



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 11 2010

• Richard M. Cooper, Esq.
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, D.C. 20005

Rec'd 8/11/2010

Re: Docket No. FDA-2005-P-0059

Dear Mr. Cooper:

This responds to your citizen petition dated June 27, 2005 (Petition), submitted on behalf of the American College of Gastroenterology.¹ You ask the Food and Drug Administration (FDA or Agency) to remove the following warning from the labeling for Diprivan (propofol) (Petition at 1-2):²

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.

After carefully considering your request, we deny it for the reasons given below. This decision is based on a review of the Petition including the scientific and medical literature accompanying the Petition, the comments submitted on the petition,³ and the experience and judgment of the Agency.

¹ This citizen petition was originally assigned docket number 2005P-0267/CP1. The number was changed to FDA-2005-P-0059 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

² The labeling for a generic drug product approved under an abbreviated new drug application (ANDA) is required to be the same as the labeling for the reference listed drug, with certain permissible differences not relevant here. See 21 U.S.C. 355(j)(2)(A)(v), 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7). Therefore, removal of the warning quoted above from the labeling for Diprivan would require removal of the warning from the labeling for all generic versions of the drug approved under an ANDA as well.

³ More than 300 comments were submitted on this Petition. A majority of the comments came from members of the anesthesiology community asking that we maintain the warning as it is currently written. However, we received a few comments from gastroenterologists, anesthesiologists, and other health care practitioners who believe that the warning should be removed.

FDA-2005-P-0059

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I. BACKGROUND

A. Diprivan

FDA approved a new drug application (NDA) for Diprivan (propofol) injectable emulsion submitted by Zeneca Inc., now AstraZeneca Pharmaceuticals LP (AstraZeneca), on October 2, 1989.⁴ Diprivan is a sterile, nonpyrogenic emulsion containing 10 milligrams (mg)/milliliter (mL) of propofol suitable for intravenous administration.

Diprivan is a sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol induces hypnosis, with minimal excitation, usually within 40 seconds from the start of injection. Diprivan is indicated for use in initiation and maintenance of monitored anesthesia care sedation, combined sedation and regional anesthesia, induction and maintenance of general anesthesia, and intensive care unit sedation of intubated, mechanically ventilated patients.⁵ Diprivan is often used to sedate patients undergoing endoscopic procedures, such as colonoscopy and esophagogastroduodenoscopy procedures.

FDA has also approved a number of ANDAs for generic versions of Diprivan. The labeling for both Diprivan and the generic propofol products includes the warning at issue in the Petition (see footnote 2).

B. Levels of Sedation and Anesthesia

The Joint Commission on Accreditation of Healthcare Organizations' (JCAHO) Comprehensive Accreditation Manual for Ambulatory Care defines the four levels of sedation and anesthesia as follows:

- *Minimal sedation (anxiolysis)*—A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- *Moderate sedation/analgesia (conscious sedation)*—A drug-induced depression of consciousness during which patients respond purposefully to

⁴ APP Pharmaceuticals, LLC is the current holder of the approved NDA (19-627) for Diprivan.

⁵ Diprivan is indicated for use in adults only, except for the induction of general anesthesia (indicated for use in patients three years of age and older only) and maintenance of general anesthesia (indicated for use in patients two months of age and older only).

verbal commands,⁶ either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

- *Deep sedation/analgesia*—A drug-induced depression of consciousness during which patients cannot be easily aroused, but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually impaired.
- *Anesthesia*—Consists of general anesthesia and spinal or major regional anesthesia. It does *not* include local anesthesia. General anesthesia is a drug-induced consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Based on these definitions, patients undergoing endoscopic procedures, particularly colonoscopies, generally require light to moderate sedation, although deep sedation may be required during certain stages of these procedures. It is possible that doses of sedative medications required to induce or maintain a state of deep sedation could inadvertently result in the induction of general anesthesia. Also, studies submitted with your Petition show that the dosing range of propofol required to achieve and maintain sedation during endoscopic procedures overlaps with the range required to achieve and maintain general anesthesia.

C. Relevant Regulations on Warnings and Precautions in Prescription Drug Product Labeling

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug product labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); 21 CFR 201.80(e)). This section must also contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (21 CFR 201.57(c)(6)(ii); 21 CFR 201.80(f)(1)).

⁶ A reflex withdrawal from a painful stimulus is not considered a purposeful response.

II. DISCUSSION

You request that FDA remove the warning from the propofol labeling stating that propofol should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.⁷ You state that propofol has several advantages over alternative sedation agents for endoscopic procedures but has a similar “risk profile” (Petition at 2). You claim the warning is no longer warranted because studies have established that propofol can be administered safely and effectively by medical professionals other than anesthesiologists and nurse anesthetists (Petition at 3-8). You believe that the requested labeling change will promote efficiency and reduce costs to payors by eliminating the need for an anesthesiologist or nurse anesthetist to be present to administer propofol during an endoscopic procedure (Petition at 1). You also suggest that the current warning places an unwarranted restriction on the ability of gastroenterologists to practice medicine (Petition at 1).

After considering your claims and the literature you provided for our review, we conclude that you have not shown that the warning is no longer warranted or appropriate. In fact, we conclude that the warning is warranted and appropriate in light of the significant risks associated with propofol, and we further conclude that the warning should help ensure that propofol is used safely. Accordingly, we will not seek to have the warning removed, reduced, or otherwise amended.

A. The Warning Is Warranted and Appropriate in Light of the Risks Associated with the Use of Propofol as a Sedation Agent for Endoscopic Procedures

You state that while propofol has several advantages over alternative sedation agents for endoscopic procedures, “the risk profile of propofol appears to be no worse than” these alternative agents. (Petition at 3). We disagree. As explained below, we believe the risks associated with propofol are significantly different from — and, in some critical respects, greater than — the risks associated with the alternative sedation agents you

⁷ The warning at issue has two components: that propofol should be administered only by persons trained in the administration of general anesthesia and that the person administering propofol should not be otherwise engaged in the conduct of the procedure. While you request that the entire warning be removed (Petition at 2, *passim*), your petition only addresses the first component of the warning. Specifically, while you contend that “[a] number of controlled and uncontrolled clinical studies have established that propofol can be administered safely and effectively by medical professionals other than anesthesiologists or nurse anesthetists” (Petition at 2), you do not appear to contend that any studies support the position that propofol could be administered safely and effectively by medical professionals — whatever their training — whose attention is divided between administering propofol and conducting the procedure itself. Nevertheless, we discuss both components of the warning in this response.

mention. We further conclude that the warning you seek to have removed is warranted and appropriate in light of the unique risks posed by propofol.

You claim that propofol is superior to alternative agents such as Versed (midazolam) and Demerol (meperidine) because it induces sedation more rapidly than a midazolam-meperidine or midazolam-fentanyl combination, results in faster recovery times than midazolam with meperidine or midazolam with fentanyl, and is associated with better post-procedure functioning than alternative sedation drugs (Petition at 2).⁸ We agree that because of the quick onset and offset of sedation associated with propofol, along with a clear sensorium following its use, practitioners might choose propofol over the routinely used alternative sedation agents for short endoscopic procedures. The issue, however, is not propofol's therapeutic advantages over alternative agents, but the safety of propofol as a sedation agent relative to the administrator's level of training in the administration of general anesthesia and relative to whether the administrator is taking part in the procedure apart from administering propofol.

You acknowledge that propofol has risks that make it unique and uniquely demanding to administer among agents used for procedural sedation (Petition at 2).⁹ We agree. Propofol has a narrow therapeutic window, that is, a narrow dosage range that produces the desired effect while staying within the safety range. The additional dosing required to deepen sedation from one level to the next is small. This means that propofol poses a significant risk that a level of sedation greater (or lesser) than that intended may be induced.

Over-sedation with propofol poses especially serious risks. Propofol is a cardiovascular depressant that causes a drop in blood pressure as well as a respiratory depressant that can cause partial airway obstruction. In particular, the possibility of apnea with arterial oxygen desaturation and hemodynamic changes, most notably hypotension, increases

⁸ We note that propofol and the alternative sedation agents you mention are in different drug classes. Fentanyl and meperidine are narcotics and not indicated for sedation. Their analgesic properties and sedative side effects allow for a significant reduction in the amount of other medications required to produce a desired level of sedation. The side effects of narcotics, particularly their respiratory depressive effects, may be enhanced when they are co-administered with benzodiazepines, like midazolam, or sedative-hypnotics, such as propofol.

Midazolam is a short-acting benzodiazepine that is indicated for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures, such as bronchoscopy, gastroscopy, and cystoscopy, among others. Midazolam, which was approved after meperidine and fentanyl, contains both a boxed warning and a partially bold warning providing detailed information on the risks involved with its use, the equipment and drugs that should be readily available when it is used, and the types of monitoring that should be used.

⁹ While the risks associated with propofol use are dose dependent, the risks pertain to patients receiving propofol for sedation as well as for general anesthesia. As the studies you submit in support of your Petition show, the propofol dose ranging used to sedate patients for endoscopic procedures, particularly colonoscopies, overlaps with propofol dose ranging used to achieve and maintain general anesthesia.

with deepening levels of sedation. These side effects tend to occur suddenly and can be of life-threatening magnitude if appropriate intervention is not instituted immediately. Furthermore, as you acknowledge, there is no reversal agent for propofol (Petition at 2), whereas there are reversal agents for the other routinely used sedation agents. A propofol dose which exceeds that needed to maintain moderate-to-deep sedation may require treatment including assisted ventilation and hemodynamic support until the patient's own spontaneous ventilation resumes.

For endoscopic procedures, particularly colonoscopies, a light-to-moderate level of sedation is needed for less stimulating parts of the procedure. However, the anesthetic requirements often increase substantially during the more painful portions of the procedure (for example, when negotiating the colonoscope through the splenic and hepatic flexures). Hence, a state of deep sedation is likely to be induced during the more painful parts of the procedure to manage pain and minimize patient movement and the concomitant risk of bowel perforation. Dosing of propofol to achieve such states of sedation has been associated with unintended induction of general anesthesia and the attendant respiratory and hemodynamic risks just described.

Under-sedation also poses risks. For example, as just noted, the risk of unnecessary patient pain or even bowel perforation during a colonoscopy may increase if an insufficient amount of propofol is administered. An inexperienced or insufficiently trained medical professional not confident in his or her ability to intervene in response to over-sedation may err on the side of administering an insufficient dose of propofol, increasing the risk of adverse events associated with under-sedation.

Furthermore, many patients presenting for endoscopic procedures are older, frequently have multiple co-morbidities, and are generally on multiple medications. Each of these factors increases the risks associated with using propofol as a sedation agent, particularly the risks of oxygen desaturation and wide swings in blood pressure.

In sum, the medical professional administering propofol should have the requisite experience, training, judgment, and undivided focus to achieve and maintain the various levels of sedation appropriate for the procedure and to monitor the patient continuously throughout the procedure and intervene quickly and appropriately as necessary.¹⁰ This means the individual in question must be qualified to detect and manage the airway, cardiovascular, and hemodynamic changes that occur when a patient enters a state of general anesthesia, and to quickly detect and respond to any complications that may arise. The warning at issue appropriately describes the clinical expertise needed to manage the risk associated with propofol as well as the need for that expertise to be dedicated solely to administering and monitoring effects of the anesthetic throughout the procedure.

¹⁰ This is especially true for endoscopic procedures, where the level of stimulation varies greatly and frequently.

Individuals trained in the administration of general anesthesia and not otherwise involved in the conduct of the procedure should be capable both of minimizing the incidence of these complications and handling them appropriately should they occur.¹¹ Others not so trained, or whose attention is divided between administering propofol and conducting other tasks associated with the procedure, may not be.

We note that the warning is consistent with the findings and policies of JCAHO, the American Association for Accreditation of Ambulatory Surgery Facilities, the Accreditation Association for Ambulatory Health Care, Inc., and the American Society of Anesthesiologists. According to the JCAHO's revised standard, *Moderate and Deep Sedation and Anesthesia Standards*, individuals administering moderate or deep sedation and anesthesia must be qualified and have the appropriate credentials to manage patients at whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally. Those practitioners must be qualified to rescue patients from general anesthesia and be competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation. A sufficient number of qualified personnel (in addition to the licensed independent practitioner performing the procedure) must also be present during the procedure to provide moderate or deep sedation.

Accordingly, we disagree with your assertion that the risk profile of propofol when used in endoscopic procedures appears to be comparable to that of alternative sedation agents. More importantly, we believe both components of the warning you seek to have removed are, in fact, appropriate and well warranted in light of the risks posed by the use of propofol — which you seem to acknowledge are both significant and materially different from those posed by the routinely used alternative sedation agents (Petition at 2). Thus, we believe that the warning should help ensure that propofol is used safely.

B. The Studies Submitted Fail to Show that the Warning is Unwarranted

You submitted 31 publications with your Petition. You assert that studies reported in these publications show that gastroenterologists and nurses supervised by them can safely and effectively administer propofol to patients for endoscopic procedures even without training in the administration of general anesthesia (Petition at 3). As previously noted (see footnote 7), your contentions concerning these studies appear to be limited to the first component of the warning (training in general anesthesia), but you seek to have the second component of the warning (involvement in the conduct of the procedure) removed as well. We address both components below.

Among the publications you submitted were 13 papers reporting on studies involving propofol administration by non-anesthesia trained personnel, 10 abstracts, a review

¹¹ The warning does not specify what constitutes sufficient training.

article, 4 opinion papers, a historical review, a case report, and a paper discussing cardiovascular complications occurring in the gastrointestinal clinic setting. While the Agency respectfully considers the opinions proffered by experts, it places greater weight on the findings of studies that are prospective, randomized, and controlled by design, adequately powered to discern outcome differences between study arms for the primary endpoint(s), and appropriately executed according to the protocol. Because the opinion papers indicate there are proponents on both sides of this issue, and the historical perspective and review articles provide no substantial data for consideration, we only evaluated the abstracts, study reports, and safety information from the case report and cardiovascular complications report.

We have reached the following conclusions based on our analysis of the articles you submitted in connection with your Petition:

- There is a significant risk of adverse events due to over-sedation when using propofol for procedural sedation, including oxygen desaturation, hypoxemia, hypotension, and bradycardia. These events can result in serious injury or death if appropriate intervention is not instituted immediately.
- Vulnerable populations, like the elderly, who often require endoscopic procedures for diagnostic and therapeutic purposes, are especially at risk of adverse events associated with propofol sedation.
- The only study comparing the safety of administration of propofol by anesthesiologists with administration of propofol by a GI (gastrointestinal) provider (i.e., a gastroenterologist or a nurse supervised by a gastroenterologist) suggests that the risk of cardiopulmonary complications is significantly reduced when propofol is administered by anesthesiologists.¹²
- In several studies assessing the relative safety of propofol versus other sedation agents administered by a GI provider, the frequency and extent of adverse events were quite significant for *both* sedation methods.¹³
- In several studies assessing the safety of administration of propofol by a GI provider with no comparator arm (i.e., no alternative sedation agent), the frequency and extent of adverse events were quite significant.¹⁴

¹² Vargo JJ et al. Cardiopulmonary complications with non-anesthesiologist-administered propofol vs. standard sedation: the CORI experience. *Gastrointest. Endosc.* 2004;59:AB132.

¹³ Vargo JJ et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology* 2002;123(1):8-16. Koshy G et al. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am. J. Gastroenterol.* 2000;95:1476-79. Carlsson U, Grattidge P. Sedation for upper gastrointestinal endoscopy: a comparative study of propofol and midazolam. *Endoscopy* 1995;27:240-43.

¹⁴ Cohen LB et al. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest. Endosc.* 2004;59:795-803. Cohen LB et al. Propofol for endoscopic sedation: a protocol for safe and effective administration by the gastroenterologist. *Gastrointest. Endosc.* 2003;58:725-32. Walker JA et al. Nurse-administered propofol sedation without anesthesia

- In several studies assessing the safety of administration of propofol by non-anesthesiologists, the GI providers received training — sometimes several months of training — from anesthesiologists.¹⁵ This included elements of training associated with the administration of general anesthesia (e.g., airway management techniques, advanced respiratory monitoring). Furthermore, several authors emphasized the need for adequate training before GI providers could administer propofol safely and effectively.¹⁶
- Several authors concluded that administration of propofol by GI providers was sufficiently safe despite the occurrence of significant sedation-related adverse events and despite the lack of any comparator arm in the studies on which they based their conclusions.¹⁷

Having carefully reviewed the studies you submitted, we first conclude that there are no data from prospective, randomized, adequately-powered,¹⁸ well-controlled clinical trials that demonstrate that gastroenterologists or nurses supervised by them who are not trained in the administration of general anesthesia can administer propofol safely and effectively. Furthermore, we conclude that the studies you submitted do not support your contention that the first component of the warning is unwarranted or inappropriate. In fact, we believe the studies, taken as a whole, support the opposite conclusion. Specifically, the studies tend to show that the risks posed by the use of propofol to sedate patients for endoscopic procedures are significant, and that substantial training, experience, and professional judgment are necessary to sufficiently mitigate those risks. Accordingly, we consider the first component of the warning wholly appropriate and warranted.

specialists in 9152 endoscopic cases in an ambulatory surgery center. *Am J. Gastroenterol.* 2003;98: 1744-50.

¹⁵ Yusoff IF et al. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. *Gastrointest. Endosc.* 2004;60:356-60. Walker JA et al. 2003 (see supra footnote 14). Heuss LT et al. Conscious sedation with propofol in elderly patients: a prospective evaluation. *Aliment. Pharmacol. Ther.* 2003;17:1493-1501. Heuss et al. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases. *Gastrointest. Endosc.* 2003;57:664-71. Heuss LT et al. Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients: a prospective, controlled study. *Am. J. Gastroenterol.* 2003;98:1751-57.

¹⁶ Yusoff IF et al. 2004 (see supra footnote 15). Kulling et al. Anesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. *Endoscopy* 2003;35:679-682.

¹⁷ Walker JA et al 2003 (see supra footnote 14). Heuss LT et al. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases. *Gastrointest. Endosc.* 2003b;57:664-71. Rex DK et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am. J. Gastroenterol.* 2002;97:1159-63.

¹⁸ We note that, as there are low rates of morbidity and mortality associated with sedation, adequately powering a study purporting to show that GI providers can safely and effectively administer propofol for endoscopic procedures is likely to require enrollment of large numbers of patients.

Furthermore, we believe your specific contention that GI providers administering propofol for sedation for endoscopic procedures poses no greater risks than GI providers administering benzodiazepine (together with a narcotic) is not sufficiently supported by the literature you submitted. Shortcomings in the relevant studies include differing findings for the cardiovascular versus respiratory outcomes, evaluation of oxygen saturation but not the hemodynamic changes during sedation, and reporting of findings in a manner that precluded further analysis or interpretation of the data. Also, as noted above, we are concerned with the frequency and extent of adverse events reported for *both* treatment arms in several of those comparison studies.

Accordingly, the contention that the incidence of adverse events was similar gives us no comfort.¹⁹ Finally, we are skeptical that the studies in question — even if the flaws just discussed were not present — could reliably predict real-world outcomes. GI providers participating in the studies you submitted may well have greater levels of training, experience, or proficiency administering propofol than the average GI provider.

We also conclude that none of the studies you have presented support your position that the second component of the warning is unwarranted and should be removed. As discussed in the previous section, we believe the warning's admonition that the person administering propofol should not be otherwise involved in the conduct of the procedure is appropriate and warranted because adverse events associated with propofol can occur suddenly and must be addressed immediately.

Accordingly, we do not find the studies you submitted persuasive, and we continue to believe, for the reasons expressed here and in the previous section, that the warning that propofol should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure is appropriate and warranted in light of the risks associated with the administration of the drug.

C. Increased Procedural Costs Do Not Support Removal of the Warning

You assert that, in accordance with the warning you seek to have removed, as many as 12 states and many hospitals require that propofol be administered only by anesthesiologists or nurse anesthetists (Petition at 2). This increases the costs of using propofol for

¹⁹ We further note that it appears that the amount of the alternative sedation agent administered in several of these studies was higher than may be indicated on the relevant drug labeling for the procedures studied. Vargo JJ et al 2002 (see supra footnote 13); Ulmer BJ, et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. Clin. Gastroenterol. Hepatol. 2003;1:425-32. To the extent the risks associated with these alternative agents are dose dependent, higher-than-normal dosing would tend to increase the incidence of complications associated with the alternative sedation agent, making propofol look safer by comparison.

endoscopic procedures because an anesthesiologist or nurse anesthetist must be present to administer propofol during an endoscopy, resulting in higher costs than if the drug were administered by the gastroenterologist or nurse working under his or her direction. (Petition at 2-3).

We first note that the warning does not state that only anesthesiologists or registered nurse anesthetists may administer propofol – it simply warns that only those “trained in the administration of general anesthesia” should administer the drug.

Hospitals and state credentialing authorities set their own rules and policies regarding the administration of drugs; FDA is not involved in that process.²⁰

You represent that the services of an anesthesiologist add about \$100 to \$400 to the cost of an endoscopic procedure (Petition at 3).²¹ But as discussed in Part II, the risks associated with propofol are significant and may result in serious injury or death. Accordingly, we continue to think the warning at issue is warranted and appropriate in light of the significant risks posed by propofol, despite any increased costs that may be associated with this warning.

D. The Warning Does Not Unduly Restrict the Practice of Gastroenterologists

You state that the requested labeling change would eliminate an unwarranted restriction on the practice of gastroenterologists (Petition at 1, 8). We disagree.

We first note that the warning simply provides guidance as to the nature of the clinical skills that allow for the safe use of propofol, and neither prohibits the use of propofol by any group of health care providers nor limits its use to a particular medical specialty.

Next, to the extent that some hospitals and state credentialing authorities have determined that only anesthesiologists or registered nurse anesthetists may administer propofol, we note again that these institutions set their own rules regarding the administration of drugs, and, in the case of propofol, they may have done so for reasons other than (or in addition to) the warning on the approved labeling (see footnote 20).

²⁰ As previously noted (see section II.A), the warning is consistent with the findings and policies of JCAHO, the American Association for Accreditation of Ambulatory Surgery Facilities, the Accreditation Association for Ambulatory Health Care, Inc., and the American Society of Anesthesiologists. Hospitals and states that restrict those who may administer propofol may be influenced by these institutions' positions quite apart from (or in addition to) the warning in the approved labeling. For that matter, they may simply be following their own judgments about the risks attending propofol use.

²¹ You make no representations concerning the costs associated with using a registered nurse anesthetist to administer propofol for an endoscopic procedure.

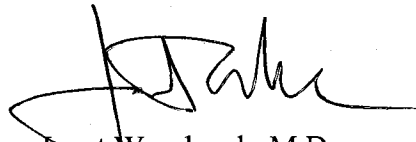
Finally, regardless of whether the warning can be said to restrict the practice of gastroenterologists, we continue to believe it is appropriate and warranted in light of the significant risks associated with propofol.

III. CONCLUSION

For the reasons described, we conclude that you have not demonstrated that the warning is inappropriate or unwarranted. In fact, we conclude that both components of the warning are appropriate in light of the significant risks associated with propofol, and we further conclude that the warning should help ensure that propofol is used safely. We therefore will not seek to have the warning removed, reduced, or otherwise amended.

For the reasons stated above, your Petition is denied.

Sincerely,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', with a stylized, flowing script.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research