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

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

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

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

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

In 1982 my treating physician sent me to

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

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

remedy that.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

went days without sleeping but never told me.

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

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

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

DR. STRAIN: Thank you. I would like to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

emergency rooms do not recognize GHB psychotic episodes.

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

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

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

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

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

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

If I were to convey to you but one

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

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

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

My name is Matt Speakman and I have

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

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

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

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

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

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

Two weeks ago I graduated from West

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

[Laughter]

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

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

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

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

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

DR. KAWAS: My apologies.

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

[Laughter]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I would like to preface my comments today by disclosing that Orphan Medical has provided my organization with a minor grant and it provided a general grant to the Narcolepsy Network who has paid for my travel and accommodations to attend this meeting.

YAWN is the first youth-focused online

narcolepsy support and advocacy organization. We work at the grass roots level to advance public awareness of narcolepsy on behalf of young adults and others whose lives are affected by this often debilitating sleep disorder.

As founder of YAWN, I believe I am in a unique position to comment on the issue currently under consideration by this committee. I do not, and have not used Xyrem for treatment of my cataplexy but as the representative of many young adults in need of an effective treatment for their narcolepsy, I am compelled to present my views on the risk management issues pertaining to the safety and efficacy of Xyrem.

Narcolepsy is most commonly diagnosed by the middle of the third decade of life, often 5-15 years after the onset of symptoms, the most dramatic of which is cataplexy. Excessive daytime sleepiness, combined with the impact of sudden attacks of cataplexy that may last from a few seconds to hours can be profoundly damaging to the interpersonal, educational and professional development of these young adults at an extremely critical point in their development. Although I am fortunate only to experience rare and mild attacks

of cataplexy, I know others who are completely incapacitated by cataplexy and have not, or would not been able to achieve their personal professional goals without a medication like Xyrem.

I submit that the risk for experiencing the negative impact of untreated cataplexy on the potential of so many young adults with narcolepsy is a serious issue that must be included in any discussion of risk management of Xyrem.

Xyrem offers a singularly important therapy for the 65-70 percent of young adults with narcolepsy who suffer with cataplexy. We must recognize the consequences of failing to approve Xyrem to treat the 1/1000 people suffering with narcolepsy. For example, after forming YAWN, I was contacted by the parents of a 16-year old boy, living in a small town not three hours away from the nearest city. This young man was bright. He did well in school, and was active in his community until his 12th birthday when he began experiencing severe episodes of cataplexy that lasted for hours.

When I first spoke to him on the phone he told me that his condition was so severe that he was forced to spend five days a week in a nursing home, and he is still there. What are the costs of

providing nursing home care in a public institution for a 16-year old boy for the next 60 to 70 years? By not adequately controlling his cataplexy, what are his chances for becoming a contributing member of our society? Unfortunately, this man's story is all too common. Unless something is done about the current environment of limited access to inadequate pharmaceutical therapies, the future of young adults suffering with cataplexy will remain bleak.

This, however, does not have to be the case. In fact, a brighter future has been achieved by the lucky few who have participated in Xyrem clinical trials. They have become success stories. To these young adults with narcolepsy Xyrem has meant the difference between a life within an institution and having the opportunity to achieve their goals, free from the physical constraints of their disease. Xyrem has enabled many young adults, my friends, to earn their Ph.D.'s or become lawyers, doctors or to simply be good parents.

These are people who took Xyrem and couldn't have succeeded otherwise. Yet, there continue to remain thousands of other talented and capable young adults who have not yet had a chance to fulfill their dreams. They are the reason I

formed YAWN and why I am here testifying before you today. We can no longer afford to neglect the potential of so many young adults by failing to provide them with the only medication known to be safe and effective. It is our responsibility to protect their right to pursue a happy and productive life by having access to medications like Xyrem that will effectively treat their disease.

Thank you for allowing me to present these remarks to you today. I urge you to approve the NDA for Xyrem. There really are lives at stake.

DR. KAWAS: Thank you, Mr. Hunter. The next one is Joe Spillane.

DR. SPILLANE: I would like to also say thank you for an opportunity to speak to the FDA and to this committee on this important issue.

I work at Broward General Medical Center which is a community hospital in south Florida. My experience with GHB is as a pharmacist and in clinical toxicology. I also teach as an associate professor at the College of Pharmacy at NOVA Southeastern University.

Our experience in the emergency department is very similar to what Dr. Dyer mentioned. We

have a lot of GHB overdoses. We had 48 overdoses associated with GHB in 1999. That number increased by 60 percent to 77 in 2000. We have more GHB overdoses than ecstasy. We have more GHB overdoses than oxicondon. I think it is important that I just underscore the immensity of the problem associated with GHB abuse. Most of our overdoses come in with people who have altered mental status and, basically, they just need a short period of supportive care, airway management. Most wake up. Many of them -- and I think this is important to point out, many of them mention that somebody had given them GHB, put it into their drinks, and so forth. As such, the media an many people have advised don't accept a drink from anybody but the bartender. We had a bartender up in our ICU about a month ago, and when he did recover I spoke with him and he said, yes, I chronically use GHB. A lot of my friends in the beverage industry also do. And, I think we can understand what the potential problems could be with that.

We have also treated five withdrawal cases and, again, the numbers might not be that big but this is just one hospital and, since it is a difficult thing to identify, we are probably

missing cases and I am sure there are cases missed throughout the country.

There have been nine deaths where, in the estimation of the medical examiner in Broward County, a county of 1.6 million people -- nine deaths were caused by GHB and I think it is important to point out that at least one of those deaths was with GHB alone, with no co-intoxicants and no alcohol level.

I guess my major concerns are with the scheduling and some of the off-label prescribing issues, and the voluntary nature of this distribution system. I kind of just want to summarize briefly by saying I think there are four questions that are major concerns of mine and I hope this committee addresses those concerns.

The first one is, is it really wise to rely upon an essentially voluntary, supposedly closed-loop distribution system, designed by the manufacturer, to prevent diversion of an increasingly popular, highly lethal, addictive and abused substance?

My second question is, is it prudent to require very little governmental regulatory oversight of such a system when the strict

adherence to that system may not be in the best financial interest of the entity responsible for that strict adherence?

My third question is, is it responsible to rely solely on those with a vested interest in demonstrating little or no diversion to verify that little or no diversion is occurring? It is my understanding that that is essentially what we may be doing here. I think there was an example of how this could be problematic just in today's proceedings. I certainly was under the impression by several people who spoke today that there was no diversion in the clinical trials. I think Dr. Mani, from the FDA, said that, indeed, there were some cases of diversion. So, I just think that is a potential concern.

My fourth question is does it demonstrate judicious foresight to establish a precedent for sort of circumventing existing scheduling and distribution processes, and couldn't such a precedent be used in the future to the financial benefit of pharmaceutical manufacturers and to the detriment of drug diversion prevention?

I would like to commend Orphan for their work and bringing a medication that they feel is

effective to those who could benefit from it. I think a mandatory, not voluntary, system of distribution, with adequate governmental regulatory controls and any restrictions on off-label prescribing would advance another one of their stated goals, which is reducing abuse and diversion. Thank you very much for having me.

DR. KAWAS: Thank you, Mr. Spillane. The next one is Ms. Mali Einen.

MS. EINEN: Hello, and thank you for the opportunity to speak before you today. I could tell you my story of my scars and bumps and bruises from my many falls from cataplexy, or I could tell you about my disappointment from having had to give up my career that I was dedicated to and loved, not to mention the loss of income and security. Instead, the part of my story I share with you today is the loss of the normal, everyday things that most parents take for granted.

My name is Mali Einen. I am a single mother from California with narcolepsy and what is considered severe cataplexy -- and a lot of nervousness. As a person with narcolepsy, I was fortunate to be diagnosed fairly quickly after the onset of my symptoms. I was diagnosed at the age

of 22 after first noticeable systems of narcolepsy, appearing at about age 22.

In the early years my cataplexy was triggered mostly by strong emotions -- a truly funny joke or my young daughter saying something adorable. As the years progressed, my cataplexy worsened, requiring less and less of an emotional trigger to cause a complete collapse -- unable to move or talk for seconds, sometimes even minutes at a time despite my daily medications.

As my daughter grew and my cataplexy worsened, I was unable to attend her performances, school programs or sports activities without several full collapses. My young, then seven or eight year old daughter would complain, why do you bother to come? You spend most of your time passed out. That is what she called cataplexy. I wondered would she ever understand that it was my joy for her success and my love for her that prevented me from participating in these milestones.

Several years later my daughter's simply relaying a story to me, excitedly, about her latest crush or her experiences with her friends would cause me to crumble, much like the film that Dr.

Mignot showed earlier today. It dawned on me that I had not only given up my experiencing anything that might involve positive emotion, it had become difficult for me to even participate as a spectator in my daughter's life.

During the years, I had been able to maintain success in my developing career as a money manager. My workaholic, nose to the grindstone withdraw kept me away from the usual office fun and water cooler moments, while allowing me to avoid embarrassing cataplexy. But this too had begun to erode. Although the various medications allowed me to keep my cataplexy partially in check, it seemed that my nighttime sleep became more and more disrupted, sleepy during the day, yet never able to sleep more than an hour or two at a time at night.

By 1996, my spotty nights of a few hours of sleep, my sneaking naps during the work day, and collapsing in exhaustion any time I sat still had affected my ability to continue to perform my job adequately. Long ago my daughter had given up on my being able to read her a story or to help her with her homework. My life had become dragging myself to and from work, attending to the basic needs of my daughter, while constantly working to

keep my emotions in check. There was little room for fun and interaction. Sole provider for my daughter and myself, I finally voluntarily left my job.

By this time I had become a complete slave to my next dose of medication to either control my cataplexy or to help keep me awake. The medications didn't make me feel well; they made me feel horrible, yet, I was their slave. I had never taken a back seat to finding better or best treatment options. I tried no less than five to seven different antidepressants over the years with varying degrees of success, but each with such a cost.

Within a year after I had left work, I became aware of a new medical study through Stanford, an experimental treatment for narcolepsy and cataplexy. I started Xyrem. My life changed! After a horrific washout period when, unmedicated, I was faced with my inability to care for myself, let alone my daughter, with mere thought causing collapse after collapse, I found that Xyrem controlled most of my cataplexy and I was thrilled how the better quality nighttime sleep allowed me to feel normal, almost good upon waking.

Although not required by the medical study, I began to voluntarily decrease my daily doses of amphetamines. The better, less disrupted nighttime sleep allowed me not to be a slave to my next dose of stimulants in order to make it through the next several hours. I now go many days without stimulants at all, and other days take 5 mg or less of Dexedrine.

I not only began to be able to listen to my daughter's glee-filled stories of her day, I started to volunteer at her school. I could joke with the kids; I could even watch Kelsey smash a winning serve across the volley ball court. I must admit, occasionally a funny story or my evening interaction with my daughter still causes my facial muscles to slacken with a bob of the head, but my daughter now uses these opportunities to give me a hard time, knowing that I will recover in a second or two and we will have fun and enjoy our life together.

I asked my now 17-year old, upon contemplating being here today, would you say my taking Xyrem has made a difference in your life? I had expected the usual teenage disinterested reply. Instead, Kelsey responded, as tears welled in her

eyes, as much as I hate it sometimes, you are really a part of my life now; you know everything that's going on with me.

It is for this that I am truly grateful to Orphan Medical and Xyrem -- and I think I forgot to say my conflicts of interest.

DR. KAWAS: That is the only reason we are going to let you go more over time.

MS. EINEN: I am a shareholder of Orphan Medical and a number of other stocks of products that I believe in. Narcolepsy Network has generously paid for my air fare and accommodations, but they have not compensated me for my time, nor am I paid for the time away from my brand-new job back in the career which I had to leave five years ago.

DR. KAWAS: Thank you, Ms. Einen. Next is Ms. Sandra Jones from California.

MS. JONES: Good afternoon, ladies and gentlemen. My name is Sandra Jones, and I am from Los Angeles, California. My travel expenses are being reimbursed by the Narcolepsy Network. I am 50 years old. It was only 19 years ago that my mother truly became a mother to me, my brother and sister. Nineteen years ago my mother began taking

what we now call Xyrem. Within a week after she started taking this medicine we noticed the incredible change in her. She could cook dinner without collapsing to the floor. She could sit down and eat dinner with us without falling asleep. She could make a sound that we hadn't heard in a very, very long time -- laughter, and more laughter without falling to the floor.

She became a totally new person to our family. That was not the case nearly thirty years ago. She quit her career as a nurse for fear of how the disease might affect her care of her patients. She became sort of a recluse in her home and we grew used to seeing her sleeping throughout the day and staying up all night. She was afraid she would fall and bring embarrassment to herself and especially to her family. People just did not understand her disease. She once collapsed at a party and people dismissed her as being a drunk. My mother didn't drink. It was what the narcolepsy had done to her.

This is an evil, evil disease and unless you have witnessed it firsthand you cannot understand the horrible ways it affects a person's live. Imagine having a newborn child, my sister,

and not being able to hold her for fear of dropping her. Imagine not being able to go to the grocery store for fear of falling in the aisle. Imagine not being able to read stories to her children because she would fall asleep, not us. Imagine not being able to drive a car for fear of collapsing behind the wheel. This was my mother.

But Xyrem changed all that. It was a difference between night and day and mother quickly rediscovered the joys that she had missed for decades -- playing games with us, going dancing, going to the movies, celebrating family birthdays and holidays. The day-to-day tasks that you and I take for granted, she could finally do as a normal person. This was the mother that we had never known until Xyrem gave us her life back and her family back. I have seen the difference. I have lived the difference. Please make this valuable medication available to people who have narcolepsy. They and their children will see the change in their lives. Thank you.

DR. KAWAS: Thank you, Ms. Jones. That concludes the section of open public hearing, and I want to thank everybody who expressed their views, information and helped the committee keep sight of

all the issues here.

We will now reopen the questions from the committee to the invited speakers, sponsor and the FDA. In particular, I would like to focus on the presentations that we had right before lunch involving the epidemiology, adverse medical events and the sponsor presentations on risk management and abuse liability. So, who wants to start the questions from the committee with regard to some of those presentations?

Continued Committee Discussion and Deliberations

DR. SIMPSON: I put up my hand under false pretenses because I had just one question really --

DR. KAWAS: We don't like false pretenses around here!

DR. SIMPSON: It was really relating to the efficacy. I mean, a lot of the presentations we have just heard give the impression that the cataplexy was, if not completely controlled, almost completely. Yet, when we look at the data we see that the median number of events at the end of some of the studies is about eight or so on drug. So, do we have any data about how many people actually had no cataplectic events?

DR. REARDAN: I think that this question

was discussed to some extent this morning. It dealt with complete cataplexy --

DR. SIMPSON: No, no, I am saying do we have data on the people who were, quote, cured? Were there any?

DR. REARDAN: We have a slide on that, I understand.

[Slide]

DR. HOUGHTON: This is an example of the long-term data, and one of the problems with the controlled GHB-2 trial is that it may be too short. The reason that the time was restricted is because of the imposition of patients on placebo for longer periods of time. But that represents a picture of the long term response in terms of percentage change. So, we have a control across all doses, demonstrated here for a 12-month period, around the 90 percent or better mark. Now, that doesn't mean to say people don't have any cataplexy, but it is certainly very significantly reduced.

DR. KAWAS: Dr. Katz?

DR. KATZ: Yes, we have seen this slide a number of times. I just want to remind the committee that this is open, uncontrolled, non-randomized data, not the sort of data that we

would ordinarily rely on to draw any sort of conclusion about effectiveness of any sort.

DR. KAWAS: Maybe the sponsor could show us some of this data from one of the randomized trials?

DR. HOUGHTON: We could show you the change in the GHB-2 study again, which is the four-week study.

[Slide]

The data is median change from baseline. We had a median incidence of 23.5 in the 9 g group, a change from baseline of 16.1. If we present that again as percentage change -- because, once again, it is complicated by the spread in the data.

DR. SIMPSON: I guess my question is if the median at the endpoint is 8.7, it means 50 percent of the people were above it and 50 percent were below. Now, how many were below, say, 1 or 2?

DR. HOUGHTON: Well, it depends on what their starting level was, and the conditions of entry were 3 cataplexy or more attacks per week. We did have patients with very high incidence. So, in terms of absolute numbers, that is a very difficult response. I am not trying to be evasive.

DR. WOLINSKY: The other piece of that

data though that you presented and might be worth looking at quickly is the randomized stop component of the trial.

DR. HOUGHTON: Sorry?

DR. WOLINSKY: When patients were randomized to be taken off --

DR. KAWAS: The 21 study.

DR. REARDAN: Right. The question is on a-patient-by-patient basis, how many patients went from X amount of cataplexy to zero cataplexy. Is that what you are trying to get at?

DR. SIMPSON: Zero or close to zero.

DR. REARDAN: That is in the data listings for the trial. We didn't bring individual breakout of the data. We brought summary information for the committee. I don't know if Dr. Mani has a recollection or Dr. Katz.

DR. KATZ: You don't have a distribution of how many events patients had? In other words, you know, X percent had two or fewer events; Y percent had between two and five events.

DR. HOUGHTON: No, we didn't break it down like that. I think the slide that you were referring to was the one that I showed with individual patient plots, and I can show you that

quickly.

[Slide]

That is just an example of absolute numbers. These were individual patients plotted. That was their incidence at the baseline, and that was some two years after this was conducted. That is the sort of response they got when their active treatment was withdrawn. That is the group in active treatment. So, in terms of just absolute numbers, that is just a snapshot. That is not a statistical presentation. It happens to be every patient that came from that original trial through into this trial, and I show it as individual plots. It is the best impression of individual patient data I can give you to answer your question.

DR. BLACK: Just a comment on that. In this section we do have placebo-controlled data and we have the number of cataplexy attacks on placebo versus active medications after patients have been on treatment for a long period. Dr. Katz' comment is very good. The data that has been generated over the open label, though it does suggest there is a time course till optimal effect of at least two months, is open label. But this is placebo-controlled data, suggesting that the

average there of cataplexy attacks per day -- I don't know if you have the numbers of that, Dr. Houghton, but it is very low during the time of treatment unless they are taken off and then on the placebo-controlled portion.

DR. KAWAS: I have a question for the company as well as probably Dr. Dyer. I want to hear both sides of why we heard such very different descriptions of the potential for withdrawal syndromes with this disorder. I recognize fully that the company has studied individuals with narcolepsy and it is possible that alone could comprise the difference, but we do have a very nice withdrawal study in study 21, which is not typically the case, and the findings that were collected from that are in fairly sharp contrast to the stories that we have heard from Dr. Dyer with regard to withdrawal syndromes, and I wondered if both sides could tell me what the difference was. Is it dose? What is the difference here?

DR. REARDAN; I will ask Dr. Balster, but I believe it is dose and frequency. Bob, do you want to comment?

DR. DYER: I doubt that we disagree. Clearly, in my set of patients and what we use

nearly as a diagnostic parameter and which patients we should admit, even though their early symptoms are mild, is the frequency with which they are using it. So, the kinetics of the drug show us a duration of activity around three or four hours. When these patients increase their frequency so that their body constantly is exposed to GHB, those are the ones that we feel become severely physically dependent and then go through this withdrawal syndrome that can have an onset within hours of discontinuing the drug.

DR. KAWAS: So, in your opinion it is frequency of dosing, not even the number of grams per day.

DR. DYER: As far as I can tell, it is frequency because if I take the sponsor's information, and for years I have spoken to the investigators that are doing this and they have said they have had no trouble. Their patients have a 12-hour drug holiday daily, which is two to maybe three times what they are calling a half-life for this drug. So, the drug is completely eliminated from the body for a time period, and the patients have that become severely addicted, all of them - I mean, that is kind of diagnostic for the severe

withdrawal, somebody who is taking it every three hours around the clock.

DR. BALSTER: Yes, I agree completely with that, and maybe the analogy that would help you understand it would be the analogy, for example, with alcohol where really alcohol can produce a very significant physical dependence but you can drink it every evening with your meal and you won't become dependent because between that evening use and the next day it has cleared the body. So, whatever physiological adjustments are necessary have corrected themselves. So, we are in complete agreement.

DR. KAWAS: Thank you. Dr. Katz?

DR. KATZ: Just as an extension of that, there was also the implication or the explicit statement that in some of those people who took it very frequently and ultimately, presumably, became addicted, they were compelled to take it more frequently. In other words, there was a tolerance that developed and they had to increase their frequency to get the same sort of pharmacologic effect.

So, I will just ask the same question that Dr. Kawas asked about withdrawal. We have heard

from the company that patients who have taken the drug for years and years and years don't develop tolerance; they don't have to increase their dose; they don't increase the frequency of self-administration. But, we are hearing that on the outside there are people in whom this phenomenon apparently does occur. So, I will ask the same question. Why the disparity?

DR. DYER: Again, there haven't been really good studies or anything scientific. It is kind of my thoughts or opinions but, again, it is accommodation because you are taking it around the clock. So you are accommodating. Also, in the patients that are taking it -- well, I don't know, they are not really patients -- in the people who are abusing it there is a lot of the feeling that if a little is good, a lot is better. They are taking it initially, these body builders, for this growth hormone burst. So, they really feel like they are doing the right thing. So, there is nothing to have them diminish their dose or hold their dose as it is. Then, once they start taking it more frequently, the duration of the drug as it wears off in three or four hours, we think, gives them kind of a dopamine surge for which then they

are going to feel a little depleted and want to take that next dose. Then there is also physical craving for that kind of high. They are awake and feeling that kind of high as opposed to the patients that are taking it immediately upon going to bed and then sleeping through this euphoric -- whatever the kids are trying to get that are abusing it -- if you can roll that into an answer.

DR. BALSTER: That is exactly the way I would see it too. Just to add one further thing to that, the way to look at tolerance, you have to understand that it occurs through different effects at different rates and in different ways. So, the therapeutic effect is one effect. The intoxicating effect is a different effect. And, commonly in abuse situations where persons are trying to maintain an intoxication, they have to escalate dose and frequency in order to do that, whereas the data obtained in these clinical trials, of course, is on the therapeutic effect.

DR. DYER: One other comment, in the alcohol abuse trials they did escalate their dose in more of a craving kind of manner. That was about 15 percent.

DR. KAWAS: Dr. Roman?

DR. ENGEL: I would like to add something, if I may, to this point that is based on the risk management system proposed by the sponsor. As you saw, the data collected by the specialty pharmacy will include dose by patient. And, because of that, the specialty pharmacy will be able to predict when is the appropriate timing for a given patient to have their prescription refilled. So, for example, there are patients attempting to refill too soon, so to speak, that will be identified and it will be an opportunity for the pharmacist to interact with the physician very quickly, before a patient might get into a situation like which Dr. Dyer is describing with an overuse syndrome.

DR. ROMAN: A question perhaps again for Dr. Balster. Is the pharmacology of GBL and 1,4-BD similar in animal experience to GHB? Number two, if there is a difference, did I understand correctly that GBL and 1,4-BD are not currently drugs of abuse?

DR. BALSTER: Well, the first question, pharmacological comparisons of GBL, GHB and 1,4-BD, these haven't been very extensively done. So, hopefully some of those NIDA grants that someone

was talking about will really take that question on. But let me say that in a number of those studies that were done to describe the pharmacology of GHB, in some of these studies actually GBL was administered to the animal with the view that it was a prodrug for GHB. I forgot who said it but someone said that so far as we know, all of the effects of GBL and 1,4-BD are really as a consequence of their conversion to GHB. I believe that would be the current state of knowledge about that although it is imperfect.

Now, the question about control, in a sense, yes, all of these drugs are potential drugs of abuse because they can be taken and basically are active in the case of precursors with metabolites. So, yes, all of these are potentially drugs of abuse. Only one of them is a controlled substance and one of them, by congressional action of last year, became what is called a listed drug, and I could explain that to you or, actually, Dr. Sannerud would know better than I what exactly that means. But it essentially means that there is limited distribution.

DR. ROMAN: So, with GBL and 1,4-BD there is no control.

DR. BALSTER: Well, as I say, for 1,4-BD, to my knowledge, there is no control. I need to step back a little bit from that because we could get into too long of a discussion about what constitutes an analog under the specific language of the legislation. So, it is possible for prosecuting attorneys to claim that one or another of these drugs are analogs of a controlled substance. The Controlled Substances Act, in a sense, regulates analogs. Now, 1,4-butanediol is questionably an analog, but that would be something that would be worked out in court. So, I am not trying to tell you that someone could absolutely, with impunity, sell 1,4-BD to children and say that it wasn't a drug of abuse because I am sure that there would be authorities and prosecutors who would try to do something about that. But in terms of the actual language of regulation, only GHB is a controlled substance.

DR. SANNERUD: GHB is a Schedule I controlled substance. Butanediol and GBL are considered controlled substance analogs under federal law, which means they can be prosecuted, as GHB, with penalties and other things would apply if someone is caught trafficking, distributing or

clandestinely manufacturing or selling these compounds as well. GBL is listed as a List I chemical, which means that there is record-keeping and registration required. There are no retail sales of butanediol, and there is a graph in here with the product. These are used in industrial uses. So, this comparison is really a little bit misleading. I don't know the numbers but GHB is not even marketed yet, so this number on production is only for clinical trials I assume.

As far as the GHB and Xyrem they are both GHB. There is no forensic analysis that is going to differentiate between the two. So, when samples are submitted to labs there is no way to tell if it is the product or if it is something that is made at home. So, for someone to say that there has never been any diversion of the product, there is no way to tell that because there is no way to differentiate between the two under forensic laboratory conditions.

Another question I wanted to address is the quota issue. Ms. Meyers brought up quotas for Schedule II compounds, the stimulants. DEA sets the quota, as it will with GHB as well. It has never been the case that drug has run out at the

end of the year because the quotas are set too low. If there is a problem with the drug manufacture the quotas can always be increased throughout the year, and they are done so on a regular basis. So, there has never been the case where a drug has run out.

DR. KAWAS: Dr. Mani?

DR. MANI: I would just like to touch upon the issue of drug diversion during the clinical trials once again briefly. Many speakers have asserted that there has been no evidence that Xyrem or GHB used in the clinical trials included in the database was diverted. That may very well be true, barring the one exception that I cited earlier, and I have no firm evidence to the contrary. However, I have gone through the NDA, reviewed the whole NDA, and I would be a little more hesitant in making that assertion, and I will tell you why, and that has to do with the way the drug was dispensed in the Scharf study which, as you know, occupied about 30 percent of the database in terms of patient numbers and about 70 percent of the database when you are talking about patient years of exposure.

What happened here was that patients saw Dr. Scharf in Cincinnati, at least for an initial

visit, and had an appropriate diagnosis made and were then enrolled in the trial and then went back to whatever part of the country they came from. Prescriptions for medication were filled based on their returning completed diaries. In some instances it appears, at least from my looking at the case report forms, that prescriptions were sometimes filled in advance or the diaries being returned, obviously to prevent the patient from running out of the drug. But the important thing is that patients were not required to return unused supplies of medication prior to getting a fresh prescription, or to provide any formal accounting of how much medication they used or did not use. In the absence of any active surveillance of that kind, as I said, I would be quite hesitant in making the assertion that no medication was diverted.

DR. REARDAN: I need to make a qualifying statement here. We do not disagree with Dr. Mani. However, under the company's clinical IND, our patients under IND didn't begin entering trials until 1996. Patients were required to document their dose; to return their bottles. The bottles were all qualified by volume in terms of what was

returned. The incident that Dr. Mani refers to, I believe, occurred in 1986, when GHB was available as a nutritional supplement and Dr. Scharf's trial, again, was clinical practice. There were a lot of issues on GCP compliance in that trial. We do not take responsibility for accountability of drug under Dr. Scharf's trial. So, I will just qualify that. Okay?

DR. MANI: I agree.

DR. FALKOWSKI: I have a question and it has to do with the fact that we are talking about a method of taking this drug where you take half the amount at bedtime and then you wake up several hours later, but don't really wake up, and take the rest of it. And, I am just wondering what would happen if you were confused. It also involves mixing it ahead of time to the right strength. I am asking this both to Dr. Dyer and the sponsor, what would happen if someone took 9 mg at once? You know, if someone got confused and took it all at once, what would be the expected outcome?

DR. REARDAN: I had a number of questions about this at the break from a couple of members of the committee -- how do they make it up, and so on. It might be worthwhile to ask Patti Engel to go

through that. The other point about narcoleptic patients waking up, maybe Dr. Black, you could comment on how they wake up and take their second dose.

DR. FALKOWSKI: Right, but my bottom line question is what would happen to a person who inadvertently took all of their dose at once, and I really insist on an answer to that. Thank you.

DR. BLACK: That question has been answered by patients who have taken inadvertently larger doses. As far as the waking up at night, the patients that are here could probably respond to that, but the overwhelming majority are awake actually before the four hours later on their own and they are fully awake. The medication is premixed so there is no mixing that needs to occur at that point. There are folks who have taken extra doses and there is more sedation that occurs with the extra duration and the period of sleep is longer with the higher dose.

DR. FALKOWSKI: Is the answer then increased sedation? Is that the answer to my direct question?

DR. BLACK: Yes, if the dose is increased there is increasing sedation and a longer sleep

period.

DR. FALKOWSKI: Okay. Dr. Dyer, could you respond to that?

DR. DYER: It is my opinion that the dose would be around 100 mg/k and at that point you are going to have coma and some of the other side effects that we see in our club goers are very likely to be what you would see. So, vomiting and aspiration is a possibility. You know, the ability to hear and react to fire alarms, children, whatever, that is all going to be blunted.

DR. FALKOWSKI: Is it a possibility then that some of these people who may have double dosed would be in a coma but who would know, you know? Is that a possibility, sponsor? I mean, who is to know?

DR. BLACK: I think that the question is a good one, and what I might call deep sleep someone else might call a coma. But when we look at the brain wave activity of the folks with the higher doses, they have nothing in the EEG that would be consistent with straightforward coma.

DR. FALKOWSKI: But you didn't take EEGs on these people when they were sleeping in situations like this.

DR. BLACK: Well, we have done EEGs on the folks when they have been sleeping at the 9 g dose but not on double the 9 g dose.

DR. FALKOWSKI: Okay.

DR. KAWAS: Dr. Katz, please.

DR. KATZ: Yes, a couple of things. Maybe the best way to get at this if it is possible is to ask the company to show us any data that they have about what happened to patients who took, let's say, a single 9 g dose. I don't know how many patients did that, but if there is data on that it would be nice to see.

So, I don't know, maybe you could look for that while I get to the second part which is, again, just another variant about the question we were talking about before, this perceived disparity between patients and non-patients who take the drug recreationally. We have heard again, not just in terms of withdrawal and addiction and tolerance but just in terms of serious adverse events, a number of the serious adverse events that we have heard about in the emergency room situation seem to have occurred at doses, presumably -- I don't know how reliable the dose information is in that setting, I am not sure, but presumably at doses that patients

routinely get and which they tolerate extremely well. So, I will ask the same disparity question again there.

DR. MIGNOT: I think you have to realize also that you are talking about narcoleptic patients who also experience daytime episodes of overwhelming sleepiness that sometimes lead to confusion, and there are a lot of horror stories about narcoleptic patients, independently of GHB, at any moment of their life where they can sometimes be in a risky situation just because they have what we call automatic behavior, this overwhelming sleep attack where they really don't know what they are doing, where they may be driving or doing something dangerous. I think that is also important to keep in mind. The danger of taking two doses at a time, if it is relatively well dispensed, for narcolepsy patients I think needs to be put in perspective for their other symptoms.

DR. REARDAN: I am only aware of one case in our database. It was a patient who inadvertently took 18 g and I think, Dr. Mani, you are well aware of that. He did fall on his head. So, it is confusing as to whether it was a result of his 18 g dose -- you know, that was the best

estimate we had -- or in the fall he hit his head, but he did end up being taken to the emergency department and did need supportive care. Oh, Bill is saying that was a normal dose. I am sorry, let me get him to clarify.

DR. HOUGHTON: Yes, I am sorry. That is one of the cases that we know very little about. It was a patient who was in the kitchen. There was a loud bang. His wife heard the noise and came in, and her husband was on the floor. So, we got no dose relationship to that event. We know nothing as to whether it is related to Xyrem.

The 18 g overdose was the patient who was supposedly sleepwalking, in the Scharf database, who supposedly then took 18 g on top of his normal dose and was taken to hospital and ended up on a ventilator.

Really, the best prevention we have of 9 g being taken together is the fact that the dose has to be made up into separate doses. The instructions to the patient are very clear. They make two doses up together, dilute it in the water; drink one when they get into bed and the other, in a sealed cup, put away. Now, if they took the second dose in ten minutes or two hours, we have

not done that study and it is very dangerous to extrapolate that sort of dosing. On one hand, I can quote the patient who took 180 g and was taken to hospital unconscious and walked out of hospital four hours later to be admitted to the psychiatric unit.

I certainly don't want to propose that as the normal pharmacodynamic response. We have not done a study that has escalated beyond the 4.5 g dose twice a night, and I think it is very dangerous to extrapolate. It is also very dangerous to extrapolate the anesthesia data or some of the data that Dr. Dyer talked about this morning. Doses were given up to 100 mg/kg intravenously. If we believe the bioequivalence data, the absolute bioavailability data, that is equivalent to at least 300 mg/kg as an anesthetic dose, and that would be the best dose relationship we could give to dose escalation. Again, without true data I am not prepared to extrapolate from that.

DR. KAWAS: Dr. Mani, do you still want the floor?

DR. MANI: Yes, very briefly, just as further evidence of how much individual variability

there is in response to this drug. There is a subject who Dr. Houghton had referred to in his presentation this morning, a healthy subject participating in a pharmacokinetic trial, a healthy young subject who received a single dose of 4.5 g and afterwards became obtunded, developed obstructed respiration perhaps because of his jaw falling back, became incontinent or urine and stool, and took a number of hours to recover but did not need any special supportive care. So, even a 4.5 g dose may not be entirely safe for everybody.

DR. HOUGHTON: That story is somewhat true but not quite accurate. The patient was easily arousable, walked to the bathroom after the event of passed urine, after resting back in bed had a normal sleep and, two hours later was awake and ate a normal lunch. So, again, I can't account for the degree of obtundation but that still represented the maximum single dose in our database. It was a single dose of 4.5 g after a 10-hour fast.

DR. MANI: Although those details about the patient being able to get up and go to the bathroom and eat her lunch, and so on, wasn't in the narrative that we have available.

DR. HOUGHTON: We were collecting urine samples every two hours and I can assure you the patient was walked to the bathroom. She certainly vomited at the time.

DR. KAWAS: Dr. Leiderman?

DR. LEIDERMAN: Very briefly because Dr. Mani raised one of the points that I wanted to, but the other question I had for the sponsor and the sleep neurophysiologists here, do you think that in some of the differential response that we are seeing in the narcolepsy patients as compared to the subjects who become dependent, addicted, have overdose problems that there may be a role not only of the basic neurophysiology of the narcoleptic brain but, of course these patients tended to be co-medicated with stimulants, and what role do you think that might be playing in the narcolepsy population?

DR. REARDAN: Is the concern that stimulants would still be present on board when they take their nightly dose of Xyrem? Is that what you are after, or what?

DR. LEIDERMAN: Well, I am asking for your thoughts on, shall we say, the differential effects of GHB on the two populations, and one of the sort

of clear differences, taking sort of the first cut, is that narcolepsy patients are co-medicated with stimulants generally, whereas the abusing drug population, if anything, is self co-medicating with other CNS depressants or using GHB at high doses alone.

DR. BLACK: I think there are a number of questions that surface. We have patients in protocols where they are wanting to remain on the protocols or wanting to be drug compliant. There are reasons that they wouldn't abuse in addition or outside of the fact of co-pharmacy with stimulants and so forth. So, it is hard to compare those two groups clearly.

I think the best we can do is speculate. We have a number of patients that were not co-treated with stimulants as well, that were on just Xyrem, and they didn't self-escalate the dose or abuse the agent either. I think the only way to do it would be to give high dose frequently to the narcolepsy patient population and see if they are similarly addictable, and then it would be also interesting to find out what percentage of the normal population is addictable as well. Obviously, those studies couldn't be done. But I

think we can't compare the two and it is real hard to try to extrapolate the information we have to do a comparison.

DR. KAWAS: Dr. Dyer, followed by Dr. Van Belle, followed by Ella Lacey, followed by the questions that the FDA has asked us to consider. In between, we will get a quick demonstration of the mixing.

DR. HOUGHTON: Could I just add one point of clarification to Dr. Leiderman's question? There were patients in all of the studies that were not on stimulants. In the GHB-2 study I think it was about 15 percent when we did a recent look at the database for Dr. Mani. So, there was at least a proportion of patients represented in the database that weren't on stimulants as concomitant medication.

DR. DYER: There was one study, I believe it was done in rats where amphetamines and then a second with caffeine, where those were shown to kind of be antidotal to GHB poisoning, where it prevents the rats' loss of riding reflex. So, there may be some of that issue if they are taking it concurrently. One of the other things about the disparity, where I don't see the disparity as being

so much is that the narcoleptics are taking their dose at night. We know pretty commonly from the surgical studies from what we see coming into the emergency room and from the adverse effects of the study, that GHB causes vomiting and incontinence. So, we are seeing that in both populations of patients.

DR. CHERVIN: Is anybody there?

DR. KAWAS: Yes, is that one of our phone consultants, Dr. Chervin or Dr. Guilleminault?

DR. CHERVIN: Sorry, it seems like we were completely cut off.

DR. KAWAS: Can you hear us now?

DR. CHERVIN: Just barely. If there is any way you can make this signal more than barely audible, it would be helpful?

DR. KAWAS: We can barely hear you but it sounds like we are going to have to get the AV people on it, if you give us a moment.

DR. CHERVIN: I do have questions if I have time to ask them.

DR. KAWAS: I know that you are on a timetable, so we will put you in the middle of the six-person pileup, if we could let the speaker that is going now finish though.

DR. DYER: So, there was another study where they took the patients and the patients that they gave the dose to and then forced or tried to maintain themselves awake, those were the patients that became confused.

The other thing is that in our emergency department study where we were trying to verify our ability to predict GHB by toxidrome, we looked at patients that came in with a GCS score less than 8 that were spontaneously breathing. So, unlike most CNS depressants that cause profound coma, generally the breathing is still spontaneous and maintained. You see mild respiratory acidosis but it is not very common that these patients need to be intubated. So, it is not contrary to be thinking that a patient might be comatose and survive the night.

DR. KAWAS: Dr. Van Belle, while we are still working on the audio, do you want to go ahead and ask your question?

DR. VAN BELLE: I just have a brief question with respect to age eligibility. Will this medication be available to people under 18 years old?

DR. REARDAN: The company has not

specifically developed data for pediatrics, and I think this would have to be something we work out with the agency but, typically, a medication approved for adults is not denied children. FDA and Congress have tried to put incentives in to get sponsors to develop pediatric information. In addition, narcolepsy is not generally a pediatric disease. I don't know if either Dr. Mignot or Dr. Black want to comment further. Dr. Katz?

DR. KATZ: Well, generally speaking, unless there is a good reason not to, we would limit the age that would be at least included in the indications or in labeling or dosage administration to the age of the lower limit of the age studied in the trials. I don't know exactly what the youngest patient was in these trials.

DR. REARDAN: Bill Houghton is saying 12.

DR. KATZ: Okay, 12. Again, if there was one patient who was 12 and everybody else was 18 and above, we would say adults or 18 and above, that kind of thing. It is true that there is no prohibition, obviously, from a physician writing a prescription for a drug for a child if it is only explicitly approved for an adult. It happens obviously all the time. But one of the questions

when we get to it with regard to risk management and that sort of thing is if there were no children studied, or children studied below a certain age, do you think attempts should be made to restrict it in this case? So, you know, it is open for discussion.

DR. MIGNOT: To answer the question, onset of the disease is roughly between 15 and 25. That is really when the bulk of the patients are coming in, especially for cataplexy, and I think it is very important to treat them early. As there is more and more knowledge about narcolepsy being an important disease and being recognized early -- I think you have heard a lot of testimony about how important it is to treat them early so that they can go through normal schooling. I think it will be very important to not be too restrictive towards the lower age.

DR. KAWAS: Dr. Lacey?

DR. LACEY: Two questions, one regarding the packaging. With the packaging being in a bottle and it is child-resistant dosing, and all, but hearing about adolescents and their involvement with GHB, I wondered if you considered other packaging. In deciding on this packaging, did you

consider individual dosage packaging at all, and what happened with that?

DR. REARDAN: We considered individual dosing packaging for sure. We thought that was a greater potential for diversion as it is easy to take those individual doses. I think maybe you would get some reassurance if Patti Engel can go through how we instruct the patients to dose and what the controls are for that. Patti?

MS. ENGEL: Thank you. To the point of individual dosing, we did speak quite extensively about that with law enforcement.

DR. LACEY: Yes, I am pretty convinced about the patient. I am more concerned about others in the household who are exposed to a bottle.

MS. ENGEL: Right. I will address that as well. On the individual dosing, law enforcement was concerned about small containers that could be stuck in a pocket or purse, or slipped in someone's drink more easily. One of the things I shared with you earlier is that the bottle itself comes with a child-resistant closure. What is difficult to see from this distance, but it is something called a press-in bottle adaptor. When the patient gets

this, there is a little well, if you will, in there. Even if a child can get this lid off, you can't drink it down. What has to happen is there is a metered syringe provided. It gets stuck in here and the patient removes a metered dose. Okay? They then have two child-resistant dosing cups and these aren't fancy. We took them because they are CPIS tested for child resistance, of course, and they put it in, preparing both doses by their bedside.

Now, the dose itself is metered. This Xyrem, to be frank, is not good tasting stuff. It is sodium oxybate. It is very salty. Many people will dilute it. How much they dilute it really is to their taste. We did not want to cherry flavor it or anything like that that may make it more attractive to children. Okay? Does that answer your question?

DR. LACEY: It really wasn't the small children that I was concerned about as I was about the older, the adolescents in the household who can open it the same as I could. So, I guess your answer was that law enforcement was concerned about the small dosages just being put in a pocket.

MS. ENGEL: That is right. Remember,

illicit use of Xyrem also falls under C-I penalties, like heroin or LSD. So, we will never be able to find a package that a 19- or a 21-year old will not be able to get into. What we do, however, is to educate the Xyrem patient on a number of occasions of the penalties should that occur. So, there is an element of patient responsibility with this.

DR. LACEY: Thank you. The second question I have is about the suicide attempts that were presented by Dr. Houghton this morning. That was in that list of adverse events I believe, and it has continued to bother me that we talk about it as a suicide attempt as though nothing else happened and I am just curious, I guess, in those attempts were some of the other adverse events also experienced by those persons who were suicide attempters?

DR. REARDAN: As you heard from Dr. Mignot, depression is very common in narcoleptics, but I will ask Bill to comment on that.

DR. HOUGHTON: In all the patients who attempted suicide there was preexisting disease. In terms of response to the dose taken, only one of the suicide attempts involved Xyrem, and that was

the patient who took a very large dose, about 300 ml of the drug which is equivalent to at least 150 g, and he became comatose, incontinent of feces and urine, continued to breathe spontaneously, was found by his wife in the bathroom, transported to the emergency medical care, did not require intubation or ventilation, and walked out of hospital four hours later to be admitted to the psychiatric unit. I certainly don't propose that as the norm. There will be certainly unconscious patients at much lower doses. So, please don't think I am proposing that as the pharmacodynamic profile of the drug. But you asked me what the side effects of the suicide event were and that is the only data that I can give you.

The second suicide event that was not fatal did not involve Xyrem. One of the fatal attempts did not involve Xyrem at all. The last suicide attack in the bipolar disorder patient was a real pharmacologic cocktail involving benzodiazepines, opiates, a number of drugs and some Xyrem.

DR. LACEY: But for those individuals who did have the suicide attempts, they did not have other -- not with the attempt directly but other

adverse events also in their report?

DR. HOUGHTON: No. One of those was a lady who had a group of people to her home. She asked them all to leave early, and when attempted to be contacted the next morning didn't respond, and when her attentions were sought she was found dead in the home.

The second attempt was a young lady who took an overdose of buspirone and told her father immediately. Her behavior was normal to that point. So, that is an example.

DR. KAWAS: Dr. Chervin or Dr. Guilleminault, can you hear us now? You guys are next in the line up.

DR. CHERVIN: Thank you. I have two questions. Please tell me if it has been covered and I just was not able to hear it, but I read in some of the material that was distributed prior to the meeting about comparisons of the therapeutic index or the therapeutic window for GHB to that of other drugs that are currently approved and used. I was wondering if perhaps Dr. Dyer or Dr. Falkowski or Dr. Balster could address that comparison.

DR. DYER: Is that the comparison of LD-50

in rats?

DR. CHERVIN: I guess it was rats, and it was LD-50 and effective dose, and they looked at the ratio.

DR. DYER: The problem I have with some of the rat data, lethal dose data, is the deaths we see are often secondary to coma. It takes high doses to cause pure respiratory depression. We have some patients that idiosyncratically have a pulmonary edema, but most of the deaths are secondary to unprotected coma and loss of airway. So, I don't know that that would extrapolate or come from rat data at all. I don't think you would see that.

DR. CHERVIN: Is there any other way to get at the issue of is Xyrem going to be more dangerous than other drugs that are used carefully when indicated?

DR. REARDAN: Dr. Chervin, I have some data on LD-50 that will help. Oral GHB has an LD-50 on the order of 9000 mg/kg in rats, and about 3500 mg/kg in mice. The IV LD-50 is about a third of that for GBL and for butanediol it is on the order of 2000 mg/kg. If you look at the effective dose, we are in the range, I believe, of about

50-120 mg/kg recommended for the narcoleptic patients. Now, that is just on an LD-50 basis. I don't know if Dr. Mani wants to comment on the therapeutic range, or Dr. Katz.

DR. KATZ: I don't think we really know. I am not sure if the animal data is relevant at all. And, I don't think we have data that, in a systematic, adequate way, explores the full dose response both with efficacy or tolerability. As you have said, you have done a trial where the maximum dose, fixed dose, was 9 g per night and, you know, we either decide that that was a tolerable dose or it wasn't. And, you have the dose response for the effectiveness, and that is all you have. As you acknowledge, you haven't explored higher doses so I don't think we really know, and I don't know how you would really get at the question of how the therapeutic window, if there is one, compares to other drugs that are in common use. Some drugs that are used, there is a belief that they have a very narrow therapeutic windows, and some are wide. I don't think you can say more than that.

DR. REARDAN: I don't disagree.

DR. GUILLEMINAULT: I have a question.

Narcoleptic patients have hypnagogic hallucinations. They may even shoot -- if a gun is available they may hurt their bed partner because they are keeping their hallucination. How much does Xyrem decrease hypnagogic hallucinations, which is a very significant side effect which may kill neighbors and may kill even bed partners?

DR. REARDAN: If I understand the question, Dr. Guilleminault, it is how much did Xyrem reduce hypnagogic hallucinations in our trials, and I guess my first response is the incidence was very low and we did not see a statistical significance in GHB-2. I don't know if Dr. Houghton wants to comment further on hypnagogic hallucinations.

Just while they are finding the data, it is fair to say that the incidence of hypnagogic hallucinations recorded in the four-week trial was very low. There was a trend towards improvement that certainly didn't reach statistical significance. There was a better representation in the long-term open-label study and we could show that but I am loathe to do so because I certainly don't want to claim it as efficacy. I think we will be able to find the GHB-2 data.

[Slide]

DR. HOUGHTON: In the Lammers study there was a reduction from 0.87 hypnagogic hallucinations per night over the 4-week treatment period to 0.28 incidence per night, with a p value of 0.008. That is one set of figures.

DR. MIGNOT: Just to sort of expand on what you said, if only about 40-60 percent of patients we narcolepsy/cataplexy have hypnagogic hallucinations as their symptoms or sleep paralysis, then obviously that must reduce the power for the trial because they have only about half of the patients they included who even had that symptom.

[Slide]

DR. REARDAN: This is a slide from GHB-3. I guess that is open label, I don't know if we want to go into that. What it shows is median change from baseline to visit number and out through 12 months. You see a median change in hypnagogic hallucinations, a reduction of 0.35 per day. Is that right?

DR. KAWAS: Dr. Penis and then Dr. Falkowski and then this committee will be looking at the questions that the FDA has asked us to vote

on.

DR. PENIX: I think we have to anticipate several different possibilities in the treatment of patients with any drug, and I am somewhat concerned about the fact that the effective dose of Xyrem appears to be the maximum dose available, number one. Secondly, in regards to the possible protective effects of stimulants on the side effect of sedation, and whether we should consider Xyrem as a monotherapy drug or as an adjunctive treatment, and the question I would like to ask -- I think Dr. Houghton may have presented this data of talked about it, of the 15 percent of patients who did not receive stimulants while on Xyrem whether there was a difference in the maximum dose escalation in those patients compared to the ones who were on stimulants. I am not sure if we can answer the question, but if there is data on that, if there is a difference.

DR. HOUGHTON: No, we don't have data separate for those on stimulants and those not on stimulants. There was only about 15 percent in that controlled trial that were not on stimulants. So, we hadn't plotted that at all. Remember that stimulants are taken in the morning and usually the

last dose at lunch because narcoleptics are really trying to sleep at night and stimulants really complicate that, and the half-life of the gama hydroxybutyrate is about an hour.

So, even after their second dose their plasma levels on awakening in the morning are extraordinarily low. So, a contribution of stimulants to change that is quite unlikely. We certainly didn't see an abnormal sleep response in the normal volunteers in any of the pharmacokinetic studies, except the one patient who became obtunded, and she was awake four hours later and ate lunch, and then went home that day. So, the only real suggestion of data I could give you in the absence or stimulants is the single dose response or the repeat dose response in the pharmacokinetic studies, and that certainly didn't appear to be different at all.

DR. BLACK: I would just comment on the notion of a potential protective effect with stimulants. With the traditional stimulants, they are relatively short acting and there is a phenomenon called rebound hypersomnia as the medication wears off -- well demonstrated in animals and humans -- where the individual becomes

more sleep than they would have been had they not taken a medication; often a problem for those with narcolepsy who are using those medications.

Rather than those stimulants keeping people more awake and less affected by the Xyrem dose, there is the potential for even greater sleepiness with that rebound hypersomnia. That has not been well explored, but I think it would be erroneous to assume that there is any protective effect from the traditional stimulants. From the longer acting stimulant, modafinil, sleep studies have been done to suggest that there is no impact one way or the other on sleep in terms of depth of sleep and so forth.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: I have to take issue -- well, I already did with the statement that Xyrem will not contribute to the public health problem of abuse of GHB-like substances because I think it will and I want to take just a few minutes to elaborate on why that might be something I couldn't cover in the confines of my 15 minutes as well as covering those other points.

I had occasion last week, in Philadelphia, to present at a conference on drug abuse addiction

professionals from around the country, and since I speak about drugs of abuse, when I got to GHB I said, so, tell me about GHB in your community. Having heard from 15 people from 15 distinct parts of the country on this, a common theme emerged and that had to do with the fact that people who were abusing it couldn't quite get the dosing right because they kept passing out. Passing out became sort of a way of life. I think in Dr. Dyer's data we even saw that as well.

This is a drug that causes people to lose consciousness and in some cases respiratory arrest. Well, I think this is particularly relevant because if dosing is the problem I believe that this will only make more attractive a predictable dose as a known entity in a prescription product. "Gee, I can get around all these dosing problems by getting the prescription."

I am also concerned that none of the sponsor's packaging that I looked at even mentions the word gamma hydroxybutyrate, or did I miss that? I looked for it; I didn't see that. That concerns me because, as we have seen with oxicodon, we know, for example and I think it is a good case, we know that narcotic addicts will seek out

prescription narcotics for predictable dosing and for predictable purity. And, we have seen an increase once long-acting oxicodon was developed -- we have seen an expansion in its prescribing not just for chronic pain but for the treatment of even acute pain. That plays out to the tune of 300,000 oxicodon prescriptions in 1998 and over 5 million oxicodon prescriptions in the year 2000.

What people have to do, what drug seekers have to do to acquire it is go to a doctor and feign pain. This happens with unsuspecting doctors and it is happening in all parts of the country.

Now, diversion of drugs does not occur by people storming with machine guns the one central manufacturing. It occurs at the patient-doctor level. And, I am very concerned about the possibility of folks who are having trouble. Again, this is a diverse population; it is not just kids using drugs. This is weight-lifters, these are people seeking effects, going to a doctor and saying, gee, you can get around all that; just go to a doctor and tell him you are sleepy. Just go to a doctor and tell him you collapsed. This is really seriously my concern about this, and I don't think that these two issues are separate. This

drug has a huge following.

DR. KAWAS: I would now like to focus on the questions that the FDA has asked us to vote on. Do you feel very strongly that your comments are necessary before that?

DR. RISTANOVIC: I am going to make a comment extremely brief. The comment is very brief because in today's time we know how to diagnose narcolepsy. So, there is no way, even if someone is trying to malinger, to be given a diagnosis without appropriate testing in the sleep lab. That is a prerequisite.

DR. KAWAS: Thank you.

DR. RISTANOVIC: That is all.

DR. KAWAS: The FDA has given us three questions that they want this panel to vote on, and a whole page and a half of other items that they would like this committee to discuss.

So, I would first like to ask them if it is acceptable to facilitate the discussion, can I make the decision to split the first question into two?

DR. KATZ: Absolutely.

DR. KAWAS: Thank you. It might be the only thing that gets done quickly today. The first

question is going to be has the sponsor demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? I am opening the floor for discussion on that. Yes, Dr. Katz?

DR. KATZ: Again, I think it is very important for us to hear a discussion about dose and which dose. I mean, I mentioned that earlier in my comments this morning, but if you could address that it would be very helpful.

DR. KAWAS: Absolutely. In fact, maybe I would like to facilitate this part because I think this is the easiest thing that is going to happen in the next hour. To my mind, there have been two pivotal studies that have suggested efficacy for this drug in relationship to cataplexy at the 9 g level. Maybe by making that not overly provocative comment we can stimulate discussion. Does anyone want to comment on the dose or the effect on cataplexy before we vote?

DR. FALKOWSKI: Is that the recommended dose? It is not. That is why I am sincerely confused because the study seemed to show efficacy at 9 g, yet, the recommended dose is something other than that and that needs explanation. I don't understand that.

DR. KAWAS: Any other comments? Richard?

DR. PENN: I was going to make it a motion so we would save some steps. I think it is very clear that what you said is a good summary of the case that, in fact, they haven't set the dose at 9. They have suggested a different dose regimen and that has to be looked into very carefully. But the one thing I think we all we agree on is your statement. I would, therefore, put it as a motion, since we are supposed to do a motion so that that has been shown.

DR. KAWAS: Would you like to make a comment, Gerald, before we pick the motion that is about to be on the floor?

DR. VAN BELLE: Sure. Well, I think it is the issue of dose response that I am struggling with in this case in terms of the pharmacokinetic model. If you assume that there is a pharmacokinetic model that is dose related, I would say if evidence has been shown for an effect at 9 there is probably an effect at 8.5 as well. Well, where do you draw the line at that time, and I don't quite know where to do that. I think there is ambiguous evidence for an effect at 6 and one study showed that. So, if you want the technical

answer, I think there is only evidence for clinical effectiveness at 9 but that ignores, to my mind, the pharmacokinetic aspects of the data so I am struggling with this.

DR. KAWAS: Could we restate Dr. Penn's motion that this committee vote on whether or not there has been efficacy demonstrated of this drug for the treatment of cataplexy and, specifically at the dosage of 9?

DR. SIMPSON: This may be my ignorance, but when something is labeled, for example, that it is efficacious at a dose of 9, does that mean that a doctor would necessarily prescribe it at 9? He could prescribe it quite a lot higher, couldn't he?

DR. PENN: That is going to get us into the next thing, which is how this is going to be monitored. Because it sounds like we want to put an absolute dose limit and we don't want to allow variability in the population. By the technical way we are going to allow this out, if they are going to be watching how much a patient can take, then is a doctor going to be allowed the latitude a patient more, and you are asking can they be given less? I think the answer is usually the doctor makes that decision. Everybody understands that is

the mean does that you have to use but that doesn't mean your patient will respond to it. So, there is the latitude unless we put into force this voluntary program.

DR. KAWAS: I would like to focus this committee back on the questions or we will never -- well, we will have everyone on a plane without a quorum in order to vote on these issues.

The first question really isn't so much about safety and what a doctor will do, the FDA has just asked us have they demonstrated efficacy for this drug in either of the two indications.

DR. FALKOWSKI: I believe they have demonstrated efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. I think that is what their studies have shown us today.

DR. KAWAS: Okay. We will be taking a vote and everyone's vote is going to count. Are there any other comments people want to make before we put Dr. Penn's motion on the floor?

DR. SIMPSON: I really agree that they haven't necessarily demonstrated efficacy in treating cataplexy but really in reducing cataplexy.

DR. KAWAS: Do you want to put your motion on the floor again?

DR. PENN: The company has shown efficacy at 9 g per day using a 4.5 divided dose for treating cataplexy in narcoleptic patients.

DR. KAWAS: These votes are going to have to be recorded individually I think. So, can we start with everyone who agrees that the sponsor has demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? Please raise your hands now.

I just want to remind everybody that the voting members of the committee actually are sort of in the central part of the table, beginning with Dr. Simpson and then going around to Dr. Penix. All who agree the company has demonstrated efficacy for cataplexy, raise your hand.

[Show of hands]

How about if we go around and identify, and start with Dr. Penix for the record?

DR. PENIX: I agree.

DR. KAWAS: Just your name.

DR. PENIX: Dr. Penix.

DR. VAN BELLE: Van Belle.

DR. PENN: Penn.

DR. KAWAS: Kawas.

DR. WOLINSKY: Wolinsky.

DR. ROMAN: Roman.

DR. KAWAS: All the people who do not feel the company has shown efficacy for the treatment of cataplexy, please raise your hand and start identifying.

[Show of hands]

DR. SIMPSON: Simpson.

DR. FALKOWSKI: Falkowski.

DR. LACEY: Lacey.

DR. KAWAS: I think that was everyone, so no abstentions in that case.

Moving on to the next hard one, has the sponsor demonstrated --

DR. KATZ: Dr. Simpson and Falkowski, I believe in your comments you said you thought there was an effect demonstrated, or something, but the vote went the other way. I just want to understand.

DR. FALKOWSKI: Right, I believe that they have demonstrated that there is some evidence of efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. These studies have been conducted on people who were already on