine within about 12 hours. We
10 can't test these people and find it. When we are
11 trying to get evidence in a drug assault case, it
12 is gone. It is really difficult to detect. And,
13 should we increase our level of detection to the
14 very, very minute nanogram kind of range, then we
15 are going to start running into the biological
16 background so we aren't even going to be able to do
17 that if we increase our ability to detect. There
18 are also very poor assays currently out there.
19 None of the hospitals have an assay for this, and
20 none of the law enforcement has a field kit for it.
21 So, it has to be taken into a lab and specifically
22 run through a complicated GC mass spec procedure to
23 get a level out, which is expensive.

24 The current documentation clearly grossly
25 underestimates the amount of use that is out there.

1 And, it is very clear that there is a little, if
2 any, safety margin with GHB use in the therapeutic
3 doses that are proposed. GHB is a very potent new
4 drug of abuse. It has been around 10 years. We
5 thought it was going to come and go as a fad, it
6 hasn't and it is not going to. The use is still
7 increasing.

8 There is a very high acute toxicity in
9 accidental overdose -- coma, bradycardia,
10 myoclonus, vomiting, aspiration -- we are seeing a
11 lot of it, and it has very high abuse and addiction
12 potential. So, I think that we have to be very
13 careful and it is very difficult to try and
14 minimize these potential risks, the risks of having
15 it get out into the drug abusing population but
16 also among patients that we are going to be giving
17 this drug to take at home. At the poison center,
18 every night at bedtime, 9 to 11 o'clock I am called
19 by people that say, oh, I'm sorry, I accidentally
20 took a double dose of my medication. What should I
21 do? In this case, they are all going to go to the
22 emergency room. There is really not a margin of
23 safety with this drug. Thanks.

24 DR. KAWAS: Thank you, Dr. Dyer. The next
25 presentation is from the sponsor, presentation on

1 risk management and abuse liability, Dr. Bob
2 Balster, from the Medical College of Virginia.

3 DR. REARDAN: Yes, I would like to now
4 introduce Dr. Balster who will present his views
5 with respect to abuse liability of Xyrem and GHB.
6 Dr. Balster is a previous chair of the FDA Drug
7 Abuse Advisory Committee and a widely published
8 abuse pharmacologist from the Medical College of
9 Virginia. He is editor and chief of a leading
10 addiction journal, Drug and Alcohol Dependence, and
11 a past president of the College on Problems of Drug
12 Abuse.

13 Sponsor Presentation on Risk Management
14 and Abuse Liability

15 DR. BALSTER: Thank you very much, Dayton.
16 Good morning or good afternoon, I guess it is now.

17 [Slide]

18 Well, as you have just heard, the
19 development of Xyrem as a medication has taken
20 place in a context of a national epidemic of the
21 abuse of its constituent GHB, and also the abuse of
22 a number of GHB-related drugs that I will tell you
23 about.

24 As Dr. Houghton told you, Orphan is very
25 well aware of this problem and has consulted many

1 drug abuse experts to try to understand the problem
2 better. My own analysis of this situation is that
3 Xyrem has certainly not contributed to the problem
4 that exists today with the abuse of this class of
5 compounds. I guess where I may disagree a bit is
6 that I am pretty convinced that Xyrem is not going
7 to be a player in this over the long term.

8 I think in order to understand and make an
9 appropriate public health response to this
10 situation, you need to know a little bit about what
11 some of the causes are of this GHB abuse problem.

12 {Slide}

13 So, I hope to make two points in this
14 presentation. The first point is that I believe
15 that the recent abuse of GHB-like substances
16 probably reflects a ready availability more than
17 their inherent pharmacological propensity for
18 abuse.

19 I think I will make this point by first
20 off reviewing for you the incredible availability
21 of these compounds, and then also review very
22 quickly scientific studies that have been done on
23 the abuse liability of GHB as it is compared to
24 other drugs of abuse you might be familiar with.
25 Secondly, I believe that Xyrem, if approved for

1 medical use, will not contribute to the public
2 health problem of the abuse of these GHB-like
3 substances in any significant way.

4 [Slide]

5 Before we continue, it is very important
6 to know the cast of characters here. I think next
7 to the federal government, the next worst developer
8 of abbreviations is a drug abuse research
9 community, with MDMA, and PCP, and GHB, and BD --
10 it must be hard to kind of keep track of the
11 players but, of course, the drug we are talking
12 about here is GHB, gamma hydroxybutyrate. But
13 there are a bunch of other drugs that are basically
14 part of this national drug abuse problem.

15 You have heard a little bit about them,
16 but these precursors, gamma butyrolactone or GBL,
17 1,4 butanediol or 1,4-BD are precursor compounds
18 that, if obtained, can be easily and readily
19 converted into GHB. They also can be consumed
20 directly because they are metabolized by the body
21 into GHB. So, they themselves are drugs of abuse
22 like GHB. Then there are others that are also
23 available.

24 Now, of all these chemicals only GHB is
25 actually a scheduled drug. It is Schedule I under

1 the Controlled Substances Act for the abusable
2 versions, GHB; Schedule III for an approved medical
3 product. So, only GHB is scheduled. Now, GBL is
4 what is called listed so its availability is
5 diminished. These others are still freely
6 available without any drug abuse controls.

7 [Slide]

8 You have heard a lot about GHB abuse but I
9 am pretty convinced that what we are seeing here is
10 something that has resulted from an amazing
11 situation of the availability of these compounds.
12 To remind you, GHB was available legally and
13 legitimately through health food stores up through
14 1990 when you could buy it anywhere, and the abuse
15 problem with this drug began during that period of
16 time.

17 Then through that time and afterwards GHB
18 could be obtained through the Internet. There was
19 an amazing number of sites set up to sell GHB.
20 Then, as GHB became less easy to get because
21 Internet sources dried up, the Internet sources
22 were selling the precursors, etc., etc. I will
23 show you some data a little bit more, but these
24 precursors are not going to disappear any time soon
25 from public availability. Now that the

1 availability of GHB has been restricted by the
2 federal scheduling actions and actions by the FDA,
3 people can now purchase the precursors and make
4 their own GHB. Essentially anyone can do that. It
5 is a very simple thing and the recipes are right
6 there on the web. As I said before, they
7 themselves are widely abused. So, we have a class
8 of chemicals here that are really basically part of
9 what has been referred to as a GHB abuse problem,
10 but it is really an abuse of a class of drugs, and
11 you saw some evidence on that.

12 [Slide]

13 At this point I want to review the
14 scientific literature on the laboratory studies of
15 the abuse potential of GHB. You may wonder why I
16 would want to do that, I mean, why would I want to
17 review literature on abuse potential when the
18 reality of GHB abuse is clear to us from
19 epidemiological data that Dr. Falkowski mentioned
20 and clinical data. The reason to do this is to try
21 to understand what the basis for this is, and to
22 know whether or not this wide abuse is due to some
23 features of this incredible availability, or
24 whether the drug has sort of the inherent
25 pharmacological desirability that you would

1 associate with a really dangerous drug like cocaine
2 or heroin where, no matter how many billions of
3 dollar we throw at the problem, we are getting
4 nowhere with it, or does GHB represent a drug which
5 is less desirable or has less propensity for use.

6 [Slide]

7 Just to remind you, there is a
8 well-established science of abuse liability
9 evaluation, and it is used in evaluating new
10 compounds that are under development. It is useful
11 in making decisions about drug abuse control, and
12 data such as these are used widely by the FDA for
13 making regulatory decisions. All of these data are
14 reviewed in your packages, but just to quickly tell
15 you, first off, GHB is a unique drug. It is not
16 just another depressant drug like barbiturates or
17 even benzodiazepines that have its own receptor and
18 its own characteristics.

19 In studies which are called drug
20 discrimination studies, which allow you in a way to
21 compare unknown drugs to known drugs of abuse,
22 again, GHB lacks equivalence to these classical
23 depressants like barbiturates or any other classes
24 of drugs to which it has been directly compared.

25 In self-administration studies -- these

1 are laboratory studies where you can actually
2 measure what we call the reinforcing effects of the
3 euphorogenic potential of these drugs -- actually
4 in this particular class of studies GHB has very
5 weak reinforcing effects. It is difficult to
6 obtain them in laboratory studies and there have
7 been a number of those. We did one of these
8 ourselves in our laboratory and we essentially
9 found no evidence of GHB self-administration under
10 conditions where we reliably get
11 self-administration of cocaine, heroin,
12 barbiturates, etc., etc.

13 The case of physical dependence is a
14 little bit more complicated. You heard from Dr.
15 Dyer about the fact that abusers can develop
16 dependence and show withdrawal signs, and there is
17 no question about that. These people are taking
18 maybe 10 or more times the therapeutic dose. We
19 are talking about 70, 80, 100 grams a day, and they
20 take them every 3 hours or so because they have to
21 maintain the blood level. Yes, in those cases you
22 get dependence, but in patients receiving Xyrem,
23 where they are getting it in lower doses and they
24 are taking it only in the evening, as you have
25 heard from the reports, there have not been

1 significant problems of dependence. So, yes, it
2 can occur in abusers but it isn't really an issue
3 in patients. Importantly, animal studies, for
4 example, where you try to show the dependence of
5 GHB and compare it, for example, to barbiturates,
6 it is not easy to develop a model for GHB
7 dependence in animal studies because it has less
8 inherent dependence producing properties than these
9 other drugs.

10 [Slide]

11 So, my conclusion when I reviewed the
12 literature on the scientific studies of GHB, when I
13 was asked to do that, I basically thought it looked
14 a lot like what I would say is a Schedule IV drug.
15 Schedule IV drugs, you remember, are
16 benzodiazepines and chloral hydrate and drugs of
17 this type, and that is sort where it fit. It isn't
18 like cocaine. It isn't like heroin. In fact, that
19 analysis of looking at the data has been made by
20 others with very much the same recommendation as
21 mine, that is, it sort of fits pharmacologically
22 with Schedule IV.

23 For example, the WHO expert committee
24 which met not too long ago to make a recommendation
25 to the UN Commission, the WHO expert committee

1 recommended Schedule IV and, in fact, the UN
2 Commission ultimately placed GHB in Schedule IV.
3 Schedule IV, under the Psychotropic Convention is
4 very analogous really to our Schedule IV that you
5 are familiar with under the Controlled Substances
6 Act.

7 [Slide]

8 We are not here to talk about GHB abuse
9 which we know is a significant problem. We are
10 here to talk about Xyrem and what its role may be
11 in the drug abuse problem in the United States.
12 There are two issues we are really worried about
13 here. Number one, we are worried about the
14 possibility that patients legitimately prescribed
15 Xyrem will abuse it in some way, or misuse it or
16 escalate and then, secondly, we are worried about
17 whether or not it might be diverted into sort of
18 illicit channels and become part of a problem in
19 that way.

20 [Slide]

21 Turning first to the issue of patients,
22 first off, I think most of you know, and it is
23 important to always know this, that the development
24 of abuse among patients receiving therapeutic doses
25 of abuse drugs is a much smaller problem than some

1 people realize. It is actually fairly unlikely to
2 occur in a general sense. Of course, in the trials
3 with Xyrem there weren't problems of abuse; there
4 wasn't evidence that people were escalating their
5 dose or complaining and asking for more, and that
6 sort of thing.

7 It is important also to recognize that
8 narcolepsy patients are patients that are receiving
9 controlled substances all the time. The stimulant
10 class of drugs, all those drugs that Dr. Mignot
11 spoke about are all scheduled compounds. In fact,
12 many of them are Schedule II where they can't even
13 get them half the time because the production
14 controls on Schedule II reduce their availability.

15 Then the issue about their dependence, if
16 you understand, for example, that with
17 benzodiazepines, when you discontinue
18 benzodiazepine administration you will often see a
19 withdrawal syndrome, well, that is because
20 benzodiazepines have this incredibly long duration
21 of action with active metabolites that accumulate
22 so that the body continually maintains levels of
23 benzodiazepines. So, when you quit using them
24 there is a withdrawal syndrome. With GHB, as you
25 saw from Dr. Houghton's presentation, the duration

1 of action is just a couple of hours. It would take
2 many, many, many multiple daily uses, way more than
3 the patients are going to get, to maintain the kind
4 of levels of GHB that would be expected to produce
5 dependence. So, yes, in abuse cases where people
6 are just going all day and all night but not with
7 patients.

8 [Slide]

9 Turning now to illicit diversion of Xyrem,
10 first off, that hasn't happened yet. So, we are
11 not aware of any diversion of any Xyrem through any
12 of the products. This is, of course, only in
13 clinical development but I think it is important to
14 know. Most importantly, the company has been very
15 much worried about this issue and has developed a
16 distribution system that you are going to hear
17 about, called the Success Program, which I
18 personally believe is going to substantially
19 prevent any opportunities for diversion. Lastly,
20 Xyrem, whether you approve it or not -- it is going
21 to make very little difference in the overall
22 availability of this whole class of chemicals in
23 the national scene.

24 [Slide]

25 To illustrate that, this slide shows you

1 the product amounts anticipated, annual production
2 amounts for this class of chemicals I mentioned to
3 you. So, if Xyrem is approved the anticipated
4 first year production amounts of gamma
5 hydroxybutyrate are about 82,000 kg. GBL, gamma
6 butyrolactone, the precursor that can be made into
7 GHB easily and consumed itself, is 83 million kg, a
8 thousand times more. 1,4-BD which is not a
9 controlled substance and has no drug abuse control
10 under it whatsoever right now, is widely available
11 through all sources in large amounts, and is made
12 in the neighborhood of 377 million kg. For those
13 of you who don't do the metric system, that is
14 400,000 tons of 1,4-BD. And, all of these drugs
15 are basically substituting for one another. So,
16 whether you take Xyrem in or out of that graph, it
17 is not going to make a difference.

18 [Slide]

19 In conclusion, I believe that the epidemic
20 of abuse of GHB-like drugs has resulted really
21 primarily from its extraordinary availability. In
22 fact, when GHB was controlled -- it is hard now to
23 get GHB. It is hard even for me to get GHB as a
24 research scientist. So, the problem has now
25 switched to these precursors that are available.

1 Secondly, the scientific studies of GHB
2 show that you are not talking here about cocaine or
3 heroin. It is a weak depressant of maybe the
4 benzodiazepine, chloral hydrate type. Thirdly, I
5 believe that Xyrem abuse is very unlikely among
6 patients for the reasons I said. Lastly, the
7 contribution of Xyrem to the public health problem,
8 which is the matter of concern, is essentially not
9 significant. So, you know, have your way with the
10 drug in terms of efficacy and safety but I don't
11 think you need to be worried that this drug is
12 going to be a major factor in the drug abuse
13 problem with this class of drugs. Thank you.

14 DR. KAWAS: Yes, a quick question, Dr.
15 Leiderman.

16 DR. LEIDERMAN: Yes, I would like to ask
17 Dr. Balster two questions. I would like you to
18 comment on the species of animal that you are
19 addressing when you talk about self-administration
20 in drug discrimination studies. Two, I would like
21 you to comment on the data that those models show
22 with other classes of drugs.

23 DR. BALSTER: All the studies are reviewed
24 on that slide on abuse potential with laboratory
25 animal studies, using fairly well developed

1 methodologies. The self-administration studies
2 that Dr. Leiderman referred to were studies that
3 were done in monkeys in sort of a standardized
4 method that is done through a program directed by
5 the College on Drug Dependence. Those are the
6 models, and I can show you data if you give me the
7 time to do it. Maybe later, if the committee is
8 interested, I can show you data. But these are
9 models in which basically it is extremely easy to
10 get animals to actually literally self-inject most
11 of the drugs of abuse -- cocaine, amphetamines,
12 opiates of all types, barbiturates, depressants,
13 benzodiazepines -- benzodiazepines are a little
14 harder but in the model that was used that I showed
15 the negative results from, benzodiazepines were the
16 positive control. So, basically the only area
17 where that model has been not very successful and
18 underestimates abuse potential is with
19 hallucinogenic drugs and marijuana type drugs.

20 DR. LEIDERMAN: Yes, many of the Schedule
21 I drugs. DR. REARDAN: We just
22 have about another ten minutes. If we can prevail
23 on the committee, we have one last speaker, and
24 that will be Patti Engel, who is going to describe
25 for you the risk management system that the company

1 has developed to help control diversion. Patti?

2 Risk Management

3 MS. ENGEL: Good afternoon. My name is
4 Patti Engel, and I am here today to talk to you
5 about the risk management program for Xyrem, which
6 we call the Xyrem Success Program.

7 [Slide]

8 This program will ensure the responsible
9 distribution of Xyrem, namely, to meet two goals.
10 First, to ensure that patients who desperately need
11 the medicine can get it. Secondly, to keep this
12 out of the hands of those people who might abuse
13 it.

14 [Slide]

15 To develop this program we consulted
16 broadly with a number of people interested in the
17 issues not only germane to patients but also that
18 of drug abuse. As you can see, we spoke with drug
19 diversion investigators, field law enforcement,
20 forensics experts, toxicologists, pharmaceutical
21 distribution experts, drug abuse trend experts.

22 [Slide]

23 Through those discussions we followed
24 FDA's proposed risk management guideline, which is
25 risk management through risk confrontation, in

1 essence egging the partners and the shareholders to
2 not only identify the issues but also assess the
3 risks, identify the options and select a strategy.
4 The program that I am going to be sharing with you
5 today is certainly a draft program that the company
6 has designed after discussions with these numerous
7 stakeholders.

8 [Slide]

9 This slide I show to you really to point
10 out the standard route of distribution of a
11 pharmaceutical product in our country today. This
12 includes not only commonly used medications like
13 products for blood pressure control or products for
14 arthritis, but also products under Schedule II,
15 including such agents as amphetamines. Typically,
16 a product is manufactured and goes to a number of
17 national, regional and local wholesalers,
18 eventually getting to 63,000 retail drugstores
19 around the country. One can only imagine the
20 number of loading docks, transport vehicles and
21 hands that touch a pharmaceutical product in this
22 traditional distribution system.

23 [Slide]

24 As we contemplated the distribution of
25 Xyrem and how to do this responsibly to meet the

1 prior stated goals, we determined that a closed
2 distribution system would best fit everyone's needs
3 for this product. The product is manufactured at
4 one single manufacturing facility. It is sent to
5 one single national specialty pharmacy. Eventually
6 it goes by courier to patients with narcolepsy.

7 [Slide]

8 The benefits of this program are that not
9 only is the product distributed from a central
10 location, but all the controls and all the records
11 are in one place.

12 [Slide]

13 So, how will this work? Because a number
14 of doctors prescribe medicines for narcolepsy, we
15 will focus our promotional efforts on those
16 physicians. They include such specialists as
17 neurologists, pulmonologists, psychiatrists,
18 internal medicine physicians and several primary
19 specialties who practice sleep medicine.

20 [Slide]

21 Our small sales force will call on these
22 physicians, communicating the clinical benefits of
23 Xyrem in narcolepsy. At those calls, the sales
24 representatives will also review with each
25 physician something that we call the physician

1 Success Program. I will go into the details of
2 this program in a more in depth fashion in just a
3 moment. But it is important to know that each
4 physician will sign that they have reviewed this
5 program with the sales representative and
6 understand the program. I should also note that at
7 no time will we embark upon physician sampling.

8 [Slide]

9 I promised to come back to the components
10 of the physician Success Program. I know that many
11 of you received copies of this but I would like to
12 highlight some of the main points. First, because
13 we know individuals all learn differently -- some
14 by hearing, some by reading, other methods -- we
15 have made this a multi-faceted program which
16 includes videos, brochures, pamphlets that describe
17 four main areas.

18 The first is to highlight to physicians
19 that the distribution process for Xyrem is
20 different, that their patients won't be able to get
21 this at the corner drugstore. The second important
22 issue that this binder points out to physicians is
23 the dosing and administration of Xyrem. The next
24 important issue is that of home storage and secure
25 handling. The fourth is an important module that

1 we call "doctor be wary" which is an educational
2 module that educates doctors about the ways that
3 drugs are commonly diverted in this country so they
4 can be aware of patients who are attempting to
5 illegitimately get a prescription from them for
6 this product. Each of the kits will also contain a
7 number of unique prescribing forms for Xyrem which
8 will be necessary in order for the prescription to
9 be filled. This is, in essence, a special
10 prescription form. As well, contact information
11 will be provided should the doctor have any
12 questions at all about the program.

13 [Slide]

14 Once the physician decides to prescribe
15 Xyrem the physician faxes this special prescription
16 to the specialty pharmacy. Now, I am going to come
17 back to how this prescription is verified. So, I
18 will ask you to hold on that point for just one
19 moment. But, based on that prescription and based
20 on the patient's geographic location, the pharmacy
21 assigns that patient to a dedicated pharmacy team.
22 So, each time that the patient deals with the
23 system they are talking with the same pharmacist
24 and the same reimbursement specialist.

25 [Slide]

1 I mentioned that as the prescription comes
2 to the specialty pharmacy there will be a number of
3 checks to determine if the physician is, in fact,
4 eligible to prescribe Xyrem. We will be utilizing
5 DEA's NTIS or National Technical Information
6 Services database to ensure that each physician has
7 an active valid medical license, and also to ensure
8 that that physician has current prescribing
9 privileges which allow him or her to prescribe
10 Schedule III medications in this country. As a
11 backup check, the specialty pharmacy will also be
12 checking with the appropriate state medical board
13 to determine that there are no pending actions on
14 the behalf of the state for that given physician.

15 [Slide]

16 As a secondary step, the specialty
17 pharmacy will also do a check on the patient in
18 essence. What they will do is when that
19 prescription comes in they will call the
20 prescribing physician's office to determine that,
21 in fact, that patient is real and a prescription
22 has, in fact, been written for that patient.

23 [Slide]

24 Once insurance reimbursement is obtained,
25 the specialty pharmacy contacts the patient, first,

1 to determine the patient or the patient designee's
2 location and availability for shipment, and also to
3 describe to them the contents of the shipment. I
4 will come back to the details of this in just a
5 moment, but it is important that you know that each
6 patient, when they get their first prescription of
7 Xyrem will receive a multi-faceted educational
8 program called the Xyrem patient Success Program,
9 and I will come back to the details of that in just
10 a moment.

11 In that same shipment they will also
12 receive their Xyrem, and that will look something
13 like this, with child resistant closure not only on
14 the primary container but also on the dosing cups
15 which are provided by the company.

16 [Slide]

17 The shipment that goes to the patient is
18 sent by a special system that has a special, unique
19 tracking system called the Rapid Trac System. this
20 system will allow detailed real-time tracking of
21 that package which is delivered only by the
22 authorized signature. If the patient or their
23 designee is not available for receipt of the
24 package at the time agreed upon with the specialty
25 pharmacy, the package will be returned to the

1 specialty pharmacy after one delivery reattempt.
2 So, a package will not sit on a delivery truck or
3 in a hub for weeks at a time or anything like that.
4 If the package is lost the system will allow an
5 investigation to begin regarding the shipment's
6 whereabouts at that point of loss.

7 [Slide]

8 I spoke a moment ago about the patient
9 Success Program. Again, this is a multi-faceted
10 program which includes video, brochures and
11 pamphlets which deal with a number of important
12 issues for patients. First addressed, of course,
13 is the distribution process since it is so
14 important that the patients understand that the
15 only way they will get Xyrem is through the special
16 pharmacy and not at their corner drugstore.

17 There is information about Xyrem's dosing
18 and administration because we feel that that is an
19 important message to be delivered in an
20 understandable and a very consistent manner.

21 There is information on home storage and
22 secure handling, and we also are very clear with
23 patients about the criminal and civil penalties
24 that the public law assigns to any illicit use of
25 Xyrem. So, if I were, as a valid narcolepsy

1 patient, to take my Xyrem prescription and use it
2 to conduct a rape or in an assault situation, or if
3 I were to sell it to someone for illicit use I
4 would be penalized, I would be subject to C.T
5 penalties. The patient Success Program also
6 includes contact information for the specialty
7 pharmacy should the patient have any questions at
8 all, and also reimbursement information.

9 [Slide]

10 After the Rapid Trac System shows that the
11 package has been received by the patient, the
12 specialty pharmacist will call the patient within
13 24 hours not only to confirm receipt of that
14 package but also to again reiterate certain
15 important points with the patient. Those include
16 the penalties for illicit use of Xyrem; Xyrem's
17 dosing and administration; home storage and secure
18 handling. The pharmacist will also take the
19 opportunity to discuss with the patient the
20 child-resistant features on the primary container
21 as well as the child-resistant features on the
22 dosing cups that are provided.

23 [Slide]

24 The central data repository designed for
25 Xyrem really allows for identification of a number

1 of unusual types of behavior, including any
2 duplicate prescriptions, any attempts of
3 over-prescribing, or any attempts at over-use by
4 patients. The benefit here is that that
5 information is available prior to filling the
6 prescription so appropriate pharmacist intervention
7 can occur.

8 [Slide]

9 As you can see, the Xyrem Success Program
10 is a comprehensive program which is designed to
11 responsibly distribute this important medication in
12 order that patients who need it have it available,
13 and it is inaccessible for those who might abuse
14 it. Thank you.

15 DR. REARDAN: Dr. Kawas, that completes
16 our presentation and we will turn this back over to
17 you.

18 DR. KAWAS: Thank you very much. I want
19 to thank all of you for all of your nice
20 presentations but, rest assured, you will have more
21 questions in the afternoon. We are running quite
22 late so we are going to cut lunch a little short
23 and we will plan on reconvening at 1:30, at which
24 time the public hearing component of this meeting
25 will happen.

1 [Whereupon, at 12:50 p.m., the proceedings
2 were recessed for lunch, to resume at 1:30 p.m.]

1 A F T E R N O O N P R O C E E D I N G S

2 DR. KAWAS: We will reconvene the meeting
3 of the Peripheral and Central Nervous System
4 Advisory Committee discussing Xyrem. We are now in
5 the open public hearing portion of this meeting,
6 and we have quite a few people that we will be
7 hearing from and additional people who want to add
8 to the list. I would like to ask all of the
9 speakers to please do their best -- not their best,
10 you must stay to five minutes. You will have a
11 one-minute warning sign with your timer. If you go
12 over, please don't take it personally but you might
13 hear my voice ending your part for the meeting.
14 This is in order to allow us to hear from everybody
15 who wants to speak, as well as to get onto the
16 deliberations of this committee. The first speaker
17 in the public forum is Sharon Fitzgerald of
18 Littleton, Colorado.

19 Open Public Hearing

20 MS. FITZGERALD: Good afternoon. I am
21 Sharon Fitzgerald from Littleton, Colorado, and I
22 am a narcoleptic. I am a volunteer member for the
23 Orphan Medical Patient Council and the Narcolepsy
24 Network is paying for my travel and my hotel to
25 allow me the privilege of speaking with you today.

1 Five minutes isn't long enough. I have provided a
2 longer version for you to read. Please, please
3 read it. It explains my experiences with the five
4 major symptoms of narcolepsy and how Xyrem gave
5 back my American dream, the ability to pursue
6 happiness without stumbling on the way when it gets
7 tough, and without literally falling on my face
8 when the goal of happiness is reached.

9 I have had daytime sleepiness since 1969.
10 It threatened my ability to be a good mother and
11 protect my children, and it trapped me in a series
12 of entry level jobs. Not knowing it had a name, I
13 tried to hide my problem from employers and I hid
14 in restrooms for many years for 15-minute naps at
15 unpredictable times lots of the time.

16 My symptoms dramatically increased and
17 worsened in 1977 when I was in law school. I was
18 raising school age kids on my own, being widowed at
19 the age of 32. In daytime, against my will, I took
20 naps in my classes, going instantly from
21 consciousness to dream state sleep, the switch
22 being so quick that I actually wrote words from my
23 dreams in my class notes about things like my
24 mother and helicopters, and wondered where they
25 came from when I read them. These were usually

1 followed by a mark where I dropped my pen as I
2 stopped writing, and that would startle me into
3 wakefulness and I would stay awake for a while and
4 take more notes.

5 Going to sleep nearly every night, my mind
6 created vivid illusions of my very worst fears,
7 often a murderous rapist breaking into my house
8 from behind wherever I was sitting or lying. My
9 knowledge of where I was, was accurate. I could
10 not scream. I was paralyzed and I couldn't turn
11 around to defend myself. These are called, as you
12 know, hypnagogic hallucinations. I didn't know
13 that at the time.

14 At the same time, the symptoms of
15 nighttime wakefulness became more severe. I
16 experienced long hours of anxiously lying awake,
17 punctuated by times of intense dreaming so real and
18 so vivid that in the daytime I couldn't remember
19 whether events I remembered were real or dreamed.
20 You may understand that I feared for my sanity, and
21 this is when I sought medical help.

22 I was my doctor's first experience with
23 narcolepsy. It took a very long time for him to
24 find a diagnosis. When he did, it was because of
25 my mild cataplexy and he found the diagnosis an

1 announced that was the good news because the bad
2 news was there was no treatment. I self-medicated
3 for years with Sudafed and coffee.

4 With determination -- if you knew me you
5 would know about it -- and special accommodations
6 from the university I actually finally managed to
7 graduate from law school, but I turned down the
8 dream job that was offered, clerking for a district
9 court judge, because I feared I would fall asleep
10 in front of the courtroom. He told me our first
11 case would be about two nuns who had been brutally
12 murdered and I feared I might experience cataplexy.

13 By this time my cataplexy had increased to
14 the point that all my facial muscles would relax
15 and my speech would become momentarily slurred. It
16 passed so quickly that I couldn't hide it. I was a
17 sole practitioner. I couldn't bill enough hours to
18 earn a living. I took Ritalin; I took
19 antidepressants unsuccessfully. I found a job with
20 the State of Colorado. It didn't require my legal
21 expertise but I got lucky, I found out about the
22 trials. I had rebound cataplexy, like what they
23 showed you in the pictures, and it was horrendous
24 for several weeks, waiting to be on Xyrem and my
25 secret was brought out at work. But they didn't

1 fire me because I told them I was going on Xyrem.

2 Its effects were immediate and dramatic.

3 I have experienced no side effects. I get good
4 restful sleep. I awaken refreshed. I stay
5 reliably awake at work with fewer stimulants and I
6 don't fall down. My supervisors noticed my
7 increased wakefulness and rewarded it with
8 committee chairmanships and memberships and, in
9 1999, a promotion. In 2000, January 1, I became an
10 administrative law judge for the Division of
11 Workers Compensation in the Colorado Department of
12 Labor and Employment. It is responsible; it is
13 emotional. I can do it. My colleagues know I have
14 narcolepsy and they know that with Xyrem it doesn't
15 interfere with my job performance. For years I was
16 unable to safely carry my children or
17 grandchildren. I carried my newborn to his first
18 examination and that is just the beginning of my
19 story.

20 DR. KAWAS: Thank you, Ms. Fitzgerald.

21 Next is Richard Gelula, the executive director of
22 the National Sleep Foundation.

23 MR. GELULA: Thank you. The National
24 Sleep Foundation is an eleven-year old organization
25 that was developed by the American Academy of Sleep

1 Medicine to educate the public about sleep and
2 sleep disorders, and our leadership has always been
3 drawn from the top tier of sleep experts, sleep
4 scientists and sleep physicians. We are
5 independent. We raise our money in a variety of
6 ways including government grants, corporate grants,
7 and many memberships, individual contributions that
8 have played a major part, particularly from people
9 and families affected by sleep disorders. Our
10 funding from Orphan Medical for the last two years
11 has been a total of 160,000 out of a two-year total
12 of about 5 million. Our budget is about 2.5
13 million a year. And, their support has gone to
14 broad activities -- sponsorship for National Sleep
15 Awareness Week where they join in with other
16 sponsors, and there is no name or brand specific
17 recognition or benefit for them. So, I wanted to
18 point that out.

19 The Foundation is qualified to address
20 this and our interest is due to the fact that we
21 have invested about a million dollars in narcolepsy
22 research, including center grants for the genetic
23 research done at Stanford. We presently have one
24 of our postgraduate fellowships at UCLA studying
25 the neurophysiology of cataplexy. We also have

1 established the National Narcolepsy Registry which
2 has registered to serum DNA registry with about 700
3 patients and family members registered. That is
4 managed at Montefiore Hospital in the Bronx, and it
5 has been a resource for seven scientific
6 investigations.

7 To summarize the position of the National
8 Sleep Foundation on sodium oxybate, the National
9 Sleep Foundation calls upon this panel to fully
10 consider the safety and efficacy of sodium oxybate
11 for the treatment of narcolepsy and cataplexy, and
12 to do so in a comprehensive context that fully
13 recognizes the extreme psychological, emotional,
14 economic, social and health toll that this
15 affliction exacts from people who suffer from it.

16 NSF does not presume to second-guess the
17 evidence that has been submitted about the safety
18 and efficacy of this drug, but it goes on record to
19 say that such considerations should only pertain to
20 affected patients and not other societal
21 considerations. It is safe and effective for
22 people with narcolepsy, like the speaker before me.
23 Sodium oxybate should be made readily available to
24 them. Any concern for illicit use should be
25 addressed strongly through other channels, such as

1 law enforcement and professional licensing. The
2 fact that narcolepsy is an orphan disease, for
3 which only one medication is currently indicated,
4 would be weighed as a factor in favor of approval
5 of sodium oxybate because it is likely that
6 availability of an approved drug will foster faster
7 diagnosis and more appropriate treatment, and will
8 also -- and we think this is very important --
9 stabilize patients who usually first experience the
10 dreadful effects of narcolepsy and cataplexy during
11 their developmental years, before the completion of
12 their educations and initiations of a career.

13 I would like to summarize a few key
14 background points. Narcolepsy and all of its
15 primary characteristics, including cataplexy, are
16 truly life-altering afflictions, a term that best
17 connotes the life-diminishing and debilitating
18 aspects of this disabling disease. Untreated,
19 narcolepsy not only causes vivid nightmares and
20 undermines the safe and secure feeling that most
21 people get when they go to sleep, but it makes
22 daily existence, both objectively and subjectively,
23 frightening and strange, even alienating to the
24 self and others. It makes the well-controlled
25 process that routinely governs the existence for

1 almost all other humans, the alternating cycle of
2 sleep and alertness, into something entirely
3 different, an uncontrollable process where the
4 maintenance of conscious attention becomes random
5 and cannot be sustained or relied upon. Both the
6 phenomenon of overwhelming sleep attacks and the
7 muscular weakness and collapse that occur with
8 cataplectic attacks undermine the sense of
9 predictability and confidence required to fully
10 develop and function in our contemporary world.

11 But a true understanding of narcolepsy
12 goes beyond physiology. The cumulative effects of
13 the distinctive daytime and nighttime
14 characteristics of this disease are truly
15 traumatic. They not only disrupt; they undermine
16 and frighten and change the core experience of the
17 individual, exacting a toll that ranges from
18 difficulty coping and functioning to total
19 disability.

20 I think some key characteristics that
21 should be taken into consideration are that
22 narcolepsy is not well understood or accepted.
23 People who suffer from this suffer alone. They
24 don't have generally the benefit of support groups,
25 even though there is a fine support organization

1 out there, but the people are just spread out.
2 There isn't enough concentration. Most people with
3 narcolepsy do not have a relative with the disease
4 such that it is even strange to them. People
5 suffer a double blow because it is thought their
6 sleepiness is volitional and a sign of laziness.

7 Thus, I think it should come as no
8 surprise that people with narcolepsy suffer from a
9 high rate of depression. It has been estimated
10 from 30-70 percent in various studies. The good
11 news is that in one study health quality of life
12 was improved through effective administration and
13 medical treatment, and I think that would pertain
14 as well to sodium oxybate.

15 In sum, the National Sleep Foundation
16 believes that narcolepsy exacts an unusual and
17 cruel toll. We really call upon this panel to
18 continue to do the professional job that brought
19 you here today and fully consider the personal,
20 psychological, emotional and human aspects of this
21 disease and the great need for an effective
22 medication. Thank you.

23 DR. KAWAS: Thank you, Mr. Gelula. The
24 next speaker is Ms. Abbey Meyers, who is president
25 of the National Organization for Rare Disorders,

1 Inc.

2 MS. MEYERS: The National Organization for
3 Rare Disorders, which is known as NORD, came
4 together initially because voluntary agencies for
5 many rare diseases worked together to pass the
6 Orphan Drug Act. So, we are the orphan drug folks
7 who work to monitor the development of these drugs.

8 I have several conflicts of interest with
9 this drug because for 20 years I begged practically
10 every company I ever met to pick up this drug and
11 to adopt it. It is a 20-year saga. And, I wrote
12 something for you that you will be able to read
13 about the history of development of the drug.

14 Also, about a year ago I bought some stock
15 in this company. If I wanted to make money I would
16 have put it in Merck, but the idea with the drugs
17 that they are developing is I feel I have to make
18 my own personal investment in the survival of the
19 company.

20 For this drug FDA, rightfully, has asked
21 for a risk management program, and there are
22 several really good models to look at, most
23 notably, I would like you to remember when you are
24 discussing the risk management what happened with
25 Clozaril because when Clozaril first got on the

1 market with the drug for schizophrenia, they had a
2 very stringent distribution program, and they were
3 sued by 30 states, attorneys general, because the
4 laws in those states said that you could not
5 restrict the distribution. In the settlement of
6 that case, the federal court assigned us, NORD,
7 with the task of distributing the drug to the
8 people in this class action settlement.

9 So, I am very sensitive to what happens.
10 FDA approved Clozaril's distribution program but
11 then the law said that they couldn't do it. So,
12 people really want the freedom to be able to get
13 the drug when they want it, when their doctor
14 prescribes it.

15 The other program you should look at is
16 thalidomide because it is an extraordinarily
17 important drug, again very orphan. Nobody wanted
18 to go near it because of the liability problem.
19 But they have a wonderful distribution program and
20 I think it should be a good model for the field
21 when there are drugs with specific dangers
22 involved.

23 I also want to give you several cautions.
24 Don't make the distribution too restrictive. For
25 example, don't allow just certain specialists to

1 prescribe it because people with narcolepsy have a
2 great deal of travel problems. Many of them don't
3 have driver's licenses in many states. They may
4 hold on to their driver's license but actually if
5 it was ever reported to the state that they had
6 narcolepsy they would lose it. It is just like
7 epilepsy. So, you have to be sensitive to that.

8 There are many current problems with
9 Ritalin and Dexedrine and the amphetamines that
10 they are using because the government limits the
11 amount of manufacture every year. So, at the end
12 of the year they run out of drug and there are
13 times when they just aren't able to fill their
14 prescriptions and they can't order it by mail order
15 because it is a controlled substance. So, these
16 people have suffered so tremendously because of
17 these distribution problems. With those drugs,
18 pharmacies don't stock a sufficient amount and they
19 will only dispense one month at a time.

20 Don't require a distribution program that
21 is going to cause legal problems. So, ask yourself
22 that, whether the program that has been designed by
23 Orphan Medical could be loosened up a bit.

24 The other thing goes back to what you were
25 talking about this morning, labeling. You know,

1 does this drug help with daytime sleepiness, etc.?
2 I want to caution you that if you label this drug
3 just for cataplexy with no effect on daytime
4 sleepiness, there are a lot of insurance companies
5 that are not going to reimburse for it. So,
6 labeling on a drug is extraordinarily important to
7 patients because of the managed care insurance
8 system. So, try to be as liberal as you can on
9 that, thinking about whether insurance companies
10 are going to say no, except to just people with a
11 particular type of narcolepsy.

12 Also, recognize that it is a unique
13 disorder that is just as crippling as epilepsy, and
14 that these people are already paying a very heavy
15 price because of the problems they have with their
16 current drugs.

17 Illegal use has to be handled, which I
18 know that you are going to do, but you must pay
19 attention to the valid use of this drug. Thank
20 you.

21 DR. KAWAS: Thank you, Ms. Meyers. You
22 are the first one who hasn't used all of your time
23 and that is greatly appreciated. The next one is
24 Robert L. Cloud, from the Narcolepsy Network.

25 MR. CLOUD: Good afternoon, and I wish to

1 thank the committee for the opportunity to address
2 you on this issue. My name is Bob Cloud, and I
3 would like to briefly talk to you, first about my
4 own long, personal use of Xyrem, and I will call it
5 Xyrem not GHB or sodium oxybate and, secondly, my
6 very serious concerns as director of Narcolepsy
7 Network, which is a national non-profit, primarily
8 patient organization. In that capacity we have
9 received funds, a minor amount of funds, perhaps
10 ten percent of our revenues, from Orphan Medical
11 over the last several years.

12 First, my personal experience with Xyrem
13 as a narcolepsy patient with cataplexy. I am 57
14 years old, married, have two adult children, and I
15 am an attorney in private practice, primarily
16 family, probate and criminal law which sometimes
17 can be intense and have a few emotions attached to
18 it.

19 I believe I am the first American to have
20 used Xyrem for narcolepsy, and I am probably the
21 longest continuing user of Xyrem which now
22 approaches 19 years every night without fail. My
23 narcolepsy/cataplexy symptoms began in the mid-30's
24 and by age 39 included severe and recurring
25 cataplexy together with excessive daytime

1 sleepiness and sudden sleep attacks. My cataplexy
2 caused numerous daily episodes of complete body
3 collapse, such that I couldn't leave my office or
4 home without risk of harm to myself or others.
5 Feeling any emotion, humor, anger or mere
6 enthusiasm, would result in sudden immediate
7 collapse. I guess we are all ignorant of what
8 diseases feel like that we don't have them, but my
9 best description of the sudden collapse of
10 cataplexy would be to imagine a puppet on strings
11 and suddenly the strings, which are your muscle
12 tone, are immediately let go and so you fall to the
13 ground immediately, and your head comes down last
14 and whips against whatever -- sidewalk or table
15 corner or escalator or whatever might be there. I
16 have been rescued by police and emergency squads
17 and life guards and well-meaning strangers and
18 friends.

19 Obviously no injury for me has been fatal
20 because I am here, but unfortunately I do know
21 others whose fall has occurred at the top of the
22 stairs and they fell down backwards and killed
23 themselves, and there are others that I don't know
24 about.

25 In 1982 my treating physician sent me to

1 Sunnybrook Medical Center in Toronto, Canada to
2 begin prescriptive use of Xyrem under the research
3 being conducted by Dr. Mortimer Mamelak. After
4 three weeks I returned home and continued using
5 Xyrem, always prescribed by my local physician
6 under his own individual investigational new drug
7 application. My severe cataplexy symptoms
8 disappeared almost overnight. I was immediately
9 able to return to my full-time law practice and I
10 have continued to this day to use Xyrem under that
11 individual application and subsequently in the
12 clinical trials under the Orphan Medical
13 application. During these 19 years, I have never
14 changed the dose. I have never experienced
15 tolerance. I have never noted side effects.
16 Simply stated, the drug is as safe and effective as
17 it was on day one. It is hard to imagine a
18 pharmaceutical product having such a quick,
19 complete, safe and enduring benefit.

20 As director of Narcolepsy Network, I have
21 said on a number of occasions that I think the
22 greatest tragedy in the treatment of people with
23 narcolepsy is that Xyrem or GHB has not been
24 available so that other patients could benefit from
25 it as I have. Hopefully, this committee will

1 remedy that.

2 We are sensitive to the reports of
3 injuries and deaths and other victimizations from
4 the abuse of GHB and, as an organization, we work
5 with law enforcement and community drug agencies to
6 partake in their activities to limit that and
7 correct that. I think it is obvious that Orphan
8 Medical is going above and beyond the call of duty
9 to also contribute to restricting the unlawful use
10 of GHB.

11 In closing, I submit that our concern for
12 patients with narcolepsy should receive your
13 highest considerations so that people can
14 rediscover their economic and particularly their
15 family lives and avoid disability. Thank you.

16 DR. KAWAS: Thank you, Mr. Cloud. The
17 next speaker is Cindy Pekarick from Pennsylvania.

18 MS. PEKARICK: Hi. My name is Cindy
19 Pekarick, and I am here today to tell you how GHB
20 killed my daughter. In October of 1998, my
21 daughter Nicole, a college student and gym
22 enthusiast met a new boyfriend who introduced her
23 to a product called Renewtrient. In November she
24 researched the product over the Internet and
25 received only positive information. She could take

1 it before bedtime and wake up in only four hours
2 feeling refreshed, well-rested, and all her muscles
3 would be completely recovered and ready for another
4 workout.

5 In December I found out she was taking
6 this supplement. I didn't believe the promises
7 made by the advertisers. Arguments ensued and she
8 promised she wouldn't drink it anymore. She was
9 away at school from mid-January until April.

10 In April she returned home. She was
11 behind in all her bills. She was black and blue on
12 her arms and legs. She stopped attending classes,
13 and she kept losing things. In May I discovered
14 she had essentially dropped out of school.

15 In June I could see mild changes in her
16 behavior. She began taking power naps, as she
17 called them. She would sleep three hours in the
18 middle of the day and get up at four o'clock and go
19 to work. She continued losing things and having
20 difficulty paying her bills. I searched her room
21 and car but found no evidence of substance abuse.

22 By July, my younger daughter, Noelle,
23 informed me that Nicole was having problems. She
24 said, "mom, she isn't taking anything bad or
25 illegal. She takes a muscle supplement that

1 doesn't agree with her. Sometimes she has bad
2 reactions and she doesn't even know it. She
3 embarrasses herself and me when she acts weird and
4 then goes to sleep. When she awakes she never
5 remembers anything that she did. She started
6 taking it once in a while so she could go to sleep
7 right away after work when she got home. Then she
8 started using it more often. It disgusts me to see
9 her out of control."

10 It was at this time I discovered Nicole
11 had been taking GHB since November. I then began
12 my own search over the Internet for more accurate
13 information. In August, Nicole was found having a
14 seizure in a public bathroom. She had urinated and
15 defecated on herself while pulling at her clothes
16 and hair and flailing her arms. She was rushed to
17 the hospital where we arrived to find her
18 unconscious, intubated, with her arms, legs and
19 waist strapped to the bed. They claimed her
20 seizure was violent. She barely had a pulse when
21 they found her.

22 It was at this time I knew my daughter was
23 addicted to whatever she was taking. There is
24 absolutely no other reason why a young, bright,
25 healthy woman would take a supplement that was

1 harmful. I begged the doctors to transfer her to a
2 treatment center for chemical dependency, but they
3 said they wouldn't do it without the patient's
4 permission. She was clueless as to why she was
5 hospitalized and she had no recall of anything that
6 happened to her. She was discharged.

7 In September, Nicole, sweating profusely,
8 with a red face and shaking hands while crying
9 said, "mom, I have to talk to you. I'm really
10 scared. I have a problem. I can't stop drinking
11 it." I stood up, wrapped my arms around her and
12 hugged her as hard as I could. I told her that she
13 was on her way to getting better, that
14 acknowledging that "g" had a hold on her was a step
15 in healing.

16 On Monday morning, on her way to the
17 treatment center, Nicole refused to go in. She
18 claimed that "g" wasn't addictive; that she did the
19 research and she was just having reactions to it.
20 She said she was now in control of her life and
21 future. She stayed in counseling and, by the end
22 of September, Nicole had applied, transferred, and
23 was accepted at the university. She was excited.
24 Things seemed okay on the surface but she was
25 hiding tremors, hallucinations and insomnia. She

1 went days without sleeping but never told me.

2 On October 3, 1999 at 2:00 p.m. she said
3 she needed to take a nap before she went to work
4 since she hadn't slept the night before. She set
5 the alarm for 4:00 p.m. but she never heard it.
6 She was in her final sleep. My firstborn child was
7 found in bed, blue, at 6:00 p.m. We found a bottle
8 of GHB in the trunk of her car. The autopsy
9 revealed she had GHB and GBL in her system at the
10 time of her death. No other chemicals were found.

11 Nicole was an honor student, captain of
12 two varsity teams and graduated third in her class.
13 For her undergraduate studies she majored in
14 biology, with a plan to major in engineering for
15 her master's degree. Her ultimate goal was to
16 become a biomedical engineer. She wanted to be
17 able to design body parts to help extend people's
18 lives. She understood that to function well, one
19 had to be healthy. She was a loving, sensitive,
20 caring and intelligent woman. Her only fault was
21 that she was naive. Thank you.

22 DR. KAWAS: Thank you, Mrs. Pekarick. The
23 next speaker is Eric Strain. Doctor Strain is from
24 the College on Problems of Drug Dependence.

25 DR. STRAIN: Thank you. I would like to

1 thank the FDA and the members of the Peripheral and
2 Central Nervous System Drug Advisory Committee for
3 providing me the opportunity to speak. My name is
4 Eric Strain. I am a professor in the Department of
5 Psychiatry at Johns Hopkins University School of
6 Medicine. I am a board-certified psychiatrist with
7 qualifications in addiction psychiatry, and I am
8 here today representing the College on Problems of
9 Drug Dependence, CPDD.

10 The College is the leading organization of
11 drug abuse scientists in the United States. I am
12 also the former chairman of the FDA's Drug Abuse
13 Advisory Committee. I have sponsored my own travel
14 to today's meeting, and I have no relationship with
15 Orphan or other pharmaceutical companies that make
16 narcolepsy products.

17 There are two point that I would like to
18 make during these brief comments. The first is
19 that the College on Problems of Drug Dependence
20 would like to emphasize the importance of
21 science-based assessments of new medications,
22 especially as they relate to issues such as abuse
23 liability evaluation and safety of abused products.
24 The College wishes to stress the long history that
25 has led to the establishment of reliable and valid

1 methods for determining abuse potential. This work
2 includes both preclinical as well as clinical
3 studies. Several academic medical centers contain
4 rich experience in this area of research. Methods
5 have been well tested, and outcomes from previous
6 studies have helped inform and guide agencies such
7 as the FDA in making determinations regarding abuse
8 potential, therapeutic efficacy, and safety of new
9 medications.

10 CPDD has played a key role in such
11 matters, as its members are the primary group that
12 have conducted such studies. The College wishes to
13 strongly and forcefully advocate that decisions
14 made by the FDA grow out of and be based upon
15 well-conducted research, and whenever possible
16 decisions should be derived from well-controlled
17 studies and data driven. In order to achieve such
18 goals, advice on substance abuse related matters
19 should be solicited from experts in the field.

20 The second point I would like to make has
21 to do with the Drug Abuse Advisory Committee. As
22 the former, and the last chairman of this advisory
23 committee of the FDA, I believe it is important for
24 me to comment upon its termination. The Drug Abuse
25 Advisory Committee has been dissolved by the FDA,

1 and in the process the FDA has lost an important
2 resource that can inform decisions regarding
3 substance abuse. To my knowledge, today's meeting
4 is the first FDA advisory committee meeting since
5 this termination where issues of drug abuse are an
6 important element in your discussions.

7 I am pleased to see that there are several
8 drug abuse experts represented here today, however,
9 I am concerned that the numbers do not allow the
10 breadth of expertise that would have been found on
11 the DAAC. Such breadth is essential to fully
12 consider all of the issues involved in advising the
13 FDA on the abuse potential of new medications, the
14 extent of the public health consequences of such
15 abuse, additional data that the FDA should require
16 companies provide, and recommendations regarding
17 post-marketing surveillance.

18 The College is particularly concerned that
19 comparable experience and knowledge brought to the
20 Drug Abuse Advisory Committee by experts in the
21 drug abuse field is no longer readily available to
22 the FDA. In my experience as chairman of the
23 committee, I was able to witness firsthand on
24 repeated occasions the value of having a group of
25 scientists and clinicians who could provide

1 informed knowledge and experience to the FDA on
2 matters such as those that appear to be on today's
3 agenda.

4 The loss of the DACC to the FDA is
5 significant and substantial, and adequate
6 representation of drug abuse issues on other
7 advisory committees needs to be clearly
8 demonstrated by the FDA. I speak on behalf of the
9 College in expressing the College's continued
10 concern regarding the dissolving of this advisory
11 committee. Given the tragic consequences of drug
12 abuse to our society, as exemplified by the
13 previous speaker, its prevalence and the growing
14 body of medications for the treatment of substance
15 abuse disorders, it is particularly concerning that
16 the FDA has decided to terminate this particular
17 advisory committee.

18 Again, I wish to thank the FDA and this
19 advisory committee for allowing me to make these
20 comments today. The hope of the College is that
21 these companies will spur tangible demonstration of
22 FDA's commitment to having adequate outside input
23 by experts in the drug abuse field in the advisory
24 committee process either through the renewal of the
25 Drug Abuse Advisory Committee or through adequate

1 and substantial representation by drug abuse
2 experts on other advisory committees where issues
3 of drug abuse may be of substantial importance.
4 Thank you.

5 DR. KAWAS: Thank you, Dr. Strain. The
6 next speaker is Deborah Zvorsec. Dr. Zvorsec is
7 from Hennepin County Medical Center in Minnesota.

8 DR. ZVORSEC: Thank you very much. My
9 research is in the area of gamma hydroxybutyrate
10 abuse toxicity, addition and withdrawal. Dr. Steve
11 Smith and I, with others, published a case series
12 in Morbidity and Mortality Weekly Report in
13 February of '99 that described adverse events due
14 to ingestion of dietary supplements containing GBL,
15 GHB precursor. I was the lead author of a case
16 series of 1,4 butanediol toxicity that was
17 published in The New England Journal of Medicine in
18 January 2001. These toxicity episodes included two
19 deaths that occurred with no co-intoxicants and no
20 evidence of aspiration or asphyxiation or
21 adulterants.

22 I will focus today on GHB addiction. In
23 the course of our work, Dr. Smith's and my name
24 were listed on the project GHB help site. We
25 received calls from over 40 addicted patients from

1 25 states, and have treated an additional 5 cases
2 of inpatient withdrawal at HCMC in Minneapolis.

3 The vast majority of these addicted people
4 began using GHB to treat insomnia, anxiety,
5 depression, chemical dependence or for
6 body-building purposes, as recommended by
7 marketers, websites and fringe pro-GHB physicians.
8 Many, indeed, began with GHB, continued with GHB
9 and never used any of the dietary supplement
10 analogs. Our patients began with small doses,
11 often only at night, and discovered that it made
12 them feel good; increased dosing frequency and, as
13 tolerance developed, needed more GHB in order to
14 feel good. Within months, they were taking GHB
15 every one to three hours around the clock to avoid
16 withdrawal symptoms. By the time they realized
17 that they might be physically dependent, attempts
18 to abstain resulted in severe anxiety, insomnia,
19 panic attacks and hallucinations.

20 Their addiction destroyed their lives.
21 They lost their spouses. They lost access to their
22 children, their jobs. They acquired tremendous
23 debt to support their habit. They became comatose
24 while driving and crashed their cars, frequently on
25 multiple occasions. They called us in absolute

1 desperation. Their detox was frequently similar to
2 the worst cases of delirium tremens, requiring
3 large and often massive doses of sedatives, often
4 with intubation.

5 Almost all patients suffered weeks or
6 months of profound depression and anxiety after
7 detox, and some also experienced muscle twitching
8 and tremors. Of the over 40 patients we have
9 worked with, only a scant handful have remained
10 GHB-free, frequently despite CD treatment. Many
11 have detox'd numerous times but continue to
12 relapse, sometimes within hours of discharge from
13 treatment. Unfortunately, many never lost faith in
14 GHB and continued to be convinced that they could
15 get back on it and use it responsibly. They
16 continue to argue its health benefits.

17 One of our patients was a 50-year old
18 businessman with his own business who began using
19 GHB, not an analog, five years ago, initially for
20 body-building purposes. Within months he had
21 increased his dosing to around the clock. His life
22 was entirely controlled by the need to have GHB
23 with him at all times. He tried numerous times to
24 quit. His wife was unaware of his addiction. She
25 described witnessing frequent frightening hypnotic

1 states, punctuated with clonic movements. She
2 believed that his frequent states of apparent
3 somnambulism were due to a sleep disorder but
4 despaired when a sleep specialist could not cure
5 him. This woman is a very bright professional who
6 was totally unaware of GHB, as is the case with
7 many family members. It was only on the morning of
8 his admission that she learned the truth. After
9 six days of detox he was through the worse and
10 appeared to be on the road to recovery.
11 Psychiatrists treated him with sleeping meds and
12 antidepressants, but within three days he was using
13 GHB again to control anxiety attacks and
14 depression.

15 GHB is perhaps the most addictive drug
16 ever abused. Experienced drug users describe a
17 euphoria that surpasses that of any other drug.
18 Availability of off-label prescription presents
19 profound personal and public health risks. The
20 fringe physicians who now promote GHB will be
21 joined by thousands of mainstream physicians with
22 the approval of the FDA. The majority of
23 physicians are ignorant of the diverse health risks
24 of GHB, as are toxicologists and law enforcement
25 officials. Users will seek Xyrem from physicians

1 who don't recognize sodium oxybate as GHB and are
2 unfamiliar with the health risks. Patients will
3 obtain prescriptions for sleep disorders, also for
4 insomnia, depression, anxiety, treatment of alcohol
5 and drug dependence and other conditions for which
6 it has been touted.

7 We know that addicts often use GHB and its
8 analogs interchangeably. Their compound of choice
9 is dependent on access, determined by cost,
10 perceived quality, ease of procurement. Clinical
11 literature reports one user who spent \$200 per day.
12 That comes to \$70,000 per year. Our patients
13 report ingestion of up to a bottle every one to two
14 days, coming to \$11,000 to \$36,000 per year. A
15 Xyrem prescription will be a bargain for such
16 users, who will then avoid the high prices, erratic
17 availability and risks of supplement and solvent
18 purchase. We know that many people are afraid to
19 buy or make their own GHB due to risks of
20 contamination or errors of production. Xyrem, a
21 pharmaceutical product of controlled quality,
22 available by legal prescription, and with very
23 little risk if found in their possession, will be
24 very attractive. We know that users are watching
25 for the release of Xyrem. Recreational drug sites

1 post links to narcolepsy sites and publications
2 about Xyrem. One hotyellow98.com, for example,
3 instructs users "click here to find out when GHB
4 will be released under the trade name of Xyrem."

5 DR. KAWAS: Your time is up, Dr. Zvorsec.
6 Please finish. Thank you very much, Dr. Zvorsec.
7 Our next speaker is Trinka Porrata of California.

8 MS. PORRATA: I wish I had time to tell
9 you the stories of 200 dead people that I know of,
10 hundreds of rape victims and thousands of GHB
11 overdoses, and About Caleb Shortridge, to whom our
12 website www.projectghb.org is dedicated, about
13 Matthew Coda and Joshua Parks to whom our GHB
14 addiction hotline is dedicated. I wish I could
15 tell you about Ben Croman, Mike Fox, Tyler Johnson
16 and other young men from New Zealand to Sweden who
17 either have or are right now considering suicide
18 because of the withdrawal from this drug; about
19 more than 300 people I personally know about who
20 are horribly addicted to GHB, and who could each
21 name at least one dozen people more just like them.

22 I have lived and breathed GHB since June
23 of 1996 when I was first assigned to handle it for
24 the LAPD. Four young men collapsed. Two literally
25 died and were brought back to life by the

1 paramedics. One thing was clear, people were dying
2 from GHB and it was being missed. It has been a
3 heartbreaking five years, mixed with the privilege
4 of learning more and teaching others to recognize
5 the rape, overdose and deaths and getting rape
6 victims into treatment and addicts help. It has
7 been very lonely at times when the agencies who
8 should care haven't.

9 DEA has reviewed and documented 71 deaths
10 related to GHB but, basically, stopped counting
11 once the drug was controlled, for obvious reasons.
12 No one at FDA has ever expressed interest in these
13 cases. My database now includes over 200
14 GHB-related deaths. In fact, Robert McCormick, of
15 the FDA's Orphan Drug Unit, told me emphatically he
16 did not care how many people had died nor were
17 addicted to it because he intended to approve it
18 anyway. Something is wrong with this picture.
19 This is the most horrid drug I have encountered in
20 25 years as a police officer.

21 Much new has come to light during the past
22 two years, none of it good. Around the world
23 countries are just now awakening to their problems
24 with GHB. Schedule IV by WHO is simply an
25 awakening to the problem. As we speak, countries

1 are restricting it. France is backing away.
2 England is struggling with it. Sweden has an
3 unrecognized addiction and suicide problem. New
4 Zealand tried it as a prescription drug and now
5 realizes they screwed up royally. NIDA is
6 currently releasing \$2 million in research on this
7 drug. This is not a time to be pushing it forward
8 on an unsuspecting American citizenry.

9 You are here today to approve GHB,
10 disguised as sodium oxybate, for use with
11 narcolepsy/cataplexy. Orphan's investors have been
12 assured that you will do so. When the last meeting
13 was cancelled the stock dropped 30 percent in
14 frustration over it. You have not seen my
15 videotapes of the day-to-day struggle of GHB
16 addicts showing that GHB clearly gives previously
17 healthy people symptoms that can only be described
18 as temporary narcolepsy/cataplexy, just like the
19 nine-year old you saw in the tape. Their heads
20 ricochet off board room tables around this country.
21 They break mirrors. They are cut up. They crash
22 cars. They die and kill others. It is destroying
23 them. Their wives are terrified of their husbands
24 and have no idea what is happening. They are
25 locked in psychiatric wards because doctors and

1 emergency rooms do not recognize GHB psychotic
2 episodes.

3 There are no answers for them. So, how
4 can you approve this drug for use? My addicts
5 suffer alone, much as narcoleptic/cataplectic
6 patients do. Many do not have insurance or their
7 insurance will not pay for this drug that is not
8 recognized as an addictive drug.

9 I am deeply concerned about the off-label
10 use policy, enabling any doctor ultimately to
11 prescribe it for any condition as I have no faith
12 that its use will be limited to
13 narcolepsy/cataplexy. Look at the chatter around
14 Orphan about fibromyalgia, a condition with vague
15 symptoms for which a drug seeker could easily get a
16 prescription. I know the vast majority of doctors
17 do not realize that sodium oxybate, Xyrem, is GHB.
18 I see no significant talk on the legitimate
19 narcolepsy websites about it, but the message
20 boards where GHB addicts hand out are buzzing. In
21 fact, the key figures in illegal GHB Internet sales
22 were posting on the website www.xyrem.com.

23 There is very little drug diversion
24 enforcement in the United States. Only a handful
25 of agencies devote any time to this. It is a small

1 portion of DEA effort. States are not prepared.
2 They are not able to handle it. Therefore,
3 Orphan's proposed voluntary -- key word, voluntary
4 -- promises of distribution are frightening.

5 More importantly, the issue goes beyond
6 diversion of Orphan's product to use of Orphan as a
7 shield for possession of GHB in general. It would
8 be unrecognized by law enforcement. Once in
9 possession of that prescription and a bottle of
10 Xyrem, the addict will be home free. There is no
11 field test kit. All investigations of GHB are
12 difficult. Encountering a prescription, real or
13 counterfeit, and a bottle of Xyrem, real or
14 counterfeit, the officer would have zero ability to
15 identify it -- none; zero; nada.

16 To those who claim real GHB is safe and
17 only street stuff is dangerous, poppycock. My
18 addicts have used everything from European
19 pharmaceutical grade to bad stuff. The
20 unprecedented split scheduling of GHB was unwise
21 and unenforceable. We were forced to accept it.
22 It was political, not science. The people in the
23 clinical trials have reason to obey; people in the
24 streets do not.

25 If I were to convey to you but one

1 thought, it would be that not enough information is
2 known about GHB to approve it for any purpose at
3 this time, and certainly not appropriate for
4 off-label use. Any approval at this point will
5 trigger an absolute further epidemic of general
6 abuse because you will create an aura that it is
7 safe. I ask you please table this issue until the
8 NIDA research comes in. Please do not make this
9 mistake.

10 DR. KAWAS: Thank you, Ms. Porrata. Our
11 next speaker is Matt Speakman from West Virginia.
12 While Mr. Speakman is coming up, I just want to
13 remind everybody I am not trying to be mean; I am
14 not trying to be difficult, but we are trying to
15 keep the public hearing section of this meeting
16 down to under two hours and that will only happen
17 if everyone sticks to their five minutes. We would
18 like to let the committee get a chance to have some
19 more discussions for everyone. So, we greatly
20 appreciate honoring the time constraints. Mr.
21 Speakman?

22 MR. SPEAKMAN: Thanks. I just wanted to
23 say thanks. This is kind of a unique experience
24 addressing doctors. It is really cool.

25 My name is Matt Speakman and I have

1 narcolepsy. I will describe very briefly my
2 experience. I have cataploxy also. My first
3 experience was in chemistry class my junior year in
4 high school. The professor pulled out the liquid
5 nitrogen experiment and was freezing flowers and
6 flicking them, making them shatter. I got very
7 excited and he called us to the front of the room
8 and, on my way up to the front of the room, I felt
9 my legs start to buckle. This was the first time
10 anything like this had happened. I had had trouble
11 laughing a little bit because cataplexy sometimes
12 has onset with laughter and emotion, but it wasn't
13 very serious.

14 I eventually just realized that I was
15 going to fall. So, I went back to my desk and
16 collapsed on the desk with my face down in my arms,
17 kind of draped over the thing. It was humiliating.
18 I couldn't move. I was awake and aware and I could
19 still hear the class kind of looking around and
20 what-not.

21 This started to happen more regularly and
22 I started to fall asleep during class. My grades
23 started slipping. I had to stop swimming. I was
24 on the swim team. Falling asleep in the pool is
25 kind of dangerous. So, I quit doing that. Most of

1 my teachers suspected drug use and I don't blame
2 them.

3 But I managed to get into the University
4 of Kentucky and I went there for a year. I was
5 unable to meet friends and my grades weren't very
6 good because I spent most of my time in my dorm
7 room. I didn't make it to class very often; very
8 hard to wake up. It is very hard to keep
9 consistent notes when you are falling asleep all
10 the time.

11 My parents weren't happy so they found,
12 you know, I needed some other treatment. So, I
13 went to a doctor in Cincinnati who was part of the
14 study for what is now Xyrem. That was four years
15 ago, and I am taking it nightly unless I pull an
16 all-night study session or something like that. I
17 don't have any withdrawal symptoms when I don't
18 take it. I don't have any side effects when I do
19 take it. I sleep well. I have no cataplexy. I am
20 here speaking to you right now and I certainly
21 wouldn't be doing this without this treatment. I
22 used to take stimulants and antidepressants to
23 control the cataplexy, none of which worked; they
24 just had nasty side effects. It wasn't very good.

25 Two weeks ago I graduated from West

1 Virginia University with honors. I am looking for
2 a job --

3 [Laughter]

4 -- and I am thinking about going to grad
5 school. That is definitely on the bill, but I am
6 going to need some money first. So, first things
7 first. Right?

8 I understand all the concerns about the
9 illicit use and that definitely needs to be
10 addressed, but this drug is working for
11 narcoleptics and, you know, I have a girlfriend and
12 I have a life, and I live normally. A couple of
13 years ago I got a job as a full-time camp counselor
14 in Maine; drove there myself; had no problems. I
15 read the review they gave me after the summer was
16 up and it said, this guy has the energy of a small
17 power plant, which was nice to hear after suffering
18 from narcolepsy for a couple of years. So, I am
19 happy. I am working on success, and I just wanted
20 to thank you for giving me the time to speak with
21 you and I hope you can work all this thing out, but
22 my main point was that the drug is working for
23 narcoleptics and I want to thank the Narcolepsy
24 Network for paying for my travel arrangements and
25 my hotel. I am not in any way tied to Orphan

1 Medical. I don't care who makes it. I just want
2 to let you guys know it is working. Thank you.

3 DR. KAWAS: Thank you, Mr. Speakman. The
4 next speaker is Charles Cichon, president of the
5 National Association of Drug Diversion
6 Investigators.

7 MR. CICHON: Good afternoon and thank you.
8 My name is Charlie Cichon.

9 DR. KAWAS: My apologies.

10 MR. CICHON: No apology. The nuns never
11 got it in grade school; nobody has ever got it
12 right. I go everywhere from Ceechon to Chicken.

13 [Laughter]

14 I have a 16-year background in law
15 enforcement, but for the last 12 years I have
16 worked in the health regulatory field with the
17 Maryland Board of Physician Quality Assurance, the
18 state medical board licensing and regulatory agency
19 for Maryland. But I am here today as the president
20 of the National Association of Drug Diversion
21 Investigators.

22 Established in 1987, the National
23 Association of Drug Diversion Investigators, NADDI,
24 was formed in Maryland, in Annapolis by a sergeant
25 in the Ann Arundel County police department. Our

1 organization is a unique organization whose members
2 are responsible for investigating, prosecuting and
3 preventing pharmaceutical drug diversion.

4 NADDI has proven to be a valuable asset to
5 law enforcement, the pharmaceutical industry and
6 health regulatory professionals. NADDI principal
7 activities comprise cooperative education and
8 training in the specifics of pharmaceutical drug
9 diversion, investigation and prosecution; the
10 sharing of investigated information and
11 communication with a wide variety of interested
12 parties with regard to the nature, scope and impact
13 of pharmaceutical drug diversion; and the
14 development of stronger effective measures to
15 combat the problem of pharmaceutical drug
16 diversion.

17 NADDI supports the safety and efficacy of
18 the new drug application, NDA 21-196, Xyrem,
19 proposed to reduce the incidence of cataplexy and
20 to improve the symptoms of daytime sleepiness for
21 persons with narcolepsy.

22 NADDI is aware that in many reported cases
23 the use of GHB has changed from homemade GHB to
24 ingesting of industrial chemicals that convert to
25 GHB in the body. (My car got towed away yesterday;

1 I lost my other glasses. I noticed that when I was
2 sitting in the back and I couldn't read my paper.
3 So, I apologize.)

4 We are also aware that there are no known
5 cases which involved Xyrem. Rather than consider
6 the above issues as tangential, Orphan Medical has
7 gotten involved, helping to educate and uncover
8 solutions in conjunction with stakeholders such as
9 NADDI. In fact, since November of 2000, an Orphan
10 representative appeared at our national conference
11 in Columbus, Ohio, and for the last several months
12 has been involved in several states in
13 multi-regional training with over 600 NADDI
14 members.

15 Input has been sought regarding
16 distribution systems that will minimize and
17 identify potential diversion situations, allowing
18 diversion investigators to more easily perform
19 their jobs. It is the job of the pharmaceutical
20 diversion professionals to investigate potential
21 diversion, however, Orphan is willing to cooperate
22 with the appropriate local, state and federal
23 agencies. Thank you.

24 DR. KAWAS: Thank you. The next one is
25 Debbie Alumbaugh from Florida.

1 MS. ALUMBAUGH: Good afternoon. My name
2 is Debbie Alumbaugh, from Florida, and I am the
3 surviving mother of Michael Tiedemann. He was 15
4 years old when he died. That was just over two
5 years ago. The cause of Michael's death was
6 aspiration vomitus and GHB toxicity.

7 Michael was a sophomore at a high school
8 in Florida. He was a black belt in karate, and he
9 was also an instructor. He had won several
10 academic awards for reading, spelling, mathematics
11 and music.

12 On October 1, 1998, Michael came home from
13 school and asked if he could go to the show with
14 his friends. It was unusual for a school night but
15 we decided to let him go. We required Michael to
16 bring home a progress report every week from school
17 and he had brought one home and he was making A's
18 and B's in all of his subjects. Before they left,
19 one of Michael's best friends came into our home
20 and they shot into Michael's bedroom. This boy was
21 only in there for five minutes and when he left
22 Michael was passing out within ten minutes of this
23 young man leaving our home.

24 We found out 18 months after Michael died
25 that when they left our home they drove three

1 blocks and started to play a game of basketball on
2 the way to the show. Michael had the ball and was
3 going for a lay-up, and when he came down he was
4 unconscious. He lay there several minutes. His
5 friends, not knowing what to do or recognizing the
6 red flags, giggled and laughed. They scooped my
7 son up and took him on to the movies. We
8 understand Michael never saw the first five minutes
9 of the movie. He passed out again.

10 When they brought our son home, my husband
11 looked at him and he asked him, Michael, are you on
12 something? Did you take something, son? He said,
13 no, dad, nothing. Brad decided not to lecture
14 Michael this late at night; he would talk to him
15 tomorrow. Brad never got that chance. Michael
16 died that night, alone in his bed.

17 The next morning, when Brad went to wake
18 Michael for school he could hear Michael's alarm
19 blaring. Michael had full intentions of getting
20 up. When he opened our son's door he knew he was
21 dead. The first thought that ran through his mind
22 was to run, run out of the house and not look back.
23 My son was on his bed, his eyes wide open, his
24 mouth hanging open, his tongue swollen so much that
25 my husband couldn't shut his mouth. He had dry

1 vomit running down his chin into a puddle on his
2 collarbone. His hands were in a clawed position
3 where he had tried to roll himself over but
4 couldn't. GHB takes away the gag reflexes and it
5 paralyzes you.

6 We didn't know why Michael had died. None
7 of his friends would speak up. It took 12 weeks
8 for us to find out that Michael had ingested GHB
9 that evening. It was the first and only time that
10 this had happened.

11 In the last three years, in Florida alone,
12 we have lost 207 young lives to these drugs. From
13 1999 to 2000 our numbers have more than doubled in
14 Florida alone.

15 After several months after Michael died,
16 he came to his father in a dream and said, dad it
17 is wrong to destroy the body the way I have done.
18 I need you and mom to go out and tell my friends
19 and my generation of people my story, our tragedy.
20 This put a burden on our hearts and we seemed to
21 stop healing until one day Michael's father
22 gathered up enough courage and strength and he made
23 the first phone call.

24 We now go to schools all over and share
25 our story with students about GHB, and the tragedy

1 of our family. Friday, June 1 our son would have
2 been 18 and he would have graduated on that day.
3 When we went to his grave one Friday, his
4 graduating class had left white roses and the
5 mascot for the graduation cap. We missed prom; we
6 missed graduation because of this drug. Our voices
7 have to be heard. Please investigate this drug.
8 It is not safe. It is killing our children and it
9 is not the pushers that are dying; it is our good
10 kids that we are losing. Thank you.

11 DR. KAWAS: Thank you, Ms. Alumbaugh. The
12 next speaker is Brian Hunter, of the Young Adults
13 with Narcolepsy.

14 MR. HUNTER: Good afternoon. My name is
15 Brian Hunter. I am the founder of Young Adults
16 with Narcolepsy or YAWN. I am also a medical
17 student at the University of Minnesota and a person
18 with narcolepsy and cataplexy.

19 I would like to preface my comments today
20 by disclosing that Orphan Medical has provided my
21 organization with a minor grant and it provided a
22 general grant to the Narcolepsy Network who has
23 paid for my travel and accommodations to attend
24 this meeting.

25 YAWN is the first youth-focused online

1 narcolepsy support and advocacy organization. We
2 work at the grass roots level to advance public
3 awareness of narcolepsy on behalf of young adults
4 and others whose lives are affected by this often
5 debilitating sleep disorder.

6 As founder of YAWN, I believe I am in a
7 unique position to comment on the issue currently
8 under consideration by this committee. I do not,
9 and have not used Xyrem for treatment of my
10 cataplexy but as the representative of many young
11 adults in need of an effective treatment for their
12 narcolepsy, I am compelled to present my views on
13 the risk management issues pertaining to the safety
14 and efficacy of Xyrem.

15 Narcolepsy is most commonly diagnosed by
16 the middle of the third decade of life, often 5-15
17 years after the onset of symptoms, the most
18 dramatic of which is cataplexy. Excessive daytime
19 sleepiness, combined with the impact of sudden
20 attacks of cataplexy that may last from a few
21 seconds to hours can be profoundly damaging to the
22 interpersonal, educational and professional
23 development of these young adults at an extremely
24 critical point in their development. Although I am
25 fortunate only to experience rare and mild attacks

1 of cataplexy, I know others who are completely
2 incapacitated by cataplexy and have not, or would
3 not been able to achieve their personal
4 professional goals without a medication like Xyrem.

5 I submit that the risk for experiencing
6 the negative impact of untreated cataplexy on the
7 potential of so many young adults with narcolepsy
8 is a serious issue that must be included in any
9 discussion of risk management of Xyrem.

10 Xyrem offers a singularly important
11 therapy for the 65-70 percent of young adults with
12 narcolepsy who suffer with cataplexy. We must
13 recognize the consequences of failing to approve
14 Xyrem to treat the 1/1000 people suffering with
15 narcolepsy. For example, after forming YAWN, I was
16 contacted by the parents of a 16-year old boy,
17 living in a small town not three hours away from
18 the nearest city. This young man was bright. He
19 did well in school, and was active in his community
20 until his 12th birthday when he began experiencing
21 severe episodes of cataplexy that lasted for hours.

22 When I first spoke to him on the phone he
23 told me that his condition was so severe that he
24 was forced to spend five days a week in a nursing
25 home, and he is still there. What are the costs of

1 providing nursing home care in a public institution
2 for a 16-year old boy for the next 60 to 70 years?
3 By not adequately controlling his cataplexy, what
4 are his chances for becoming a contributing member
5 of our society? Unfortunately, this man's story is
6 all too common. Unless something is done about the
7 current environment of limited access to inadequate
8 pharmaceutical therapies, the future of young
9 adults suffering with cataplexy will remain bleak.

10 This, however, does not have to be the
11 case. In fact, a brighter future has been achieved
12 by the lucky few who have participated in Xyrem
13 clinical trials. They have become success stories.
14 To these young adults with narcolepsy Xyrem has
15 meant the difference between a life within an
16 institution and having the opportunity to achieve
17 their goals, free from the physical constraints of
18 their disease. Xyrem has enabled many young
19 adults, my friends, to earn their Ph.D.'s or become
20 lawyers, doctors or to simply be good parents.

21 These are people who took Xyrem and
22 couldn't have succeeded otherwise. Yet, there
23 continue to remain thousands of other talented and
24 capable young adults who have not yet had a chance
25 to fulfill their dreams. They are the reason I

1 formed YAWN and why I am here testifying before you
2 today. We can no longer afford to neglect the
3 potential of so many young adults by failing to
4 provide them with the only medication known to be
5 safe and effective. It is our responsibility to
6 protect their right to pursue a happy and
7 productive life by having access to medications
8 like Xyrem that will effectively treat their
9 disease.

10 Thank you for allowing me to present these
11 remarks to you today. I urge you to approve the
12 NDA for Xyrem. There really are lives at stake.

13 DR. KAWAS: Thank you, Mr. Hunter. The
14 next one is Joe Spillane.

15 DR. SPILLANE: I would like to also say
16 thank you for an opportunity to speak to the FDA
17 and to this committee on this important issue.

18 I work at Broward General Medical Center
19 which is a community hospital in south Florida. My
20 experience with GHB is as a pharmacist and in
21 clinical toxicology. I also teach as an associate
22 professor at the College of Pharmacy at NOVA
23 Southeastern University.

24 Our experience in the emergency department
25 is very similar to what Dr. Dyer mentioned. We

1 have a lot of GHB overdoses. We had 48 overdoses
2 associated with GHB in 1999. That number increased
3 by 60 percent to 77 in 2000. We have more GHB
4 overdoses than ecstasy. We have more GHB overdoses
5 than oxicondon. I think it is important that I
6 just underscore the immensity of the problem
7 associated with GHB abuse. Most of our overdoses
8 come in with people who have altered mental status
9 and, basically, they just need a short period of
10 supportive care, airway management. Most wake up.
11 Many of them -- and I think this is important to
12 point out, many of them mention that somebody had
13 given them GHB, put it into their drinks, and so
14 forth. As such, the media and many people have
15 advised don't accept a drink from anybody but the
16 bartender. We had a bartender up in our ICU about
17 a month ago, and when he did recover I spoke with
18 him and he said, yes, I chronically use GHB. A lot
19 of my friends in the beverage industry also do.
20 And, I think we can understand what the potential
21 problems could be with that.

22 We have also treated five withdrawal cases
23 and, again, the numbers might not be that big but
24 this is just one hospital and, since it is a
25 difficult thing to identify, we are probably

1 missing cases and I am sure there are cases missed
2 throughout the country.

3 There have been nine deaths where, in the
4 estimation of the medical examiner in Broward
5 County, a county of 1.6 million people -- nine
6 deaths were caused by GHB and I think it is
7 important to point out that at least one of those
8 deaths was with GHB alone, with no co-intoxicants
9 and no alcohol level.

10 I guess my major concerns are with the
11 scheduling and some of the off-label prescribing
12 issues, and the voluntary nature of this
13 distribution system. I kind of just want to
14 summarize briefly by saying I think there are four
15 questions that are major concerns of mine and I
16 hope this committee addresses those concerns.

17 The first one is, is it really wise to
18 rely upon an essentially voluntary, supposedly
19 closed-loop distribution system, designed by the
20 manufacturer, to prevent diversion of an
21 increasingly popular, highly lethal, addictive and
22 abused substance?

23 My second question is, is it prudent to
24 require very little governmental regulatory
25 oversight of such a system when the strict

1 adherence to that system may not be in the best
2 financial interest of the entity responsible for
3 that strict adherence?

4 My third question is, is it responsible to
5 rely solely on those with a vested interest in
6 demonstrating little or no diversion to verify that
7 little or no diversion is occurring? It is my
8 understanding that that is essentially what we may
9 be doing here. I think there was an example of how
10 this could be problematic just in today's
11 proceedings. I certainly was under the impression
12 by several people who spoke today that there was no
13 diversion in the clinical trials. I think Dr.
14 Mani, from the FDA, said that, indeed, there were
15 some cases of diversion. So, I just think that is
16 a potential concern.

17 My fourth question is does it demonstrate
18 judicious foresight to establish a precedent for
19 sort of circumventing existing scheduling and
20 distribution processes, and couldn't such a
21 precedent be used in the future to the financial
22 benefit of pharmaceutical manufacturers and to the
23 detriment of drug diversion prevention?

24 I would like to commend Orphan for their
25 work and bringing a medication that they feel is

1 effective to those who could benefit from it. I
2 think a mandatory, not voluntary, system of
3 distribution, with adequate governmental regulatory
4 controls and any restrictions on off-label
5 prescribing would advance another one of their
6 stated goals, which is reducing abuse and
7 diversion. Thank you very much for having me.

8 DR. KAWAS: Thank you, Mr. Spillane. The
9 next one is Ms. Mali Einen.

10 MS. EINEN: Hello, and thank you for the
11 opportunity to speak before you today. I could
12 tell you my story of my scars and bumps and bruises
13 from my many falls from cataplexy, or I could tell
14 you about my disappointment from having had to give
15 up my career that I was dedicated to and loved, not
16 to mention the loss of income and security.
17 Instead, the part of my story I share with you
18 today is the loss of the normal, everyday things
19 that most parents take for granted.

20 My name is Mali Einen. I am a single
21 mother from California with narcolepsy and what is
22 considered severe cataplexy -- and a lot of
23 nervousness. As a person with narcolepsy, I was
24 fortunate to be diagnosed fairly quickly after the
25 onset of my symptoms. I was diagnosed at the age

1 of 22 after first noticeable systems of narcolepsy,
2 appearing at about age 22.

3 In the early years my cataplexy was
4 triggered mostly by strong emotions -- a truly
5 funny joke or my young daughter saying something
6 adorable. As the years progressed, my cataplexy
7 worsened, requiring less and less of an emotional
8 trigger to cause a complete collapse -- unable to
9 move or talk for seconds, sometimes even minutes at
10 a time despite my daily medications.

11 As my daughter grew and my cataplexy
12 worsened, I was unable to attend her performances,
13 school programs or sports activities without
14 several full collapses. My young, then seven or
15 eight year old daughter would complain, why do you
16 bother to come? You spend most of your time passed
17 out. That is what she called cataplexy. I
18 wondered would she ever understand that it was my
19 joy for her success and my love for her that
20 prevented me from participating in these
21 milestones.

22 Several years later my daughter's simply
23 relaying a story to me, excitedly, about her latest
24 crush or her experiences with her friends would
25 cause me to crumble, much like the film that Dr.

1 Mignot showed earlier today. It dawned on me that
2 I had not only given up my experiencing anything
3 that might involve positive emotion, it had become
4 difficult for me to even participate as a spectator
5 in my daughter's life.

6 During the years, I had been able to
7 maintain success in my developing career as a money
8 manager. My workaholic, nose to the grindstone
9 withdraw kept me away from the usual office fun and
10 water cooler moments, while allowing me to avoid
11 embarrassing cataplexy. But this too had begun to
12 erode. Although the various medications allowed me
13 to keep my cataplexy partially in check, it seemed
14 that my nighttime sleep became more and more
15 disrupted, sleepy during the day, yet never able to
16 sleep more than an hour or two at a time at night.

17 By 1996, my spotty nights of a few hours
18 of sleep, my sneaking naps during the work day, and
19 collapsing in exhaustion any time I sat still had
20 affected my ability to continue to perform my job
21 adequately. Long ago my daughter had given up on
22 my being able to read her a story or to help her
23 with her homework. My life had become dragging
24 myself to and from work, attending to the basic
25 needs of my daughter, while constantly working to

1 keep my emotions in check. There was little room
2 for fun and interaction. Sole provider for my
3 daughter and myself, I finally voluntarily left my
4 job.

5 By this time I had become a complete slave
6 to my next dose of medication to either control my
7 cataplexy or to help keep me awake. The
8 medications didn't make me feel well; they made me
9 feel horrible, yet, I was their slave. I had never
10 taken a back seat to finding better or best
11 treatment options. I tried no less than five to
12 seven different antidepressants over the years with
13 varying degrees of success, but each with such a
14 cost.

15 Within a year after I had left work, I
16 became aware of a new medical study through
17 Stanford, an experimental treatment for narcolepsy
18 and cataplexy. I started Xyrem. My life changed!
19 After a horrific washout period when, unmedicated,
20 I was faced with my inability to care for myself,
21 let alone my daughter, with mere thought causing
22 collapse after collapse, I found that Xyrem
23 controlled most of my cataplexy and I was thrilled
24 how the better quality nighttime sleep allowed me
25 to feel normal, almost good upon waking.

1 Although not required by the medical
2 study, I began to voluntarily decrease my daily
3 doses of amphetamines. The better, less disrupted
4 nighttime sleep allowed me not to be a slave to my
5 next dose of stimulants in order to make it through
6 the next several hours. I now go many days without
7 stimulants at all, and other days take 5 mg or less
8 of Dexedrine.

9 I not only began to be able to listen to
10 my daughter's glee-filled stories of her day, I
11 started to volunteer at her school. I could joke
12 with the kids; I could even watch Kelsey smash a
13 winning serve across the volley ball court. I must
14 admit, occasionally a funny story or my evening
15 interaction with my daughter still causes my facial
16 muscles to slacken with a bob of the head, but my
17 daughter now uses these opportunities to give me a
18 hard time, knowing that I will recover in a second
19 or two and we will have fun and enjoy our life
20 together.

21 I asked my now 17-year old, upon
22 contemplating being here today, would you say my
23 taking Xyrem has made a difference in your life? I
24 had expected the usual teenage disinterested reply.
25 Instead, Kelsey responded, as tears welled in her

1 eyes, as much as I hate it sometimes, you are
2 really a part of my life now; you know everything
3 that's going on with me.

4 It is for this that I am truly grateful to
5 Orphan Medical and Xyrem -- and I think I forgot to
6 say my conflicts of interest.

7 DR. KAWAS: That is the only reason we are
8 going to let you go more over time.

9 MS. EINEN: I am a shareholder of Orphan
10 Medical and a number of other stocks of products
11 that I believe in. Narcolepsy Network has
12 generously paid for my air fare and accommodations,
13 but they have not compensated me for my time, nor
14 am I paid for the time away from my brand-new job
15 back in the career which I had to leave five years
16 ago.

17 DR. KAWAS: Thank you, Ms. Einen. Next is
18 Ms. Sandra Jones from California.

19 MS. JONES: Good afternoon, ladies and
20 gentlemen. My name is Sandra Jones, and I am from
21 Los Angeles, California. My travel expenses are
22 being reimbursed by the Narcolepsy Network. I am
23 50 years old. It was only 19 years ago that my
24 mother truly became a mother to me, my brother and
25 sister. Nineteen years ago my mother began taking

1 what we now call Xyrem. Within a week after she
2 started taking this medicine we noticed the
3 incredible change in her. She could cook dinner
4 without collapsing to the floor. She could sit
5 down and eat dinner with us without falling asleep.
6 She could make a sound that we hadn't heard in a
7 very, very long time -- laughter, and more laughter
8 without falling to the floor.

9 She became a totally new person to our
10 family. That was not the case nearly thirty years
11 ago. She quit her career as a nurse for fear of
12 how the disease might affect her care of her
13 patients. She became sort of a recluse in her home
14 and we grew used to seeing her sleeping throughout
15 the day and staying up all night. She was afraid
16 she would fall and bring embarrassment to herself
17 and especially to her family. People just did not
18 understand her disease. She once collapsed at a
19 party and people dismissed her as being a drunk.
20 My mother didn't drink. It was what the narcolepsy
21 had done to her.

22 This is an evil, evil disease and unless
23 you have witnessed it firsthand you cannot
24 understand the horrible ways it affects a person's
25 live. Imagine having a newborn child, my sister,

1 and not being able to hold her for fear of dropping
2 her. Imagine not being able to go to the grocery
3 store for fear of falling in the aisle. Imagine
4 not being able to read stories to her children
5 because she would fall asleep, not us. Imagine not
6 being able to drive a car for fear of collapsing
7 behind the wheel. This was my mother.

8 But Xyrem changed all that. It was a
9 difference between night and day and mother quickly
10 rediscovered the joys that she had missed for
11 decades -- playing games with us, going dancing,
12 going to the movies, celebrating family birthdays
13 and holidays. The day-to-day tasks that you and I
14 take for granted, she could finally do as a normal
15 person. This was the mother that we had never
16 known until Xyrem gave us her life back and her
17 family back. I have seen the difference. I have
18 lived the difference. Please make this valuable
19 medication available to people who have narcolepsy.
20 They and their children will see the change in
21 their lives. Thank you.

22 DR. KAWAS: Thank you, Ms. Jones. That
23 concludes the section of open public hearing, and I
24 want to thank everybody who expressed their views,
25 information and helped the committee keep sight of

1 all the issues here.

2 We will now reopen the questions from the
3 committee to the invited speakers, sponsor and the
4 FDA. In particular, I would like to focus on the
5 presentations that we had right before lunch
6 involving the epidemiology, adverse medical events
7 and the sponsor presentations on risk management
8 and abuse liability. So, who wants to start the
9 questions from the committee with regard to some of
10 those presentations?

11 Continued Committee Discussion and Deliberations

12 DR. SIMPSON: I put up my hand under false
13 pretenses because I had just one question really --

14 DR. KAWAS: We don't like false pretenses
15 around here!

16 DR. SIMPSON: It was really relating to
17 the efficacy. I mean, a lot of the presentations
18 we have just heard give the impression that the
19 cataplexy was, if not completely controlled, almost
20 completely. Yet, when we look at the data we see
21 that the median number of events at the end of some
22 of the studies is about eight or so on drug. So,
23 do we have any data about how many people actually
24 had no cataplectic events?

25 DR. REARDAN: I think that this question

1 was discussed to some extent this morning. It
2 dealt with complete cataplexy --

3 DR. SIMPSON: No, no, I am saying do we
4 have data on the people who were, quote, cured?
5 Were there any?

6 DR. REARDAN: We have a slide on that, I
7 understand.

8 [Slide]

9 DR. HOUGHTON: This is an example of the
10 long-term data, and one of the problems with the
11 controlled GHB-2 trial is that it may be too short.
12 The reason that the time was restricted is because
13 of the imposition of patients on placebo for longer
14 periods of time. But that represents a picture of
15 the long term response in terms of percentage
16 change. So, we have a control across all doses,
17 demonstrated here for a 12-month period, around the
18 90 percent or better mark. Now, that doesn't mean
19 to say people don't have any cataplexy, but it is
20 certainly very significantly reduced.

21 DR. KAWAS: Dr. Katz?

22 DR. KATZ: Yes, we have seen this slide a
23 number of times. I just want to remind the
24 committee that this is open, uncontrolled,
25 non-randomized data, not the sort of data that we

1 would ordinarily rely on to draw any sort of
2 conclusion about effectiveness of any sort.

3 DR. KAWAS: Maybe the sponsor could show
4 us some of this data from one of the randomized
5 trials?

6 DR. HOUGHTON: We could show you the
7 change in the GHB-2 study again, which is the
8 four-week study.

9 [Slide]

10 The data is median change from baseline.
11 We had a median incidence of 23.5 in the 9 g group,
12 a change from baseline of 16.1. If we present that
13 again as percentage change -- because, once again,
14 it is complicated by the spread in the data.

15 DR. SIMPSON: I guess my question is if
16 the median at the endpoint is 8.7, it means 50
17 percent of the people were above it and 50 percent
18 were below. Now, how many were below, say, 1 or 2?

19 DR. HOUGHTON: Well, it depends on what
20 their starting level was, and the conditions of
21 entry were 3 cataplexy or more attacks per week.
22 We did have patients with very high incidence. So,
23 in terms of absolute numbers, that is a very
24 difficult response. I am not trying to be evasive.

25 DR. WOLINSKY: The other piece of that

1 data though that you presented and might be worth
2 looking at quickly is the randomized stop component
3 of the trial.

4 DR. HOUGHTON: Sorry?

5 DR. WOLINSKY: When patients were
6 randomized to be taken off --

7 DR. KAWAS: The 21 study.

8 DR. REARDAN: Right. The question is on
9 a-patient-by-patient basis, how many patients went
10 from X amount of cataplexy to zero cataplexy. Is
11 that what you are trying to get at?

12 DR. SIMPSON: Zero or close to zero.

13 DR. REARDAN: That is in the data listings
14 for the trial. We didn't bring individual breakout
15 of the data. We brought summary information for
16 the committee. I don't know if Dr. Mani has a
17 recollection or Dr. Katz.

18 DR. KATZ: You don't have a distribution
19 of how many events patients had? In other words,
20 you know, X percent had two or fewer events; Y
21 percent had between two and five events.

22 DR. HOUGHTON: No, we didn't break it down
23 like that. I think the slide that you were
24 referring to was the one that I showed with
25 individual patient plots, and I can show you that

1 quickly.

2 [Slide]

3 That is just an example of absolute
4 numbers. These were individual patients plotted.
5 That was their incidence at the baseline, and that
6 was some two years after this was conducted. That
7 is the sort of response they got when their active
8 treatment was withdrawn. That is the group in
9 active treatment. So, in terms of just absolute
10 numbers, that is just a snapshot. That is not a
11 statistical presentation. It happens to be every
12 patient that came from that original trial through
13 into this trial, and I show it as individual plots.
14 It is the best impression of individual patient
15 data I can give you to answer your question.

16 DR. BLACK: Just a comment on that. In
17 this section we do have placebo-controlled data and
18 we have the number of cataplexy attacks on placebo
19 versus active medications after patients have been
20 on treatment for a long period. Dr. Katz' comment
21 is very good. The data that has been generated
22 over the open label, though it does suggest there
23 is a time course till optimal effect of at least
24 two months, is open label. But this is
25 placebo-controlled data, suggesting that the

1 average there of cataplexy attacks per day -- I
2 don't know if you have the numbers of that, Dr.
3 Houghton, but it is very low during the time of
4 treatment unless they are taken off and then on the
5 placebo-controlled portion.

6 DR. KAWAS: I have a question for the
7 company as well as probably Dr. Dyer. I want to
8 hear both sides of why we heard such very different
9 descriptions of the potential for withdrawal
10 syndromes with this disorder. I recognize fully
11 that the company has studied individuals with
12 narcolepsy and it is possible that alone could
13 comprise the difference, but we do have a very nice
14 withdrawal study in study 21, which is not
15 typically the case, and the findings that were
16 collected from that are in fairly sharp contrast to
17 the stories that we have heard from Dr. Dyer with
18 regard to withdrawal syndromes, and I wondered if
19 both sides could tell me what the difference was.
20 Is it dose? What is the difference here?

21 DR. REARDAN: I will ask Dr. Balster, but
22 I believe it is dose and frequency. Bob, do you
23 want to comment?

24 DR. DYER: I doubt that we disagree.
25 Clearly, in my set of patients and what we use

1 nearly as a diagnostic parameter and which patients
2 we should admit, even though their early symptoms
3 are mild, is the frequency with which they are
4 using it. So, the kinetics of the drug show us a
5 duration of activity around three or four hours.
6 When these patients increase their frequency so
7 that their body constantly is exposed to GHB, those
8 are the ones that we feel become severely
9 physically dependent and then go through this
10 withdrawal syndrome that can have an onset within
11 hours of discontinuing the drug.

12 DR. KAWAS: So, in your opinion it is
13 frequency of dosing, not even the number of grams
14 per day.

15 DR. DYER: As far as I can tell, it is
16 frequency because if I take the sponsor's
17 information, and for years I have spoken to the
18 investigators that are doing this and they have
19 said they have had no trouble. Their patients have
20 a 12-hour drug holiday daily, which is two to maybe
21 three times what they are calling a half-life for
22 this drug. So, the drug is completely eliminated
23 from the body for a time period, and the patients
24 have that become severely addicted, all of them.
25 I mean, that is kind of diagnostic for the severe

1 withdrawal, somebody who is taking it every three
2 hours around the clock.

3 DR. BALSTER: Yes, I agree completely with
4 that, and maybe the analogy that would help you
5 understand it would be the analogy, for example,
6 with alcohol where really alcohol can produce a
7 very significant physical dependence but you can
8 drink it every evening with your meal and you won't
9 become dependent because between that evening use
10 and the next day it has cleared the body. So,
11 whatever physiological adjustments are necessary
12 have corrected themselves. So, we are in complete
13 agreement.

14 DR. KAWAS: Thank you. Dr. Katz?

15 DR. KATZ: Just as an extension of that,
16 there was also the implication or the explicit
17 statement that in some of those people who took it
18 very frequently and ultimately, presumably, became
19 addicted, they were compelled to take it more
20 frequently. In other words, there was a tolerance
21 that developed and they had to increase their
22 frequency to get the same sort of pharmacologic
23 effect.

24 So, I will just ask the same question that
25 Dr. Kawas asked about withdrawal. We have heard

1 from the company that patients who have taken the
2 drug for years and years and years don't develop
3 tolerance; they don't have to increase their dose;
4 they don't increase the frequency of
5 self-administration. But, we are hearing that on
6 the outside there are people in whom this
7 phenomenon apparently does occur. So, I will ask
8 the same question. Why the disparity?

9 DR. DYER: Again, there haven't been
10 really good studies or anything scientific. It is
11 kind of my thoughts or opinions but, again, it is
12 accommodation because you are taking it around the
13 clock. So you are accommodating. Also, in the
14 patients that are taking it -- well, I don't know,
15 they are not really patients -- in the people who
16 are abusing it there is a lot of the feeling that
17 if a little is good, a lot is better. They are
18 taking it initially, these body builders, for this
19 growth hormone burst. So, they really feel like
20 they are doing the right thing. So, there is
21 nothing to have them diminish their dose or hold
22 their dose as it is. Then, once they start taking
23 it more frequently, the duration of the drug as it
24 wears off in three or four hours, we think, gives
25 them kind of a dopamine surge for which then they

1 are going to feel a little depleted and want to
2 take that next dose. Then there is also physical
3 craving for that kind of high. They are awake and
4 feeling that kind of high as opposed to the
5 patients that are taking it immediately upon going
6 to bed and then sleeping through this euphoric --
7 whatever the kids are trying to get that are
8 abusing it -- if you can roll that into an answer.

9 DR. BALSTER: That is exactly the way I
10 would see it too. Just to add one further thing to
11 that, the way to look at tolerance, you have to
12 understand that it occurs through different effects
13 at different rates and in different ways. So, the
14 therapeutic effect is one effect. The intoxicating
15 effect is a different effect. And, commonly in
16 abuse situations where persons are trying to
17 maintain an intoxication, they have to escalate
18 dose and frequency in order to do that, whereas the
19 data obtained in these clinical trials, of course,
20 is on the therapeutic effect.

21 DR. DYER: One other comment, in the
22 alcohol abuse trials they did escalate their dose
23 in more of a craving kind of manner. That was
24 about 15 percent.

25 DR. KAWAS: Dr. Roman?

1 DR. ENGEL: I would like to add something,
2 if I may, to this point that is based on the risk
3 management system proposed by the sponsor. As you
4 saw, the data collected by the specialty pharmacy
5 will include dose by patient. And, because of
6 that, the specialty pharmacy will be able to
7 predict when is the appropriate timing for a given
8 patient to have their prescription refilled. So,
9 for example, there are patients attempting to
10 refill too soon, so to speak, that will be
11 identified and it will be an opportunity for the
12 pharmacist to interact with the physician very
13 quickly, before a patient might get into a
14 situation like which Dr. Dyer is describing with an
15 overuse syndrome.

16 DR. ROMAN: A question perhaps again for
17 Dr. Balster. Is the pharmacology of GBL and 1,4-BD
18 similar in animal experience to GHB? Number two,
19 if there is a difference, did I understand
20 correctly that GBL and 1,4-BD are not currently
21 drugs of abuse?

22 DR. BALSTER: Well, the first question,
23 pharmacological comparisons of GBL, GHB and 1,4-BD,
24 these haven't been very extensively done. So,
25 hopefully some of those NIDA grants that someone

1 was talking about will really take that question
2 on. But let me say that in a number of those
3 studies that were done to describe the pharmacology
4 of GHB, in some of these studies actually GBL was
5 administered to the animal with the view that it
6 was a prodrug for GHB. I forgot who said it but
7 someone said that so far as we know, all of the
8 effects of GBL and 1,4-BD are really as a
9 consequence of their conversion to GHB. I believe
10 that would be the current state of knowledge about
11 that although it is imperfect.

12 Now, the question about control, in a
13 sense, yes, all of these drugs are potential drugs
14 of abuse because they can be taken and basically
15 are active in the case of precursors with
16 metabolites. So, yes, all of these are potentially
17 drugs of abuse. Only one of them is a controlled
18 substance and one of them, by congressional action
19 of last year, became what is called a listed drug,
20 and I could explain that to you or, actually, Dr.
21 Sannerud would know better than I what exactly that
22 means. But it essentially means that there is
23 limited distribution.

24 DR. ROMAN: So, with GBL and 1,4-BD there
25 is no control.

1 DR. BALSTER: Well, as I say, for 1,4-BD,
2 to my knowledge, there is no control. I need to
3 step back a little bit from that because we could
4 get into too long of a discussion about what
5 constitutes an analog under the specific language
6 of the legislation. So, it is possible for
7 prosecuting attorneys to claim that one or another
8 of these drugs are analogs of a controlled
9 substance. The Controlled Substances Act, in a
10 sense, regulates analogs. Now, 1,4-butanediol is
11 questionably an analog, but that would be something
12 that would be worked out in court. So, I am not
13 trying to tell you that someone could absolutely,
14 with impunity, sell 1,4-BD to children and say that
15 it wasn't a drug of abuse because I am sure that
16 there would be authorities and prosecutors who
17 would try to do something about that. But in terms
18 of the actual language of regulation, only GHB is a
19 controlled substance.

20 DR. SANNERUD: GHB is a Schedule I
21 controlled substance. Butanediol and GBL are
22 considered controlled substance analogs under
23 federal law, which means they can be prosecuted, as
24 GHB, with penalties and other things would apply if
25 someone is caught trafficking, distributing or

1 clandestinely manufacturing or selling these
2 compounds as well. GBL is listed as a List I
3 chemical, which means that there is record-keeping
4 and registration required. There are no retail
5 sales of butanediol, and there is a graph in here
6 with the product. These are used in industrial
7 uses. So, this comparison is really a little bit
8 misleading. I don't know the numbers but GHB is
9 not even marketed yet, so this number on production
10 is only for clinical trials I assume.

11 As far as the GHB and Xyrem they are both
12 GHB. There is no forensic analysis that is going
13 to differentiate between the two. So, when samples
14 are submitted to labs there is no way to tell if it
15 is the product or if it is something that is made
16 at home. So, for someone to say that there has
17 never been any diversion of the product, there is
18 no way to tell that because there is no way to
19 differentiate between the two under forensic
20 laboratory conditions.

21 Another question I wanted to address is
22 the quota issue. Ms. Meyers brought up quotas for
23 Schedule II compounds, the stimulants. DEA sets
24 the quota, as it will with GHB as well. It has
25 never been the case that drug has run out at the

1 end of the year because the quotas are set too low.
2 If there is a problem with the drug manufacture the
3 quotas can always be increased throughout the year,
4 and they are done so on a regular basis. So, there
5 has never been the case where a drug has run out.

6 DR. KAWAS: Dr. Mani?

7 DR. MANI: I would just like to touch upon
8 the issue of drug diversion during the clinical
9 trials once again briefly. Many speakers have
10 asserted that there has been no evidence that Xyrem
11 or GHB used in the clinical trials included in the
12 database was diverted. That may very well be true,
13 barring the one exception that I cited earlier, and
14 I have no firm evidence to the contrary. However,
15 I have gone through the NDA, reviewed the whole
16 NDA, and I would be a little more hesitant in
17 making that assertion, and I will tell you why, and
18 that has to do with the way the drug was dispensed
19 in the Scharf study which, as you know, occupied
20 about 30 percent of the database in terms of
21 patient numbers and about 70 percent of the
22 database when you are talking about patient years
23 of exposure.

24 What happened here was that patients saw
25 Dr. Scharf in Cincinnati, at least for an initial

1 visit, and had an appropriate diagnosis made and
2 were then enrolled in the trial and then went back
3 to whatever part of the country they came from.
4 Prescriptions for medication were filled based on
5 their returning completed diaries. In some
6 instances it appears, at least from my looking at
7 the case report forms, that prescriptions were
8 sometimes filled in advance or the diaries being
9 returned, obviously to prevent the patient from
10 running out of the drug. But the important thing
11 is that patients were not required to return unused
12 supplies of medication prior to getting a fresh
13 prescription, or to provide any formal accounting
14 of how much medication they used or did not use.
15 In the absence of any active surveillance of that
16 kind, as I said, I would be quite hesitant in
17 making the assertion that no medication was
18 diverted.

19 DR. REARDAN: I need to make a qualifying
20 statement here. We do not disagree with Dr. Mani.
21 However, under the company's clinical IND, our
22 patients under IND didn't begin entering trials
23 until 1996. Patients were required to document
24 their dose; to return their bottles. The bottles
25 were all qualified by volume in terms of what was

1 returned. The incident that Dr. Mani refers to, I
2 believe, occurred in 1986, when GH3 was available
3 as a nutritional supplement and Dr. Scharf's trial,
4 again, was clinical practice. There were a lot of
5 issues on GCP compliance in that trial. We do not
6 take responsibility for accountability of drug
7 under Dr. Scharf's trial. So, I will just qualify
8 that. Okay?

9 DR. MANI: I agree.

10 DR. FALKOWSKI: I have a question and it
11 has to do with the fact that we are talking about a
12 method of taking this drug where you take half the
13 amount at bedtime and then you wake up several
14 hours later, but don't really wake up, and take the
15 rest of it. And, I am just wondering what would
16 happen if you were confused. It also involves
17 mixing it ahead of time to the right strength. I
18 am asking this both to Dr. Dyer and the sponsor,
19 what would happen if someone took 9 mg at once?
20 You know, if someone got confused and took it all
21 at once, what would be the expected outcome?

22 DR. REARDAN: I had a number of questions
23 about this at the break from a couple of members of
24 the committee -- how do they make it up, and so on.
25 It might be worthwhile to ask Patti Engel to go

1 through that. The other point about narcoleptic
2 patients waking up, maybe Dr. Black, you could
3 comment on how they wake up and take their second
4 dose.

5 DR. FALKOWSKI: Right, but my bottom line
6 question is what would happen to a person who
7 inadvertently took all of their dose at once, and I
8 really insist on an answer to that. Thank you.

9 DR. BLACK: That question has been
10 answered by patients who have taken inadvertently
11 larger doses. As far as the waking up at night,
12 the patients that are here could probably respond
13 to that, but the overwhelming majority are awake
14 actually before the four hours later on their own
15 and they are fully awake. The medication is
16 premixed so there is no mixing that needs to occur
17 at that point. There are folks who have taken
18 extra doses and there is more sedation that occurs
19 with the extra duration and the period of sleep is
20 longer with the higher dose.

21 DR. FALKOWSKI: Is the answer then
22 increased sedation? Is that the answer to my
23 direct question?

24 DR. BLACK: Yes, if the dose is increased
25 there is increasing sedation and a longer sleep

1 period.

2 DR. FALKOWSKI: Okay. Dr. Dyer, could you
3 respond to that?

4 DR. DYER: It is my opinion that the dose
5 would be around 100 mg/k and at that point you are
6 going to have coma and some of the other side
7 effects that we see in our club goers are very
8 likely to be what you would see. So, vomiting and
9 aspiration is a possibility. You know, the ability
10 to hear and react to fire alarms, children,
11 whatever, that is all going to be blunted.

12 DR. FALKOWSKI: Is it a possibility then
13 that some of these people who may have double dosed
14 would be in a coma but who would know, you know?
15 Is that a possibility, sponsor? I mean, who is to
16 know?

17 DR. BLACK: I think that the question is a
18 good one, and what I might call deep sleep someone
19 else might call a coma. But when we look at the
20 brain wave activity of the folks with the higher
21 doses, they have nothing in the EEG that would be
22 consistent with straightforward coma.

23 DR. FALKOWSKI: But you didn't take EEGs
24 on these people when they were sleeping in
25 situations like this.

1 DR. BLACK: Well, we have done EEGs on the
2 folks when they have been sleeping at the 9 g dose
3 but not on double the 9 g dose.

4 DR. FALKOWSKI: Okay.

5 DR. KAWAS: Dr. Katz, please.

6 DR. KATZ: Yes, a couple of things. Maybe
7 the best way to get at this if it is possible is to
8 ask the company to show us any data that they have
9 about what happened to patients who took, let's
10 say, a single 9 g dose. I don't know how many
11 patients did that, but if there is data on that it
12 would be nice to see.

13 So, I don't know, maybe you could look for
14 that while I get to the second part which is,
15 again, just another variant about the question we
16 were talking about before, this perceived disparity
17 between patients and non-patients who take the drug
18 recreationally. We have heard again, not just in
19 terms of withdrawal and addiction and tolerance but
20 just in terms of serious adverse events, a number
21 of the serious adverse events that we have heard
22 about in the emergency room situation seem to have
23 occurred at doses, presumably -- I don't know how
24 reliable the dose information is in that setting, I
25 am not sure, but presumably at doses that patients

1 routinely get and which they tolerate extremely
2 well. So, I will ask the same disparity question
3 again there.

4 DR. MIGNOT: I think you have to realize
5 also that you are talking about narcoleptic
6 patients who also experience daytime episodes of
7 overwhelming sleepiness that sometimes lead to
8 confusion, and there are a lot of horror stories
9 about narcoleptic patients, independently of GHB,
10 at any moment of their life where they can
11 sometimes be in a risky situation just because they
12 have what we call automatic behavior, this
13 overwhelming sleep attack where they really don't
14 know what they are doing, where they may be driving
15 or doing something dangerous. I think that is also
16 important to keep in mind. The danger of taking
17 two doses at a time, if it is relatively well
18 dispensed, for narcolepsy patients I think needs to
19 be put in perspective for their other symptoms.

20 DR. REARDAN: I am only aware of one case
21 in our database. It was a patient who
22 inadvertently took 18 g and I think, Dr. Mani, you
23 are well aware of that. He did fall on his head.
24 So, it is confusing as to whether it was a result
25 of his 18 g dose -- you know, that was the best

1 estimate we had -- or in the fall he hit his head,
2 but he did end up being taken to the emergency
3 department and did need supportive care. Oh, Bill
4 is saying that was a normal dose. I am sorry, let
5 me get him to clarify.

6 DR. HOUGHTON: Yes, I am sorry. That is
7 one of the cases that we know very little about.
8 It was a patient who was in the kitchen. There was
9 a loud bang. His wife heard the noise and came in,
10 and her husband was on the floor. So, we got no
11 dose relationship to that event. We know nothing
12 as to whether it is related to Xyrem.

13 The 18 g overdose was the patient who was
14 supposedly sleepwalking, in the Scharf database,
15 who supposedly then took 18 g on top of his normal
16 dose and was taken to hospital and ended up on a
17 ventilator.

18 Really, the best prevention we have of 9 g
19 being taken together is the fact that the dose has
20 to be made up into separate doses. The
21 instructions to the patient are very clear. They
22 make two doses up together, dilute it in the water;
23 drink one when they get into bed and the other, in
24 a sealed cup, put away. Now, if they took the
25 second dose in ten minutes or two hours, we have

1 not done that study and it is very dangerous to
2 extrapolate that sort of dosing. On one hand, I
3 can quote the patient who took 180 g and was taken
4 to hospital unconscious and walked out of hospital
5 four hours later to be admitted to the psychiatric
6 unit.

7 I certainly don't want to propose that as
8 the normal pharmacodynamic response. We have not
9 done a study that has escalated beyond the 4.5 g
10 dose twice a night, and I think it is very
11 dangerous to extrapolate. It is also very
12 dangerous to extrapolate the anesthesia data or
13 some of the data that Dr. Dyer talked about this
14 morning. Doses were given up to 100 mg/kg
15 intravenously. If we believe the bioequivalence
16 data, the absolute bioavailability data, that is
17 equivalent to at least 300 mg/kg as an anesthetic
18 dose, and that would be the best dose relationship
19 we could give to dose escalation. Again, without
20 true data I am not prepared to extrapolate from
21 that.

22 DR. KAWAS: Dr. Mani, do you still want
23 the floor?

24 DR. MANI: Yes, very briefly, just as
25 further evidence of how much individual variability

1 there is in response to this drug. There is a
2 subject who Dr. Houghton had referred to in his
3 presentation this morning, a healthy subject
4 participating in a pharmacokinetic trial, a healthy
5 young subject who received a single dose of 4.5 g
6 and afterwards became obtunded, developed
7 obstructed respiration perhaps because of his jaw
8 falling back, became incontinent of urine and
9 stool, and took a number of hours to recover but
10 did not need any special supportive care. So, even
11 a 4.5 g dose may not be entirely safe for
12 everybody.

13 DR. HOUGHTON: That story is somewhat true
14 but not quite accurate. The patient was easily
15 arousable, walked to the bathroom after the event
16 of passed urine, after resting back in bed had a
17 normal sleep and, two hours later was awake and ate
18 a normal lunch. So, again, I can't account for the
19 degree of obtundation but that still represented
20 the maximum single dose in our database. It was a
21 single dose of 4.5 g after a 10-hour fast.

22 DR. MANI: Although those details about
23 the patient being able to get up and go to the
24 bathroom and eat her lunch, and so on, wasn't in
25 the narrative that we have available.

1 DR. HOUGHTON: We were collecting urine
2 samples every two hours and I can assure you the
3 patient was walked to the bathroom. She certainly
4 vomited at the time.

5 DR. KAWAS: Dr. Leiderman?

6 DR. LEIDERMAN: Very briefly because Dr.
7 Mani raised one of the points that I wanted to, but
8 the other question I had for the sponsor and the
9 sleep neurophysiologists here, do you think that in
10 some of the differential response that we are
11 seeing in the narcolepsy patients as compared to
12 the subjects who become dependent, addicted, have
13 overdose problems that there may be a role not only
14 of the basic neurophysiology of the narcoleptic
15 brain but, of course these patients tended to be
16 co-medicated with stimulants, and what role do you
17 think that might be playing in the narcolepsy
18 population?

19 DR. REARDAN: Is the concern that
20 stimulants would still be present on board when
21 they take their nightly dose of Xyrem? Is that
22 what you are after, or what?

23 DR. LEIDERMAN: Well, I am asking for your
24 thoughts on, shall we say, the differential effects
25 of GHB on the two populations, and one of the sort

1 of clear differences, taking sort of the first cut,
2 is that narcolepsy patients are co-medicated with
3 stimulants generally, whereas the abusing drug
4 population, if anything, is self co-medicating with
5 other CNS depressants or using GHB at high doses
6 alone.

7 DR. BLACK: I think there are a number of
8 questions that surface. We have patients in
9 protocols where they are wanting to remain on the
10 protocols or wanting to be drug compliant. There
11 are reasons that they wouldn't abuse in addition or
12 outside of the fact of co-pharmacy with stimulants
13 and so forth. So, it is hard to compare those two
14 groups clearly.

15 I think the best we can do is speculate.
16 We have a number of patients that were not
17 co-treated with stimulants as well, that were on
18 just Xyrem, and they didn't self-escalate the dose
19 or abuse the agent either. I think the only way to
20 do it would be to give high dose frequently to the
21 narcolepsy patient population and see if they are
22 similarly addictable, and then it would be also
23 interesting to find out what percentage of the
24 normal population is addictable as well.
25 Obviously, those studies couldn't be done. But I

1 think we can't compare the two and it is real hard
2 to try to extrapolate the information we have to do
3 a comparison.

4 DR. KAWAS: Dr. Dyer, followed by Dr. Van
5 Belle, followed by Ella Lacey, followed by the
6 questions that the FDA has asked us to consider.
7 In between, we will get a quick demonstration of
8 the mixing.

9 DR. HOUGHTON: Could I just add one point
10 of clarification to Dr. Leiderman's question?
11 There were patients in all of the studies that were
12 not on stimulants. In the GHB-2 study I think it
13 was about 15 percent when we did a recent look at
14 the database for Dr. Mani. So, there was at least
15 a proportion of patients represented in the
16 database that weren't on stimulants as concomitant
17 medication.

18 DR. DYER: There was one study, I believe
19 it was done in rats where amphetamines and then a
20 second with caffeine, where those were shown to
21 kind of be antidotal to GHB poisoning, where it
22 prevents the rats' loss of riding reflex. So,
23 there may be some of that issue if they are taking
24 it concurrently. One of the other things about the
25 disparity, where I don't see the disparity as being

1 so much is that the narcoleptics are taking their
2 dose at night. We know pretty commonly from the
3 surgical studies from what we see coming into the
4 emergency room and from the adverse effects of the
5 study, that GHB causes vomiting and incontinence.
6 So, we are seeing that in both populations of
7 patients.

8 DR. CHERVIN: Is anybody there?

9 DR. KAWAS: Yes, is that one of our phone
10 consultants, Dr. Chervin or Dr. Guilleminault?

11 DR. CHERVIN: Sorry, it seems like we were
12 completely cut off.

13 DR. KAWAS: Can you hear us now?

14 DR. CHERVIN: Just barely. If there is
15 any way you can make this signal more than barely
16 audible, it would be helpful?

17 DR. KAWAS: We can barely hear you but it
18 sounds like we are going to have to get the AV
19 people on it, if you give us a moment.

20 DR. CHERVIN: I do have questions if I
21 have time to ask them.

22 DR. KAWAS: I know that you are on a
23 timetable, so we will put you in the middle of the
24 six-person pileup, if we could let the speaker that
25 is going now finish though.

1 DR. DYER: So, there was another study
2 where they took the patients and the patients that
3 they gave the dose to and then forced or tried to
4 maintain themselves awake, those were the patients
5 that became confused.

6 The other thing is that in our emergency
7 department study where we were trying to verify our
8 ability to predict GHB by toxidrome, we looked at
9 patients that came in with a GCS score less than 8
10 that were spontaneously breathing. So, unlike most
11 CNS depressants that cause profound coma, generally
12 the breathing is still spontaneous and maintained.
13 You see mild respiratory acidosis but it is not
14 very common that these patients need to be
15 intubated. So, it is not contrary to be thinking
16 that a patient might be comatose and survive the
17 night.

18 DR. KAWAS: Dr. Van Belle, while we are
19 still working on the audio, do you want to go ahead
20 and ask your question?

21 DR. VAN BELLE: I just have a brief
22 question with respect to age eligibility. Will
23 this medication be available to people under 18
24 years old?

25 DR. REARDAN: The company has not

1 specifically developed data for pediatrics, and I
2 think this would have to be something we work out
3 with the agency but, typically, a medication
4 approved for adults is not denied children. FDA
5 and Congress have tried to put incentives in to get
6 sponsors to develop pediatric information. In
7 addition, narcolepsy is not generally a pediatric
8 disease. I don't know if either Dr. Mignot or Dr.
9 Black want to comment further. Dr. Katz?

10 DR. KATZ: Well, generally speaking,
11 unless there is a good reason not to, we would
12 limit the age that would be at least included in
13 the indications or in labeling or dosage
14 administration to the age of the lower limit of the
15 age studied in the trials. I don't know exactly
16 what the youngest patient was in these trials.

17 DR. REARDAN: Bill Houghton is saying 12.

18 DR. KATZ: Okay, 12. Again, if there was
19 one patient who was 12 and everybody else was 18
20 and above, we would say adults or 18 and above,
21 that kind of thing. It is true that there is no
22 prohibition, obviously, from a physician writing a
23 prescription for a drug for a child if it is only
24 explicitly approved for an adult. It happens
25 obviously all the time. But one of the questions

1 when we get to it with regard to risk management
2 and that sort of thing is if there were no children
3 studied, or children studied below a certain age,
4 do you think attempts should be made to restrict it
5 in this case? So, you know, it is open for
6 discussion.

7 DR. MIGNOT: To answer the question, onset
8 of the disease is roughly between 15 and 25. That
9 is really when the bulk of the patients are coming
10 in, especially for cataplexy, and I think it is
11 very important to treat them early. As there is
12 more and more knowledge about narcolepsy being an
13 important disease and being recognized early -- I
14 think you have heard a lot of testimony about how
15 important it is to treat them early so that they
16 can go through normal schooling. I think it will
17 be very important to not be too restrictive towards
18 the lower age.

19 DR. KAWAS: Dr. Lacey?

20 DR. LACEY: Two questions, one regarding
21 the packaging. With the packaging being in a
22 bottle and it is child-resistant dosing, and all,
23 but hearing about adolescents and their involvement
24 with GHB, I wondered if you considered other
25 packaging. In deciding on this packaging, did you

1 consider individual dosage packaging at all, and
2 what happened with that?

3 DR. REARDAN: We considered individual
4 dosing packaging for sure. We thought that was a
5 greater potential for diversion as it is easy to
6 take those individual doses. I think maybe you
7 would get some reassurance if Patti Engel can go
8 through how we instruct the patients to dose and
9 what the controls are for that. Patti?

10 MS. ENGEL: Thank you. To the point of
11 individual dosing, we did speak quite extensively
12 about that with law enforcement.

13 DR. LACEY: Yes, I am pretty convinced
14 about the patient. I am more concerned about
15 others in the household who are exposed to a
16 bottle.

17 MS. ENGEL: Right. I will address that as
18 well. On the individual dosing, law enforcement
19 was concerned about small containers that could be
20 stuck in a pocket or purse, or slipped in someone's
21 drink more easily. One of the things I shared with
22 you earlier is that the bottle itself comes with a
23 child-resistant closure. What is difficult to see
24 from this distance, but it is something called a
25 press-in bottle adaptor. When the patient gets

1 this, there is a little well, if you will, in
2 there. Even if a child can get this lid off, you
3 can't drink it down. What has to happen is there
4 is a metered syringe provided. It gets stuck in
5 here and the patient removes a metered dose. Okay?
6 They then have two child-resistant dosing cups and
7 these aren't fancy. We took them because they are
8 CPIS tested for child resistance, of course, and
9 they put it in, preparing both doses by their
10 bedside.

11 Now, the dose itself is metered. This
12 Xyrem, to be frank, is not good tasting stuff. It
13 is sodium oxybate. It is very salty. Many people
14 will dilute it. How much they dilute it really is
15 to their taste. We did not want to cherry flavor
16 it or anything like that that may make it more
17 attractive to children. Okay? Does that answer
18 your question?

19 DR. LACEY: It really wasn't the small
20 children that I was concerned about as I was about
21 the older, the adolescents in the household who can
22 open it the same as I could. So, I guess your
23 answer was that law enforcement was concerned about
24 the small dosages just being put in a pocket.

25 MS. ENGEL: That is right. Remember,

1 illicit use of Xyrem also falls under C-I
2 penalties, like heroin or LSD. So, we will never
3 be able to find a package that a 19- or a 21-year
4 old will not be able to get into. What we do,
5 however, is to educate the Xyrem patient on a
6 number of occasions of the penalties should that
7 occur. So, there is an element of patient
8 responsibility with this.

9 DR. LACEY: Thank you. The second
10 question I have is about the suicide attempts that
11 were presented by Dr. Houghton this morning. That
12 was in that list of adverse events I believe, and
13 it has continued to bother me that we talk about it
14 as a suicide attempt as though nothing else
15 happened and I am just curious, I guess, in those
16 attempts were some of the other adverse events also
17 experienced by those persons who were suicide
18 attempters?

19 DR. REARDAN: As you heard from Dr.
20 Mignot, depression is very common in narcoleptics,
21 but I will ask Bill to comment on that.

22 DR. HOUGHTON: In all the patients who
23 attempted suicide there was preexisting disease.
24 In terms of response to the dose taken, only one of
25 the suicide attempts involved Xyrem, and that was

1 the patient who took a very large dose, about 300
2 ml of the drug which is equivalent to at least 150
3 g, and he became comatose, incontinent of feces and
4 urine, continued to breathe spontaneously, was
5 found by his wife in the bathroom, transported to
6 the emergency medical care, did not require
7 intubation or ventilation, and walked out of
8 hospital four hours later to be admitted to the
9 psychiatric unit. I certainly don't propose that
10 as the norm. There will be certainly unconscious
11 patients at much lower doses. So, please don't
12 think I am proposing that as the pharmacodynamic
13 profile of the drug. But you asked me what the
14 side effects of the suicide event were and that is
15 the only data that I can give you.

16 The second suicide event that was not
17 fatal did not involve Xyrem. One of the fatal
18 attempts did not involve Xyrem at all. The last
19 suicide attack in the bipolar disorder patient was
20 a real pharmacologic cocktail involving
21 benzodiazepines, opiates, a number of drugs and
22 some Xyrem.

23 DR. LACEY: But for those individuals who
24 did have the suicide attempts, they did not have
25 other -- not with the attempt directly but other

1 adverse events also in their report?

2 DR. HOUGHTON: No. One of those was a
3 lady who had a group of people to her home. She
4 asked them all to leave early, and when attempted
5 to be contacted the next morning didn't respond,
6 and when her attentions were sought she was found
7 dead in the home.

8 The second attempt was a young lady who
9 took an overdose of buspirone and told her father
10 immediately. Her behavior was normal to that
11 point. So, that is an example.

12 DR. KAWAS: Dr. Chervin or Dr.
13 Guillemainault, can you hear us now? You guys are
14 next in the line up.

15 DR. CHERVIN: Thank you. I have two
16 questions. Please tell me if it has been covered
17 and I just was not able to hear it, but I read in
18 some of the material that was distributed prior to
19 the meeting about comparisons of the therapeutic
20 index or the therapeutic window for GHB to that of
21 other drugs that are currently approved and used.
22 I was wondering if perhaps Dr. Dyer or Dr.
23 Falkowski or Dr. Balster could address that
24 comparison.

25 DR. DYER: Is that the comparison of LD-50

1 in rats?

2 DR. CHERVIN: I guess it was rats, and it
3 was LD-50 and effective dose, and they looked at
4 the ratio.

5 DR. DYER: The problem I have with some of
6 the rat data, lethal dose data, is the deaths we
7 see are often secondary to coma. It takes high
8 doses to cause pure respiratory depression. We
9 have some patients that idiosyncratically have a
10 pulmonary edema, but most of the deaths are
11 secondary to unprotected coma and loss of airway.
12 So, I don't know that that would extrapolate or
13 come from rat data at all. I don't think you would
14 see that.

15 DR. CHERVIN: Is there any other way to
16 get at the issue of is Xyrem going to be more
17 dangerous than other drugs that are used carefully
18 when indicated?

19 DR. REARDAN: Dr. Chervin, I have some
20 data on LD-50 that will help. Oral GHB has an
21 LD-50 on the order of 9000 mg/kg in rats, and about
22 3500 mg/kg in mice. The IV LD-50 is about a third
23 of that for GBL and for butanediol it is on the
24 order of 2000 mg/kg. If you look at the effective
25 dose, we are in the range, I believe, of about

1 50-120 mg/kg recommended for the narcoleptic
2 patients. Now, that is just on an LD-50 basis. I
3 don't know if Dr. Mani wants to comment on the
4 therapeutic range, or Dr. Katz.

5 DR. KATZ: I don't think we really know.
6 I am not sure if the animal data is relevant at
7 all. And, I don't think we have data that, in a
8 systematic, adequate way, explores the full dose
9 response both with efficacy or tolerability. As
10 you have said, you have done a trial where the
11 maximum dose, fixed dose, was 9 g per night and,
12 you know, we either decide that that was a
13 tolerable dose or it wasn't. And, you have the
14 dose response for the effectiveness, and that is
15 all you have. As you acknowledge, you haven't
16 explored higher doses so I don't think we really
17 know, and I don't know how you would really get at
18 the question of how the therapeutic window, if
19 there is one, compares to other drugs that are in
20 common use. Some drugs that are used, there is a
21 belief that they have a very narrow therapeutic
22 windows, and some are wide. I don't think you can
23 say more than that.

24 DR. REARDAN: I don't disagree.

25 DR. GUILLEMINAULT: I have a question.

1 Narcoleptic patients have hypnagogic
2 hallucinations. They may even shoot -- if a gun is
3 available they may hurt their bed partner because
4 they are keeping their hallucination. How much
5 does Xyrem decrease hypnagogic hallucinations,
6 which is a very significant side effect which may
7 kill neighbors and may kill even bed partners?

8 DR. REARDAN: If I understand the
9 question, Dr. Guilleminault, it is how much did
10 Xyrem reduce hypnagogic hallucinations in our
11 trials, and I guess my first response is the
12 incidence was very low and we did not see a
13 statistical significance in GHB-2. I don't know if
14 Dr. Houghton wants to comment further on hypnagogic
15 hallucinations.

16 Just while they are finding the data, it
17 is fair to say that the incidence of hypnagogic
18 hallucinations recorded in the four-week trial was
19 very low. There was a trend towards improvement
20 that certainly didn't reach statistical
21 significance. There was a better representation in
22 the long-term open-label study and we could show
23 that but I am loathe to do so because I certainly
24 don't want to claim it as efficacy. I think we
25 will be able to find the GHB-2 data.

1 [Slide]

2 DR. HOUGHTON: In the Lammers study there
3 was a reduction from 0.87 hypnagogic hallucinations
4 per night over the 4-week treatment period to 0.28
5 incidence per night, with a p value of 0.008. That
6 is one set of figures.

7 DR. MIGNOT: Just to sort of expand on
8 what you said, if only about 40-60 percent of
9 patients with narcolepsy/cataplexy have hypnagogic
10 hallucinations as their symptoms or sleep
11 paralysis, then obviously that must reduce the
12 power for the trial because they have only about
13 half of the patients they included who even had
14 that symptom.

15 [Slide]

16 DR. REARDAN: This is a slide from GHB-3.
17 I guess that is open label, I don't know if we want
18 to go into that. What it shows is median change
19 from baseline to visit number and out through 12
20 months. You see a median change in hypnagogic
21 hallucinations, a reduction of 0.35 per day. Is
22 that right?

23 DR. KAWAS: Dr. Penz and then Dr.
24 Falkowski and then this committee will be looking
25 at the questions that the FDA has asked us to vote

1 on.

2 DR. PENIX: I think we have to anticipate
3 several different possibilities in the treatment of
4 patients with any drug, and I am somewhat concerned
5 about the fact that the effective dose of Xyrem
6 appears to be the maximum dose available, number
7 one. Secondly, in regards to the possible
8 protective effects of stimulants on the side effect
9 of sedation, and whether we should consider Xyrem
10 as a monotherapy drug or as an adjunctive
11 treatment, and the question I would like to ask --
12 I think Dr. Houghton may have presented this data
13 of talked about it, of the 15 percent of patients
14 who did not receive stimulants while on Xyrem
15 whether there was a difference in the maximum dose
16 escalation in those patients compared to the ones
17 who were on stimulants. I am not sure if we can
18 answer the question, but if there is data on that,
19 if there is a difference.

20 DR. HOUGHTON: No, we don't have data
21 separate for those on stimulants and those not on
22 stimulants. There was only about 15 percent in
23 that controlled trial that were not on stimulants.
24 So, we hadn't plotted that at all. Remember that
25 stimulants are taken in the morning and usually the

1 last dose at lunch because narcoleptics are really
2 trying to sleep at night and stimulants really
3 complicate that, and the half-life of the gama
4 hydroxybutyrate is about an hour.

5 So, even after their second dose their
6 plasma levels on awakening in the morning are
7 extraordinarily low. So, a contribution of
8 stimulants to change that is quite unlikely. We
9 certainly didn't see an abnormal sleep response in
10 the normal volunteers in any of the pharmacokinetic
11 studies, except the one patient who became
12 obtunded, and she was awake four hours later and
13 ate lunch, and then went home that day. So, the
14 only real suggestion of data I could give you in
15 the absence of stimulants is the single dose
16 response or the repeat dose response in the
17 pharmacokinetic studies, and that certainly didn't
18 appear to be different at all.

19 DR. BLACK: I would just comment on the
20 notion of a potential protective effect with
21 stimulants. With the traditional stimulants, they
22 are relatively short acting and there is a
23 phenomenon called rebound hypersomnia as the
24 medication wears off -- well demonstrated in
25 animals and humans -- where the individual becomes

1 more sleep than they would have been had they not
2 taken a medication; often a problem for those with
3 narcolepsy who are using those medications.

4 Rather than those stimulants keeping
5 people more awake and less affected by the Xyrem
6 dose, there is the potential for even greater
7 sleepiness with that rebound hypersomnia. That has
8 not been well explored, but I think it would be
9 erroneous to assume that there is any protective
10 effect from the traditional stimulants. From the
11 longer acting stimulant, modafinil, sleep studies
12 have been done to suggest that there is no impact
13 one way or the other on sleep in terms of depth of
14 sleep and so forth.

15 DR. KAWAS: Dr. Falkowski?

16 DR. FALKOWSKI: I have to take issue --
17 well, I already did with the statement that Xyrem
18 will not contribute to the public health problem of
19 abuse of GHB-like substances because I think it
20 will and I want to take just a few minutes to
21 elaborate on why that might be something I couldn't
22 cover in the confines of my 15 minutes as well as
23 covering those other points.

24 I had occasion last week, in Philadelphia,
25 to present at a conference on drug abuse addiction

1 professionals from around the country, and since I
2 speak about drugs of abuse, when I got to GHB I
3 said, so, tell me about GHB in your community.
4 Having heard from 15 people from 15 distinct parts
5 of the country on this, a common theme emerged and
6 that had to do with the fact that people who were
7 abusing it couldn't quite get the dosing right
8 because they kept passing out. Passing out became
9 sort of a way of life. I think in Dr. Dyer's data
10 we even saw that as well.

11 This is a drug that causes people to lose
12 consciousness and in some cases respiratory arrest.
13 Well, I think this is particularly relevant because
14 if dosing is the problem I believe that this will
15 only make more attractive a predictable dose as a
16 known entity in a prescription product. "Gee, I can
17 get around all these dosing problems by getting the
18 prescription."

19 I am also concerned that none of the
20 sponsor's packaging that I looked at even mentions
21 the word gamma hydroxybutyrate, or did I miss that?
22 I looked for it; I didn't see that. That concerns
23 me because, as we have seen with oxycodone, we know,
24 for example and I think it is a good case, we
25 know that narcotic addicts will seek out

1 prescription narcotics for predictable dosing and
2 for predictable purity. And, we have seen an
3 increase once long-acting oxycodone was developed --
4 we have seen an expansion in its prescribing not
5 just for chronic pain but for the treatment of even
6 acute pain. That plays out to the tune of 300,000
7 oxycodone prescriptions in 1998 and over 5 million
8 oxycodone prescriptions in the year 2000.

9 What people have to do, what drug seekers
10 have to do to acquire it is go to a doctor and
11 feign pain. This happens with unsuspecting doctors
12 and it is happening in all parts of the country.

13 Now, diversion of drugs does not occur by
14 people storming with machine guns the one central
15 manufacturing. It occurs at the patient-doctor
16 level. And, I am very concerned about the
17 possibility of folks who are having trouble.
18 Again, this is a diverse population; it is not just
19 kids using drugs. This is weight-lifters, these
20 are people seeking effects, going to a doctor and
21 saying, gee, you can get around all that; just go
22 to a doctor and tell him you are sleepy. Just go
23 to a doctor and tell him you collapsed. This is
24 really seriously my concern about this, and I don't
25 think that these two issues are separate. This

1 drug has a huge following.

2 DR. KAWAS: I would now like to focus on
3 the questions that the FDA has asked us to vote on.
4 Do you feel very strongly that your comments are
5 necessary before that?

6 DR. RISTANOVIC: I am going to make a
7 comment extremely brief. The comment is very brief
8 because in today's time we know how to diagnose
9 narcolepsy. So, there is no way, even if someone
10 is trying to malingering, to be given a diagnosis
11 without appropriate testing in the sleep lab. That
12 is a prerequisite.

13 DR. KAWAS: Thank you.

14 DR. RISTANOVIC: That is all.

15 DR. KAWAS: The FDA has given us three
16 questions that they want this panel to vote on, and
17 a whole page and a half of other items that they
18 would like this committee to discuss.

19 So, I would first like to ask them if it
20 is acceptable to facilitate the discussion, can I
21 make the decision to split the first question into
22 two?

23 DR. KATZ: Absolutely.

24 DR. KAWAS: Thank you. It might be the
25 only thing that gets done quickly today. The first

1 question is going to be has the sponsor
2 demonstrated efficacy of Xyrem for the proposed
3 indication to treat cataplexy? I am opening the
4 floor for discussion on that. Yes, Dr. Katz?

5 DR. KATZ: Again, I think it is very
6 important for us to hear a discussion about dose
7 and which dose. I mean, I mentioned that earlier
8 in my comments this morning, but if you could
9 address that it would be very helpful.

10 DR. KAWAS: Absolutely. In fact, maybe I
11 would like to facilitate this part because I think
12 this is the easiest thing that is going to happen
13 in the next hour. To my mind, there have been two
14 pivotal studies that have suggested efficacy for
15 this drug in relationship to cataplexy at the 9 g
16 level. Maybe by making that not overly provocative
17 comment we can stimulate discussion. Does anyone
18 want to comment on the dose or the effect on
19 cataplexy before we vote?

20 DR. FALKOWSKI: Is that the recommended
21 dose? It is not. That is why I am sincerely
22 confused because the study seemed to show efficacy
23 at 9 g, yet, the recommended dose is something
24 other than that and that needs explanation. I
25 don't understand that.

1 DR. KAWAS: Any other comments? Richard?

2 DR. PENN: I was going to make it a motion
3 so we would save some steps. I think it is very
4 clear that what you said is a good summary of the
5 case that, in fact, they haven't set the dose at 9.
6 They have suggested a different dose regimen and
7 that has to be looked into very carefully. But the
8 one thing I think we all we agree on is your
9 statement. I would, therefore, put it as a motion,
10 since we are supposed to do a motion so that that
11 has been shown.

12 DR. KAWAS: Would you like to make a
13 comment, Gerald, before we pick the motion that is
14 about to be on the floor?

15 DR. VAN BELLE: Sure. Well, I think it is
16 the issue of dose response that I am struggling
17 with in this case in terms of the pharmacokinetic
18 model. If you assume that there is a
19 pharmacokinetic model that is dose related, I would
20 say if evidence has been shown for an effect at 9
21 there is probably an effect at 8.5 as well. Well,
22 where do you draw the line at that time, and I
23 don't quite know where to do that. I think there
24 is ambiguous evidence for an effect at 6 and one
25 study showed that. So, if you want the technical

1 answer, I think there is only evidence for clinical
2 effectiveness at 9 but that ignores, to my mind,
3 the pharmacokinetic aspects of the data so I am
4 struggling with this.

5 DR. KAWAS: Could we restate Dr. Penn's
6 motion that this committee vote on whether or not
7 there has been efficacy demonstrated of this drug
8 for the treatment of cataplexy and, specifically at
9 the dosage of 9?

10 DR. SIMPSON: This may be my ignorance,
11 but when something is labeled, for example, that it
12 is efficacious at a dose of 9, does that mean that
13 a doctor would necessarily prescribe it at 9? He
14 could prescribe it quite a lot higher, couldn't he?

15 DR. PENN: That is going to get us into
16 the next thing, which is how this is going to be
17 monitored. Because it sounds like we want to put
18 an absolute dose limit and we don't want to allow
19 variability in the population. By the technical
20 way we are going to allow this out, if they are
21 going to be watching how much a patient can take,
22 then is a doctor going to be allowed the latitude a
23 patient more, and you are asking can they be given
24 less? I think the answer is usually the doctor
25 makes that decision. Everybody understands that is

1 the mean does that you have to use but that doesn't
2 mean your patient will respond to it. So, there is
3 the latitude unless we put into force this
4 voluntary program.

5 DR. KAWAS: I would like to focus this
6 committee back on the questions or we will never --
7 well, we will have everyone on a plane without a
8 quorum in order to vote on these issues.

9 The first question really isn't so much
10 about safety and what a doctor will do, the FDA has
11 just asked us have they demonstrated efficacy for
12 this drug in either of the two indications.

13 DR. FALKOWSKI: I believe they have
14 demonstrated efficacy for reducing cataplexy in
15 cataplectic narcoleptics on stimulant drugs. I
16 think that is what their studies have shown us
17 today.

18 DR. KAWAS: Okay. We will be taking a
19 vote and everyone's vote is going to count. Are
20 there any other comments people want to make before
21 we put Dr. Penn's motion on the floor?

22 DR. SIMPSON: I really agree that they
23 haven't necessarily demonstrated efficacy in
24 treating cataplexy but really in reducing
25 cataplexy.

1 DR. KAWAS: Do you want to put your motion
2 on the floor again?

3 DR. PENN: The company has shown efficacy
4 at 9 g per day using a 4.5 divided dose for
5 treating cataplexy in narcoleptic patients.

6 DR. KAWAS: These votes are going to have
7 to be recorded individually I think. So, can we
8 start with everyone who agrees that the sponsor has
9 demonstrated efficacy of Xyrem for the proposed
10 indication to treat cataplexy? Please raise your
11 hands now.

12 I just want to remind everybody that the
13 voting members of the committee actually are sort
14 of in the central part of the table, beginning with
15 Dr. Simpson and then going around to Dr. Penix.
16 All who agree the company has demonstrated efficacy
17 for cataplexy, raise your hand.

18 [Show of hands]

19 How about if we go around and identify,
20 and start with Dr. Penix for the record?

21 DR. PENIX: I agree.

22 DR. KAWAS: Just your name.

23 DR. PENIX: Dr. Penix.

24 DR. VAN BELLE: Van Belle.

25 DR. PENN: Penn.

1 DR. KAWAS: Kawas.

2 DR. WOLINSKY: Wolinsky.

3 DR. ROMAN: Roman.

4 DR. KAWAS: All the people who do not feel
5 the company has shown efficacy for the treatment of
6 cataplexy, please raise your hand and start
7 identifying.

8 [Show of hands]

9 DR. SIMPSON: Simpson.

10 DR. FALKOWSKI: Falkowski.

11 DR. LACEY: Lacey.

12 DR. KAWAS: I think that was everyone, so
13 no abstentions in that case.

14 Moving on to the next hard one, has the
15 sponsor demonstrated --

16 DR. KATZ: Dr. Simpson and Falkowski, I
17 believe in your comments you said you thought there
18 was an effect demonstrated, or something, but the
19 vote went the other way. I just want to
20 understand.

21 DR. FALKOWSKI: Right, I believe that they
22 have demonstrated that there is some evidence of
23 efficacy for reducing cataplexy in cataplectic
24 narcoleptics on stimulant drugs. These studies
25 have been conducted on people who were already on

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 if 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. WOI,INSKY: 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 oxycodon
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 gammahydroxybuterate 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 happens.

2 We won't be down at the first line making
3 sure that the pharmacist is calling the patients
4 within 24 hours. But, like many other things,
5 there is an understanding that the company is
6 responsible for making sure any given system of
7 surveillance is working appropriately and we have
8 interactions with them periodically.

9 So that is as far as we have gotten.

10 DR. LEIDERMAN: There are also precedents,
11 at least for independent monitoring committees.
12 And that has certainly been in approval agreements
13 in the past. So that is the kind of thing that I
14 think we need to work out.

15 DR. KAWAS: Unless there are any more
16 burning comments or thoughts or theories, I would
17 really like to thank the company, the agency, the
18 members of the panel and all the invited speakers
19 as well as the speakers from the public forum for
20 this interesting and challenging day

21 This meeting is now adjourned.

22 [Whereupon, at 6:00 p.m., the meeting was
23 adjourned.]

24

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Risk Management Through Responsible Distribution
and Appropriate Education
Xyrem Success Program

Patti Engel, R.N., BSN

Vice President of Marketing & Sales,
Orphan Medical, Inc.

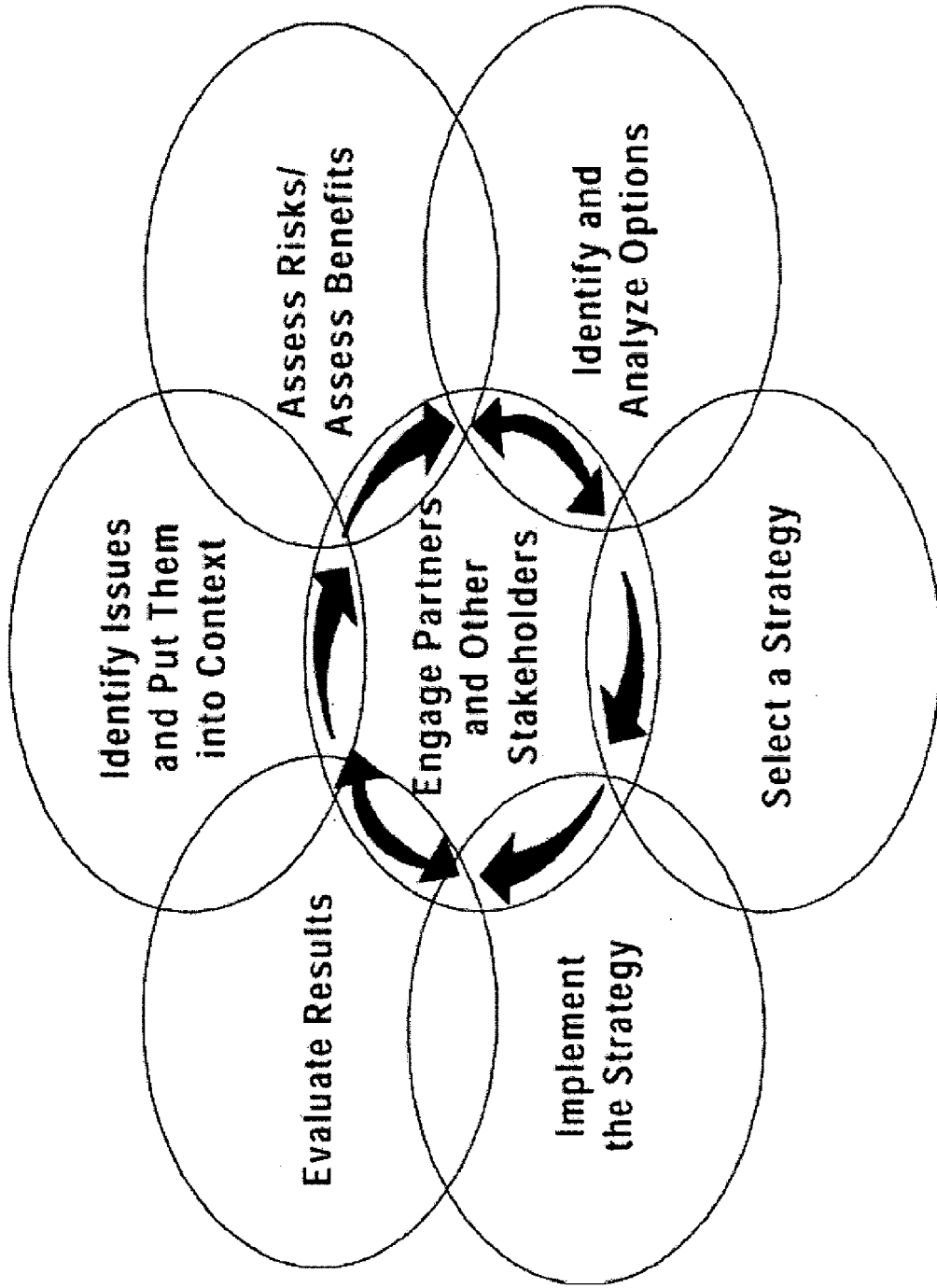
Xyrem Success Program

- ◆ A comprehensive system designed to ensure responsible distribution and use of Xyrem
- ◆ Goals:
 - ◆ Allow access to Xyrem for patients who need it
 - ◆ Make Xyrem inaccessible to those who would use it inappropriately

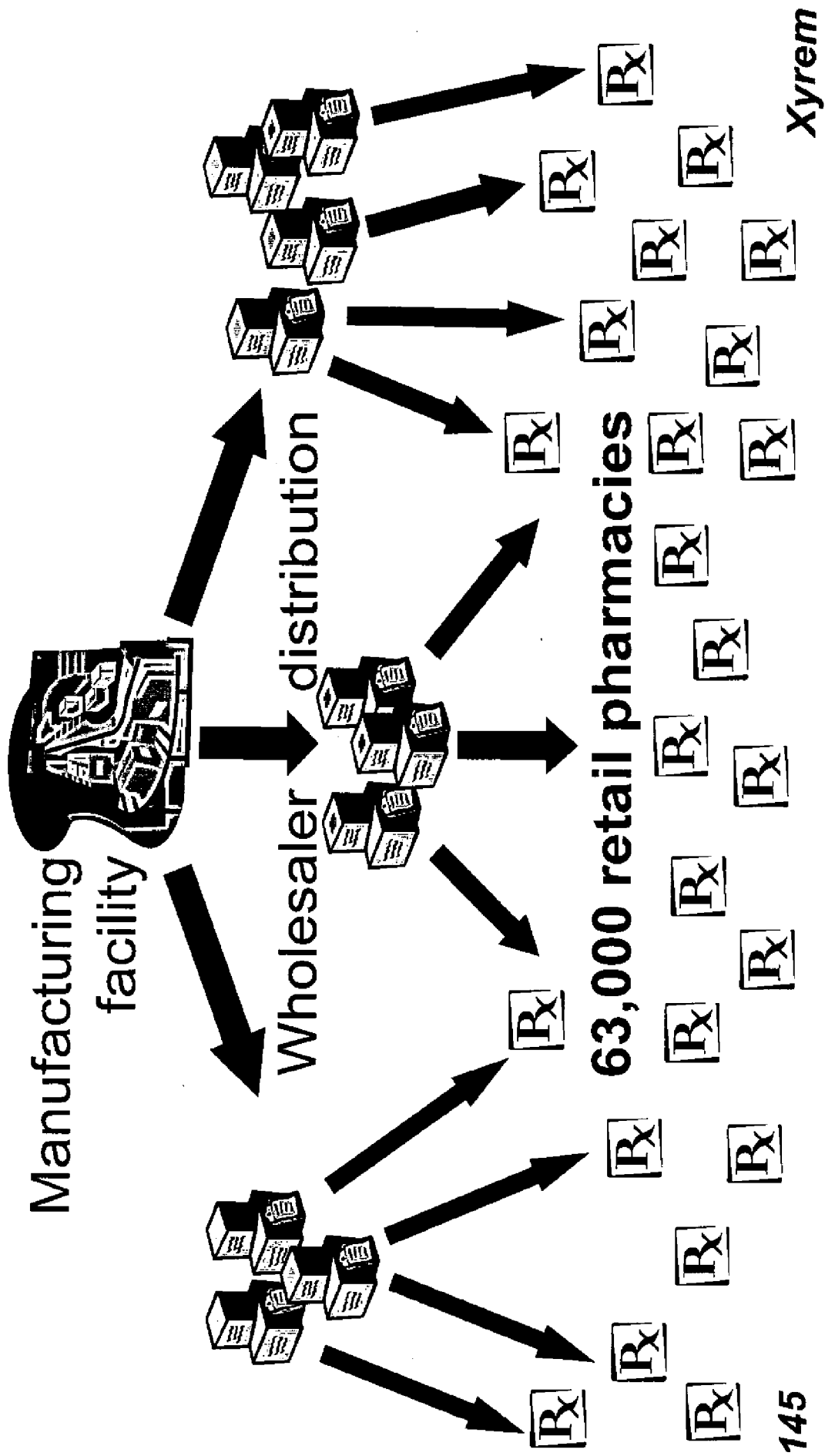
Xyrem Success Program

- ◆ Initiated by Orphan Medical and developed after extensive consultation with:
 - Narcolepsy patients
 - Toxicologists
 - Patient/Family support groups
 - Forensics experts
 - Physicians who treat narcolepsy
 - Drug diversion investigators
 - Emergency medicine physicians
 - Field law enforcement
 - State controlled substance authorities
 - Poison control center directors
 - Drug abuse trend experts
 - Pharmaceutical distribution experts

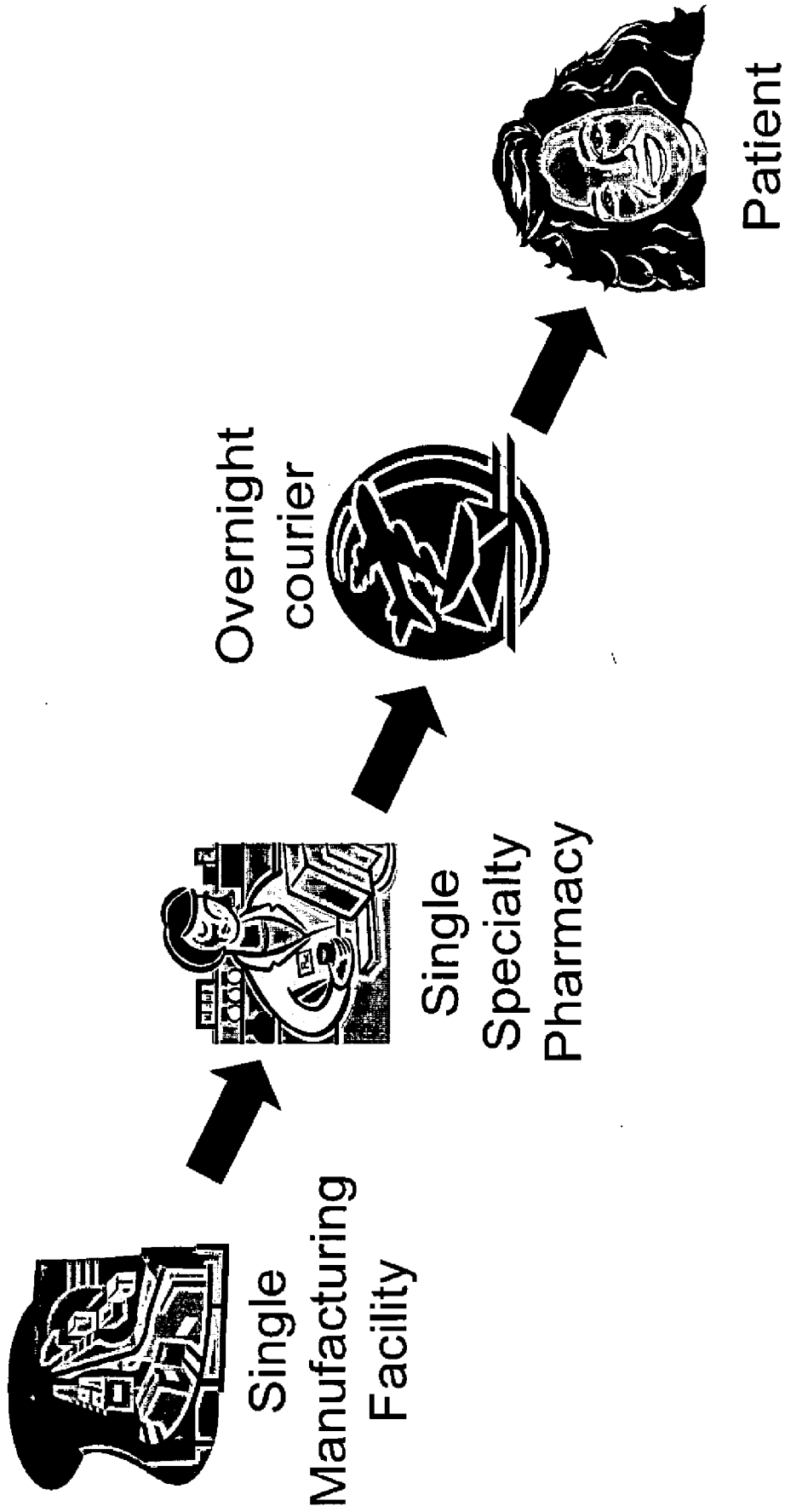
Risk Management Through Risk Confrontation



Standard Pharmaceutical Distribution



Xyrem Closed Distribution System



Xyrem's Distribution

- ◆ One Specialty Pharmacy
- ◆ Xyrem distributed from a single location
 - ◆ Controls
 - ◆ Records

Physician Promotion and Education

- ◆ Xyrem promotional and educational efforts will focus on potential physician prescribers
- ◆ Key specialties include:
 - ◆ Neurology
 - ◆ Pulmonary diseases
 - ◆ Psychiatry
 - ◆ Internal medicine
 - ◆ Sleep medicine (includes several primary specialties)

Physician Promotion and Education

- ◆ Approximately 35 sales representatives will call on physicians and their clinical staffs
 - ◆ Communicate clinical benefits of Xyrem
 - ◆ Present Xyrem Physician Success ProgramSM
 - ◆ Physician signature required
- ◆ No physician sampling

Physician Success Program Materials

- ◆ Multi-faceted education program
- ◆ Distribution process
- ◆ Xyrem dosing and administration
- ◆ Home storage and secure handling
- ◆ “Doctor be wary”
- ◆ Unique prescription form
- ◆ Contact information at Specialty Pharmacy

Prescription Process

- ◆ Physician decides to prescribe Xyrem
- ◆ Physician faxes a special Rx to Specialty Pharmacy
- ◆ Specialty Pharmacy assigns patient to dedicated pharmacy team

Physician Verification

- ◆ Specialty Pharmacy verifies physician is “eligible” to prescribe Xyrem:
 - ◆ DEA’s NTIS database
 - ◆ MD licensure
 - ◆ Current CIII prescribing privileges
 - ◆ State medical board

Patient Verification

- ◆ Specialty Pharmacy calls prescribing physician's office
- ◆ Verify the Rx

Pre-Shipment Patient Counseling

- ◆ Specialty Pharmacy contacts patient:
- ◆ Determine patient/designee location and availability for receipt of Rx shipment
- ◆ Explain contents of shipment

Rapid Trac® System

- ◆ Detailed, real-time tracking
- ◆ Delivered **ONLY** by authorized signature
- ◆ If patient/designee unavailable, package returned to Specialty Pharmacy after one re-delivery attempt
- ◆ If lost, investigation begins regarding shipment's whereabouts

Patient Success Program Materials

- ◆ Multi-faceted education program
 - ◆ Distribution process
 - ◆ Xyrem dosing and administration
 - ◆ Home storage and secure handling
 - ◆ Criminal and civil penalties for illicit use
- ◆ Contact information at Specialty Pharmacy
- ◆ Reimbursement information

Post-receipt Contact

- ◆ Once received, Specialty Pharmacist contacts patient within 24 hours to:
 - ◆ Confirm receipt of package
 - ◆ Discuss with patient:
 - ◆ Penalties for illicit use
 - ◆ Xyrem dosing and administration
 - ◆ Home storage and secure handling
 - ◆ Discuss child resistant packaging

Benefits of Central Data Repository

- ◆ Identification of:
 - ◆ Duplicate prescriptions
 - ◆ Over-prescribing
 - ◆ Over-use by patients
- ◆ Information *prior* to filling Rx
- ◆ Appropriate pharmacist intervention

Xyrem Success Program

- ◆ A comprehensive program that ensures the responsible distribution of Xyrem, resulting in:
 - ◆ Availability of Xyrem to patients who need it
 - ◆ Inaccessibility to those who would use it illicitly

Xyrem Closed Distribution System

