U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS

ADVISORY COMMITTEE

OPEN SESSION

Thursday, November 10, 2005

9:00 a.m.

Food and Drug Administration
Advisors and Consultants Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

ADVISORY COMMITTEE REPRODUCTIVE HEALTH DRUGS

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FDA Presenters:

Dan Mellon, Ph.D.
Mwango Kashoki, M.D.
Joan Buenconsejo, Ph.D.
Arthur Simone, M.D., Ph.D.
Lisa Basham-Cruz, M.S.
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Carolyn L. Yancey, M.D.
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C O N T E N T S

P R O C E E D I N G S

Call to Order

CHAIR FARRAR: Good morning. My name is John Farrar. I'm the acting chair for this meeting. I'd like to call the meeting to order.

Introduction of Committee

CHAIR FARRAR: I'd like to start, perhaps, going around the table introducing ourselves, and where you're from.

Jim, do you want to start?

DR. EISENACH: I'm Jim Eisenach, an anesthesiologist from Wake Forest University.

DR. HENTHORN: Tom Henthorn from the University of Colorado, Department of Anesthesiology,

DR. DWORKIN: Bob Dworkin from the University of Rochester.

DR. WLODY: David Wlody. I'm an anesthesiologist at the State University of New York, Downstate Medical Center.

CHAIR FARRAR: I'm John Farrar, a neurologist at the University of Pennsylvania, and

a clinical epidemiologist.

DR. FERRETTI-ACETO: Victoria Ferretti-Aceto, the Executive Secretary for the Anesthetic and Life Support Drugs Advisory Committee.

DR. RAPPAPORT: I'm Bob Rappaport. I'm the Director of the Division of Anesthesia, Analgesia and Rheumatology Products at the FDA.

DR. SIMONE: I'm Art Simone, Lead Medical Officer--Acting Lead Medical Officer--for Anesthetics in the same Division.

DR. KASHOKI: Mwongo Kashoki, Acting Pain Team Leader, same division.

DR. HERTZ: Sharon Hertz, Deputy Director.

DR. SORIANO: Sulpicio Soriano, Children's Hospital, Boston, Department of Anesthesia.

DR. ROCA: Rigoberto Roca, Deputy Director.

Open Public Hearing Session

CHAIR FARRAR: We need to read some guidance about this particular meeting.

Both the Food and Drug Administration and the public believe in a transparent process for

information gathering and decision-making. To ensure such transparency at the open public hearing sessions of the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

With that, I'd like to open the public hearing.

[Pause.]

Apparently the AV is not working quite up to snuff.

The first speaker is Eugene Sinclair, the AM Society of Anesthesiologists.

Dr. Sinclair?

James Sinclair, M.D., American Society of Anesthesiologists

DR. SINCLAIR: Good morning. My name is Dr. Eugene P. Sinclair. I have no financial conflicts involved with this testimony that I am about to give.

I am a board certified anesthesiologist and immediate past president of the American Society of Anesthesiologists--or ASA. For our 40,000 member physicians, patient safety is paramount.

I am here today to present ASA's position on FDA Petition #2005P-0267, which seeks to remove the warning language from the package insert for

the anesthetic drug propofol--or Diprivan. A formal letter form ASA stating our concerns was sent to the FDA on October 19, 2005. ASA strongly believes that the requested label change should be denied. Neither clinical data nor the best interests of patient safety support the request.

I will elaborate on the major points covered in our letter: first, the risk that propofol may induce a state of general anesthesia necessitating that the physician be able to recognize and manage life-threatening anesthetic complications; and, second, crucial evidence that it may be safely administered by clinicians not trained in anesthesiology.

The first and foremost point is that propofol is a powerful anesthetic agent that can produce varying levels of sedation along the continuum from sedation to general anesthesia. It is not possible to predict how an individual patient will respond within this continuum. Because of propofol's extremely rapid onset and high potency, the desired level of sedation is

easily and often exceeded. Wide variation in individual response to a standard intravenous dose of propofol often causes a patient to enter an unintended state of general anesthesia within as little as 30 seconds. There is also an impressive 20-fold variation among individuals in the rate of metabolism of propofol. It is imperative to note that propofol has no antagonist or reversal medications--in contrast to benzodiazepines and narcotics, the other sedatives that are currently used by non-anesthesiologist physicians.

Due to the potential for rapid, profound changes in sedative and anesthetic depth, and the lack of antagonist agents, drugs such a propofol require special attention. This means that the clinician administering propofol must have the technical skill, knowledge and experience instantaneously to recognize and rescue a patient experiencing any of the sequella of general anesthesia, which include life-threatening respiratory and cardiovascular emergencies.

Therefore, the physician should have the

education and training to manage the potential medical complications of sedation and anesthesia. The physician should be proficient in recognizing and managing the often subtle signs of adverse respiratory or cardiovascular events to prevent complications such as hypoxia, hypoventilation, bradycardia, tachycardia, hypotension, hypertension And failure to rescue has consistently--and reported in the gastroenterology literature as a prominent cause of poor outcomes. In particular, that literature shows greater rates of complications among patients with imperfect health and patients who are older than 50 years of age.

Some state health agencies are also aware of the threat to patient safety. Between the years 2001 and 2004, no fewer than 38 deaths related to the performance of endoscopies in ambulatory surgery centers were reported to the Florida Health Care Administration Board of Medicine.

We note that many gastroenterologists work with anesthesiologists or CRNAs and are unwilling to jeopardize patient safety. For that reason,

some of ACG's own members oppose its stance on propofol, and the ACG's immediate past president has said that he believes 'that this is the most internally divisive issue in clinical gastroenterology at this time."

Privileges to administer general anesthesia awarded by the facility in which a physician practice are the best indicator of satisfactory training and experience in the use of propofol. Removal of the warning label from the propofol package insert will encourage the use of propofol by practitioners with inadequate training and experience--particularly in non-accredited facilities where credentialing is not required, such as private offices.

With 20 percent of procedures already being performed in private offices, and the proportion expected to grow, this will pose a major patient safety risk. Not all private offices or endoscopy centers are equipped or staffed for emergency care--even lacking the basic skill to perform emergency endotracheal intubation. Nor are

they located within a couple of minutes of anesthesiologist or emergency physician services. We have heard of facilities relying on a 911 call as their front-line emergency system. This is not acceptable.

The ACG petition also seeks the removal of the portion of the propofol label warning that the individual administering propofol should not be involved in the conduct of the diagnostic or surgical procedure. We are concerned that granting the petition would make it more likely--especially in the private offices mentioned above--that the gastroenterologist performing the endoscopic procedure might not use a second clinician to administer the propofol and monitor the patient continuously with no other responsibilities. A designated individual, other than the practitioner performing the procedure, with no other responsibilities must be present to monitor the patient throughout the procedure. This is indispensable to the safety of sedation with population.

The ACG presented many studies in support of their position. We asked Methodology Group of the ASA Committee on Practice Parameters to analyze the studies cited, using standard techniques for assessing the strength of literature and the preparation of evidence-based practice parameters. The methodologists concluded that the studies did not provide sufficient statistical or meta-analytical evidence to address the two major safety concerns: first, use of propofol by non-anesthesiologists; and, second, the involvement of the same physician responsible for the sedation in the conduct of the surgical or diagnostic procedure.

Only on of the studies sufficiently addressed the administration of propofol by anesthesiologists compared to non-anesthesiologists. In a recent abstract of that study, the investigators, not surprisingly, concluded that the administration of propofol by anesthesiologists is associated with a lower relative risk of cardiopulmonary complications

compared to its administration by non-anesthesiologists.

Another reason why the studies cited in the petition fail to establish the safety of propofol is that the expected anesthesia mortality rate in healthy patients is one in every 300,000 cases. All of the studies combined do not encompass 300,000 patients. The number of cases required for statistical significance far exceeds that number.

The American Society of Anesthesiologists is proud of its success in bringing the rate down to this level, but doubts that clinicians with less skill, training and experience than its members can achieve an equivalent safety record when administering deep sedation or general anesthesia.

Removing the warning label from population would encourage its wider use by other non-anesthesiologists, and the number of complications would be even greater if that were to occur. For example, emergency room physicians face particular risks, since their patients are not

usually fasting, and thus can be expected to have a higher incidence of aspiration. Pediatricians have even greater challenges titrating propofol for their immature patients.

There is no evidence to show that patient safety would be protected by the proposed labeling modification.

Given the totally inconclusive research presented to this committee on the safety of propofol administration--with or without continuous monitoring of the patient--by non-anesthesiologists, and the irrelevance of economic concerns discussed in the ACG petition.

The FDA must deny the petition and should not change the warning label on propofol.

Thank you.

CHAIR FARRAR: Are there any clarifications? Requests by members of the committee?

[No response.]

All right--next I'd ask Carol Rose, M.D., testifying as a private citizen.

Carol Rose, M.D.

DR. ROSE: Thank you very much. My name is Dr. Carol Rose, I am a board certified anesthesiologist at the University to Pittsburgh Medical Center, and a former member of this FDA committee on Anesthesia and Life Support Drugs.

I have no financial conflicts.

I am here today to share my comments on what I believe to be a significant risk to anesthesia patient safety.

Propofol, a potent and commonly used anesthetic agent currently carries a warning label which mandates that it should be administered only by persons trained in the administration of general anesthesia. On June 28th, the American College of Gastroenterology filed a petition with the FDA seeking to remove that warning.

In trained hands, propofol offers many advantages over other drugs used for sedation because of its rapid onset and short duration of action. However, some practitioners have been lulled into a false sense of security, allowing the

drug's good safety profile to influence their beliefs that propofol is safer than it really is.

Propofol dosing and titration is variable, based on the patient's tolerance to the drug. Profound changes can occur rapidly, and a patient can go from breathing normally to a full respiratory arrest in seconds, even at low doses--and without warning from typical assessment parameters. Similar to midazolam, the side effects of propofol include apnea and hypotension. The propofol warning label expressly states that overdosage is likely to cause cardiorespiratory depression which should be treated by artificial ventilation with oxygen.

The risks of this medication are quite significant if administered improperly. My concern with lessening the label's restrictions is that individuals who lack the proper and extensive training in anesthesia will be unfamiliar with vital functions such as assessing respiratory status, supporting, maintaining, manipulating, and/or intubating the airway in order to keep

patients safety sedated.

Many non-anesthesia care providers are unaware of the differences between conscious sedation--also known as "moderate sedation--and deep sedation and general anesthesia, or are unable to maintain that difference when they intend to. Tangential to that, they lack the day-to-day experience working with this and other potent anesthetic agents. Again, just like midazolam, where a number of fatal overdoses were seen in gastroenterologists' offices, the use of propofol by non-anesthesia trained providers could result in similar disasters.

And I will tell you that the facility where I work, when the gastroenterologists were in charge o the sedation in the GI lab, we had multiple Condition A and Condition C's, which are the overhead calls for help for resuscitation. And when the anesthesia department took over the care of those patients in the GI lab, those calls essentially went to zero.

According to a November 1st article

published by the Institute for Safe Medication Practices, a gastroenterologist asked a nurse to prepare "10 mL" of the drug for a patient undergoing endoscopy. And 10 mg/mL, that requested dose was 100 mg, a dose far too large for the circumstance. The nurse obtained the drug from an automated dispensing cabinet via override before she transcribed the order to the patient's record. Another nurse--who was trained in the use of moderate sedation, but not deep sedation or anesthesia--assisted the gastroenterologist. After questioning the physician about the dose, she began administering the propofol via an infusion pump. The patient suddenly experienced respiratory arrest. Fortunately, ICU staff were able to help with the emergency, and quickly intubated and ventilated the patient.

A similar case involved a Florida physician who thought he could safely administer propofol himself while performing a breast augmentation. Unfortunately, this patient, a young woman, died of hypoxic encephalopathy because he

failed to notice the patient's rapidly declining respiratory status, as had his surgical assistant, who was not qualified to monitor patients under deep sedation or anesthesia.

And I have that ISMP report here. And I would like to read the conclusion of that ISMP report.

"The debate about who should be allowed to administer propofol may continue. But one thing is clear: whenever propofol is used for sedation or anesthesia, it should be administered only by persons who are trained in the administration of drugs that cause deep sedation and general anesthesia; and, number two, able to intubate the patient if necessary; and, number three, not involved simultaneously in the procedure itself."

In brief, the American Society of Anesthesiologists, the American Association of Nurse Anesthetists, and the American Association for the Accreditation of Ambulatory Surgical Facilities believe that only persons trained in the administration of general anesthesia, who are not

simultaneously involved in the procedures, should administer propofol to non-ventilated patients.

The Pennsylvania Society of Anesthesiologists--of which I am a past president--and the Pennsylvania Association of Nurse Anesthetists has previously issued a joint statement in this regard. I have supplied the committee with a copy of that statement. And you will note the final paragraph--which is the essence of it--states that the drug should be administered "by a practitioner with training and experience in the management of general anesthesia."

The importance of that statement is that no one--even an experienced anesthesiologist--can predict when sedation will progress into a general anesthetic. Therefore that person must be able to manage a general anesthetic in all ways--and, in this case, must be able to do all aspects of airway management and maintenance of vital signs.

As a physician who is an anesthesiologist, I see no benefit in lessening the restrictions of this warning label. As a medical doctor, I am

reminded of the section of the Hippocratic Oath, which reads: I will seek the counsel of particularly skilled physicians where indicated for the benefit of my patient," and "I will follow that method of treatment which according to my ability and judgment, I consider for the benefit of my patient, and abstain from whatever is harmful or mischievous."

It is my opinion that the efforts of this petition seem to contradict these statements. Lessening these restrictions would result in many adverse outcomes and a reduction in the quality of care provided to the patients.

And I would like to quote one of our recent past presidents of the American Society of Anesthesiologists, who used his motto for his entire year of presidency. And he said, "After all, it is all about the patients."

So, for patients' safety sake, we request that you not change the label of this drug.

Thank you again for allowing me the opportunity to speak before you. And I would be

happy to answer any questions that you may have.

CHAIR FARRAR: Any issues or clarifications requested by the committee?

[No response.]

DR. ROSE: Thank you.

CHAIR FARRAR: Thank you very much.

And our last speaker in this segment is Mark Koch, M.D., M.B.A., for Somnia, Incorporated.

Marc Koch, M.D., M.B.A.,, Somnia, Incorporated

DR. KOCH: I'd like to thank the committee for allowing me a few minutes to share my thoughts on the petition put forth by the American College of Gastroenterology.

My name is Dr. Marc Koch, and I am a Board Certified Anesthesiologist, Certified Pain Management doctor, and assistant clinical adjunct processor of anesthesia at SUNY at Stoneybrook. I also serve as president and chief executive officer of Somnia. Somnia is an anesthesia management company. In 2006, we will anesthetize over 100,000 patients in the ambulatory setting in nine states.

We are very familiar with the clinical

applications of this drug as specifically discussed here today.

We have seen clinically, in the operating room, in all the states where we cover, where this drug is an extremely potent drug. In the GI literature where they talk about this drug, they talk about giving 30 mg, a few cc's at a time, and discuss how that's safe.

As a practicing anesthesiologist, I can tell you a pure sedative drug like propofol, at a low dose like that, will cause disinhibition. When the sigmoidoscope gets flexed, when something painful occurs, the patient's going to react. What will happen clinically is more frequent doses will be given, and large doses will be given--until such time as the patient cannot move. When the patient cannot move, they have therefore slipped into deep sedation or general anesthesia. That is a clinical reality.

When this drug is being used, it's being used to cause deep sedation or general anesthesia. Even some of the studies by the GI folks have shown

that the BIS monitor--which monitors the level of arousal--indicates that the patients are under general anesthesia.

As other speakers have mentioned here today, there's no antagonist to this drug. The degradation could vary by 20-fold, and the responsive patients could vary remarkably. A dose which could have me talking here to you right now could put somebody else to sleep, and could put somebody else somewhere in between.

The net point I wanted to talk about briefly was specialization. Medicine has come an enormous way through specialization. Fifteen years ago, 20 years ago, when there were just gastroenterologists, now we have hepatologists, nutritionists, pancreatologists--you name it. And that's the because the body of literature, the ability to keep abreast and take the best care of patients is achieved by studying less and knowing more.

And we feel that this petition is taking a step backwards. It's encouraging people--licensed

practical nurses, registered nurses, medical assistants, or other physicians not trained in general anesthesia, to be handling potent anesthetic agents with no reversal agents with no reversal agents. To us that is worrisome, it is dangerous, and the results could be catastrophic.

My third point is the data. The data which they have put forth takes a look at 100,000 patients. Some studies have much less, some a little bit more. If you take a look at their studies, the one thing I could say with absolute certainty is there is no conclusive proof that this medication, used by folks who are not trained in the administration of general anesthesia, in the multitude of settings in which it will be used, will result in the same patient outcomes as in the hands of anesthesiologists or trained anesthesia professionals.

Don't forget: 20 percent of all surgery occurs in physicians' offices. More than half occurs in ambulatory surgery centers. These facilities are far away from an ICU. They're far

away from an emergency room. They're far away from an anesthesia work group.

We're not the only people who feel this way. In addition to the American Society of Anesthesiologists, the American Association of Nurse Anesthetists, the Joint Commission on Accreditation of Health Organizations, the American Association for the Accreditation of Ambulatory Surgical, Facilities, the Nursing Boards of more than 12 states--and additional state legislatures, like Pennsylvania and New Jersey, have said conclusively, without recourse, that this medication should only be used by people who are trained in general anesthesia.

We've also spoken to many anesthesiologists to get their feedback on this: do we speak alone or do we speak in unison? We have over 300 signatures of anesthesiologists, which represents--they're just a little bit less than 1 percent that we got in one meeting, from people who felt the same way.

And the most important point I want to get

to--and I saved what I consider to be my most important point for last: 20 percent of all surgery occurs in office-based facilities. Veristan and SMG marketing have done studies which have shown this to be the case. Many payers are implementing programs to contain costs by shifting procedures from the hospital to the surgery center to office-based surgical facilities. There are fewer indirect costs, and a more cost-effective environment can be achieved. Many payers are initiating programs that are going to shift procedures to less intensive, less costly settings, which means patients are going to receive anesthesia in these settings.

If this label change goes through, we could find up to 20 percent of patients being cared for--from an anesthesia point of view--in environments that are very far away from hospitals, very far away from surgery centers, very far away from ICUs and ERs--20 percent.

I want to just put this in sort of a real situation here. You know, one out of every five of

us who may undergo a procedure may have it occur on the 13th floor of a commercial office building. It may occur in a storefront endoscopy suite, with a check-cashing store on one side, and a grocery store on the other. Would you feel comfortable if the gastroenterologist, along with a medical assistant, was administering you a does of propofol for your procedure? Far away from the hospital, far away from the ER, far away from the ICU?

If you don't feel comfortable with that situation, then I think it speaks for itself about why this petition should be declined.

I'd be happy to answer any questions.

CHAIR FARRAR: Any questions or clarifications?

[No response.]

DR. ROSE: Thank you very much.

CHAIR FARRAR: Okay--thank you.

I believe that that concludes the session. So we conclude the open public hearing session for the Anesthesia and Life Support Drug Advisory Committee Meeting on November 10, 2005.

We will ask for everyone who's not a member of the committee to leave the room. Those that will be participating in the closed session, please have your FDA identification ready, as we'll be signing you in before we re-enter the room.

Thank you.

[Whereupon, at 9:43 a.m., the open meeting concluded, the Committee to reconvene in closed session immediately following.]

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