

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](http://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](http://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 cataplexy 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 GHB 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 Guilleminault, 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 we 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. Penis 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