Propofol Use in the Outpatient Setting
Education Committee
Enterprise Risk Management Task Force

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Propofol Enterprise Risks

Affects Multiple Risk Domains
- Legal and Regulatory Risk
- Financial Risk
- Technology Risk
- Human Capital Risk
Propofol: The Benefits

Intravenous Sedative Hypnotic agent used in the induction and maintenance of anesthesia and sedation.

– Provides a faster onset of sedation (40 seconds) and rapid recovery with little or no residual drowsiness.

– Administered in multiple venues

10/12/2011
Increased Use of Propofol for Sedation

- GI Endoscopy units
- Procedural sedation in the ED
- MRI sedations in Radiology
- Cardioversions in Cardiology
What Are the Risks?

- Considered a high risk medication by the Institute of Safe Medication Practices.

- May be unpredictable with rapid profound effects, including respiratory arrest.

- No reversal agents exist—patients must be intubated with assisted respiration and or require CPR.

10/12/2011
What are the Legal Risks?

Case # 1 “Believing that propofol was “used all the time in ICU, a gastroenterologist asked a nurse to prepare 10 ml (10 mg per ml) of the drug for a patient undergoing endoscopy. The nurse obtained the drug from an automated dispensing cabinet via override before she transcribed the order to the patient’s record.
What are the Legal Risks?

After questioning the physician about the dose, 100mg—a very high dose, she began administering the drug via an infusion pump. The patient suddenly went into respiratory arrest. Fortunately, ICU staff were able to help with the emergency and quickly intubated and ventilated the patient.

— (Source ISMP)
What Are the Legal Risks?

2009 Case # 2 - A patient with sleep apnea died during a routine colonoscopy. The patient told the CRNA that he had had difficult intubations in the past and also needed to use a continuous positive airway pressure machine while sleeping. The CRNA administered a lower dose of Propofol but the patient’s condition deteriorated. The CRNA tried intubate but could not manage. A cricothyroidotomy was done and CPR lasted 45 minutes which was unsuccessful. The family alleged the CRNA should have been supervised while administering anesthesia. No trial date has been set.

(source: Outpatient Surgery Magazine E-weekly Newsletter, May 10, 2010.)
What Are the Legal Risks?

Case #3 A 40-year-old patient was admitted with injuries to the face and subarachnoid hemorrhaging. The patient received propofol but was not intubated. The patient was then taken to radiology for a CT scan. While in radiology, the patient became bradycardic and suffered a cardiac arrest. The patient was resuscitated but died two days later.

(Source: PA Patient Safety Advisory, Vol. 3 2006)

10/12/2011
What are the Regulatory Ramifications?

The revised 2011 CMS Interpretive Guidelines requires hospitals to establish and implement policies and procedures based on nationally recognized guidelines addressing whether specific clinical situations involve anesthesia versus analgesia.

The new revisions do not alter CMS’s position that only the persons delineated at 42 CFR 482.52(a) may provide general anesthesia, regional anesthesia and monitored anesthesia care/deep sedation.)

10/12/2011
What Are the Regulatory Ramifications?

Condition of Participation-Anesthesia 42 CFR 482.52(a)

- Considered deep sedation/analgesia and included in Monitored Anesthesia Care. May only be administered by a qualified anesthesiologist; a doctor of medicine or osteopathy; a dentist, oral surgeon or podiatrist who is qualified to administer anesthesia under state law; a CRNA under supervision of an anesthesiologist who is immediately available if needed; and an anesthesiologist assistant who is under supervision of an anesthesiologist who is immediately available.
JCAHO Standards

Requires a sufficient number of staff, in addition to the person performing the procedure, be present to perform the procedure, monitor and recover the patient.

Standards include ensuring that qualified individuals have credentials and privileges and/or proven competencies to manage and rescue patients at whatever level of sedation or anesthesia is planned for and/or achieved. (JCAHO Standard PC.13.20)
What Are the Regulatory Ramifications?

The FDA considers Propofol to be an anesthetic agent and should be administered by persons trained in the administration of general anesthesia.
FDA Rejects Petition to Remove Restrictive Labeling on Propofol

Manufacturer labeling: Propofol is used in patients who are not intubated or mechanically ventilated in a CCU, the drug should only be administered by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.
Financial Risk: Reimbursement Issues

Unwillingness of insurers to reimburse anesthesia care for some procedures such as diagnostic endoscopy has increased the use of nurse-administered propofol.

Untrained nurses may be caught in the middle of the debate and feel pressured to administer propofol.
Human Capital Risk

Nurse-administered Propofol falls under each state's Nurse Practice Act.

More than a dozen states specifically consider this function beyond the scope of nursing practice.

New York State Board of Nursing: “Propofol is not an appropriate agent for administration by Registered Nurses unless they are CRNAs. The only exception are intubated and ventilated patients in a CCU based on an appropriate medical order.”

10/12/2011
Societies Endorsing Nurse-Administered Propofol

- The American College of Gastroenterology-RN’s can administer under their supervision.
- American Society of Gastroenterology Nurses
Technology Issues and Standards

Who Sets the Standards for Monitoring Patients in the Outpatient Setting?

- Supplemental oxygen
- Oxygen saturation
- Airway management
- Use of Capnography to monitor end-tidal CO2 as an indicator of respiratory depression before a patient becomes hypoxic. Not always used in endoscopy procedures. (recommended by ASA)
- Availability of Rapid Response Teams for patients who slip into deep sedation.

10/12/2011
Recommended Safety Practices
Established by One Hospital

- All patients scheduled to receive Propofol are required to arrive 1 ½ hour before the procedure to be evaluated by an anesthesiologist. Based on the evaluation, the procedure can be performed in the OR suite.
- Pre-screening by an Anesthesiologist of patients with ASA III and above.
- All providers who are allowed to use Propofol sedation must be appropriately trained and credentialed. (Source: Board of Registration in Medicine: Use of Propofol in the Outpatient Setting. August, 2011.)
Thanks!
Use of Propofol in the Outpatient Setting
Erin M. Donovan, Director of Quality & Risk & Deborah Black-Pisick, RPh, Clinical Manager, Pharmacy
Lowell General Hospital

Propofol, an intravenous sedative hypnotic agent used for the induction and maintenance of anesthesia and sedation, is being used with increasing frequency at Lowell General and other hospitals for sedation in the endoscopy setting. Reasons for this increase in use include faster onset of sedation, a more rapid recovery, little or no residual drowsiness after awakening, no interference with GI motility, and increased patient and practitioner satisfaction. Propofol is highly lipid soluble, and has a much faster onset of action than does midazolam. It also has a very short plasma half life (1-4 minutes), compared with that of midazolam (30 minutes), allowing for rapid recovery without the amnesia sometimes associated with midazolam. The biggest risk associated with propofol is its narrow therapeutic index that may produce a deeper level of sedation than desired with a relatively small change in dose. In addition, unlike benzodiazepines, there is no reversal agent available for propofol, but the effects of even a higher than desired dose generally do not last for more than a few minutes. In addition, any adverse effect will be seen while the medication is being administered, unlike benzodiazepines, which due to active metabolites, may cause prolonged symptoms after the procedure.

Lowell General Hospital took a fresh look at safety practices surrounding the use of propofol in Endoscopy following an adverse case outcome. A 61 year old woman underwent a colonoscopy with propofol administered by an experienced CRNA. She was closely monitored throughout. Shortly after the procedure, she began to develop tachypnea and hypoxemia. Her condition continued to worsen and she was ultimately admitted to the ICU and intubated.

A close examination at this case revealed several issues. The patient was not a good historian and key elements of her past surgical and medical history had not been shared with her endoscopy team. She had multiple healthcare providers in the outpatient setting. Our review prompted the team to reconsider the evaluation and clearance process for propofol patients.

Given the very low rate of serious occurrences in this outpatient setting, it also became clear, that there was no clear protocol for management of these patients once an adverse event occurred. Was the patient best managed under the Anesthesiologist or under the Gastroenterologist? Where should the patient continue to be treated? In Endoscopy or PACU? What kind of support is available in the outpatient setting?

Members of the Anesthesiology and Gastroenterology departments met to evaluate our systems and improve the safety of our patients. The following practices were put into place:

1. Patients with an ASA class of III and above who require propofol sedation for their endoscopy procedure are now required to be seen in pre-screening by an Anesthesiologist. Pre-screening generally occurs two weeks ahead of the planned procedure. This allows the Anesthesiologist to evaluate the patient and triage the procedure to the appropriate site, whether that be Endoscopy or the OR.

2. All patients scheduled to receive propofol are required to arrive 1½ hours before their procedure to be evaluated by an Anesthesiologist. This allows adequate time for the Anesthesiologist to gather a medical history and request and review blood tests, electrocardiograms, and radiology reports. Based on the anesthesiologist’s evaluation of the patient, the procedure can be rescheduled to be performed in the OR suite.

3. Clear protocols were put into place for staff to access medical assistance following these types of procedures. The gastroenterologist was designated the primary provider responsible for the patient’s continuing medical care. The scope of the hospital’s internal Rapid Response Team areas was further broadened to include service to outpatient areas as needed.

In addition to Endoscopy, propofol is used in other outpatient locations for example, cardioversions in Cardiology and MRI sedations in Radiology. Block time was established in these areas for propofol cases. By scheduling set times, Anesthesiology was able to assign staff to actively assess and manage these patients as well as support the other units who rely on their services, including the main OR and Labor & Delivery.

These safety measures have proved beneficial to date. Patients undergo a much more thorough assessment and as a result several propofol cases have been shifted to the OR. Serious adverse incidents related to the use of propofol have been non-existent. These steps have provided a much safer environment for our patients and greater security for our staff.
Dear Mr. Cooper:

This responds to your citizen petition dated June 27, 2005 (Petition), submitted on behalf of the American College of Gastroenterology. 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):  

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, 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.
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 esophagastroduodenoscopy 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

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\(^4\) 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, 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)).

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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). 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). 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

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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. 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.

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\[10\] 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. 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

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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.\(^\text{12}\)
- 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.\(^\text{13}\)
- 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.\(^\text{14}\)


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. 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.

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.

Having carefully reviewed the studies you submitted, we first conclude that there are no data from prospective, randomized, adequately-powered, 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.


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,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Who Administers Propofol in Your Organization?

What are the necessary credentials for administering propofol (DIPRIVAN) for moderate and deep sedation? Healthcare facilities in Pennsylvania and across the country are asking this question. The American College of Gastroenterology and others contend that the safety profile of propofol is such that a gastroenterologist, registered nurse under their supervision, and other “qualified medical professionals” can safely and effectively administer the drug without specific training in the administration of general anesthesia. However, drug manufacturers and several anesthesiology professional organizations believe this may place patients at undue risk. What constitutes safe practice for this high-alert medication?

At Issue
The use of propofol during endoscopic, radiologic, and other procedures is growing in hospitals, ambulatory surgical facilities, and physician offices across the country. Propofol offers certain advantages over other drugs used for sedation when used by trained and credentialed practitioners because it:

- Has a rapid onset and a short duration of action.
- Allows patients to wake up, recover, and return to baseline activities and diet sooner than some other sedation agents.
- Reduces the need for opioids, resulting in less nausea and vomiting.

However, practitioners may develop a false sense of security, allowing the perceived safety profile of propofol to influence their belief that the drug poses minimal risk. In untrained hands, propofol can be deadly. Administration to a non-ventilator-assisted patient by a practitioner who is not trained to administer drugs that cause deep sedation and general anesthesia is not safe, even if the drug is given under the supervision of a physician performing the procedure.

Further complicating the situation is that several insurance companies have decided that propofol administration in the office setting by gastroenterologists or their assistants is acceptable and safe for some procedures. Therefore, these insurers will no longer reimburse for anesthesiology services performed for some procedures in office settings. In the article “RNs Pushing Propofol,” Meltzer states that this unwillingness to reimburse anesthesia care for procedures in which propofol is used, such as diagnostic endoscopy, has increased the use of nurse-administered propofol. As a result, untrained practitioners may be caught in the middle of the debate and feel pressured to administer propofol.

Medication Errors
The Pennsylvania Patient Safety Reporting System (PA-PSRS) has received over 100 medical and medication error reports in which the use of propofol has been cited. Sixteen percent (16%) of these reports have been classified as Serious Events, including four patient deaths in which propofol may have played a role. Here is one example:

A 40-year-old patient was admitted with injuries to the face and subarachnoid hemorrhaging. The patient received propofol but was not intubated. The patient was then taken to radiology for a CT scan. While in radiology, the patient became bradycardic and suffered a cardiac arrest. The patient was resuscitated but died two days later.

Another example was reported by the Institute for Safe Medication Practices (ISMP) in November 2005. A gastroenterologist who thought propofol was “used all the time in ICU” asked a nurse to prepare “10 mL” (10 mg/mL) of propofol for a patient undergoing endoscopy. The nurse retrieved the drug from an automated dispensing cabinet via the override function. Another nurse who was trained in the use of moderate sedation, but not deep sedation or anesthesia, assisted the gastroenterologist. She questioned the physician regarding the dose but began administering the propofol via an infusion pump. The patient experienced respiratory arrest. Fortunately, other ICU staff members were able to help with the emergency and quickly intubated and ventilated the patient.
Another case involved a physician who thought he could safely administer propofol while performing breast augmentation. However, he and his surgical assistant, neither of whom were able and/or qualified to monitor patients under deep sedation or anesthesia, failed to recognize the patient’s rapidly deteriorating respiratory status. The patient, a young woman, died of hypoxic encephalopathy.

In another example, nurses in one particular facility have reported being asked to administer “a little more” propofol if the patient moved after the anesthesiologist left the room. In these cases, the anesthesiologist would leave the propofol syringe attached to the IV port after placing the block and leave the nurses in the room to monitor the patient. The nurses reluctantly complied initially. Later, they brought the issue to the attention of hospital leaders, citing that they were worried about the safety of this practice.

Professional Society Viewpoints
There is a difference in opinion among professional societies about the necessary credentials for individuals administering propofol for sedation. In brief, the American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists, and American Association for Accreditation of Ambulatory Surgery Facilities believe that safe administration of propofol to non-ventilator-assisted patients is limited to individuals trained in the administration of general anesthesia who are not simultaneously involved in the procedure. The ASA also suggests that, if this is not possible, non-anesthesia staff who administer propofol be qualified to rescue patients whose level of sedation becomes deeper than intended and who enter, if briefly, a state of general anesthesia. The ASA’s “Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists” is available on their website.

In contrast, the American College of Gastroenterology, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, and Society of Gastroenterology Nurses and Associates endorse nurse-administered propofol under the direction of a physician if state regulations allow it, if the nurse is trained in the use of drugs causing deep sedation, and if the nurse is capable of rescuing patients from general anesthesia or severe respiratory depression.

Joint Commission on Accreditation of Healthcare Facilities (JCAHO) Standard
JCAHO Standard PC.13.20 requires, for the administration of moderate or deep sedation, that a sufficient number of staff, in addition to the person performing the procedure, be present to perform the procedure, monitor and recover the patient. The person administering the sedative agent must be qualified to manage the patient at whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally. While there may be a need for additional monitoring personnel for the procedure, the person administering the sedation must be qualified to monitor the patient.

Product Labeling
Manufacturers of propofol state in the product labeling that:

- The drug should be administered only by persons trained in the administration of general anesthesia and not involved in the surgical/diagnostic procedure.
- Monitored anesthesia care (MAC) patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation.

The official labeling also indicates that propofol should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management when sedating intubated, mechanically ventilated adult patients in the ICU.

The American College of Gastroenterology has petitioned the FDA to remove the following text from the DIPRIVAN (propofol) product label: “For general anesthesia or 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.” However, the FDA has not made a final ruling on this petition, and as of March 2006 the labeling as presented above continues to be the official and approved labeling for propofol products.

Variable Effects
Propofol dosing and titration is variable, as it is based on the patient’s response and tolerance to the drug. Profound changes in respiratory status can occur rapidly. A patient can go from breathing normally to a full respiratory arrest in seconds, even at low doses, without warning from typical assessment parameters.
Who Administers Propofol in Your Organization? (Continued)

No Reversal Agent
Unlike other agents used for sedation (e.g., midazolam, morphine), propofol has no reversal agent.

State Boards
More than a dozen states specifically consider nurse-administered propofol beyond the scope of nursing practice according to their Nurse Practice Acts. Pennsylvania does not have an official advisory opinion or declaratory statement regarding the administration of propofol by nurses.

The Pennsylvania Code stipulates that the administration of anesthesia is a proper function of a registered nurse who has successfully completed an accredited education program for nurse anesthetists and who works in cooperation with a surgeon or dentist. The code also specifies that a registered nurse who is not a certified registered nurse anesthetist may administer intravenous conscious sedation medications during minor therapeutic and diagnostic procedures.

Safe Practice Strategies
Unfortunately, there is no easy answer to the question of who to allow to administer propofol in your organization. The process requires input from many parties. A good first step may be to convene a multidisciplinary team consisting of administration, nurses, pharmacists, and physicians (including representatives from anesthesia, gastroenterology, radiology, surgery, and other physicians from areas that may administer or monitor propofol) to:

- Review state regulations to ascertain which practitioners may or may not be able to administer propofol within their respective scope of practice.
- Evaluate the literature and various position statements available from professional societies such as the ASA, American Association of Nurse Anesthetists, and others. See the Resources section below for selected societies and web addresses.
- Establish policies and practice guidelines for the administration of propofol (or other agents such as thiopental, methohexital, or etomidate) to non-ventilator-assisted patients undergoing minor surgical or diagnostic procedures.
- Define qualifications of professionals who can administer propofol to non-ventilator-assisted patients during procedures.
- If nurse-administered propofol is agreed upon as acceptable, specify the circumstances and required education and mentorship to be accomplished beforehand and competencies to be evaluated and met periodically. Keep in mind that ACLS certification alone may not be sufficient for this purpose.
- Evaluate locations where propofol administration is appropriate, and ensure that those areas are able to follow the developed criteria for administration, including expertise and availability of equipment to intubate patients.
- Define and document the intended level of sedation that patients should receive. Ensure that all patients, even if moderate sedation is intended, are able to be monitored and rescued from deep sedation.
- Establish a continuous monitoring process and assessment criteria (e.g., vital signs, oxygen saturation, capnography) for non-ventilator-assisted patients who are receiving propofol.
- Ensure that equipment is readily accessible at the point of care to maintain a patent airway, provide oxygen, intubate, ventilate, and offer circulatory resuscitation.

Conclusion
Propofol, an injectable emulsion, is a high-alert medication according to ISMP. Based on the action and nature of the medication and the number of error reports submitted to PA-PSRS and other organizations, the safest strategy is to limit propofol use to healthcare professionals with specialized training in administering, monitoring, and treating its untoward effects. However, errors can still occur despite the presence of a trained healthcare professional. The largest number of events involving propofol received by PA-PSRS occurred in the ICU and OR—practice settings designed with constant supervision in place.

While the debate will continue over the appropriate credentials for administering and monitoring propofol, one thing is clear: whenever propofol is used for sedation/anesthesia, it should be administered only by persons who are capable of recognizing and treating any untoward effects with this largely beneficial, but potentially deadly, agent.

Resources
American Society of Anesthesiologists (www.asahq.org)
American Association of Nurse Anesthetists (www.aana.com)
Who Administers Propofol in Your Organization? (Continued)

American Association for Accreditation of Ambulatory Surgery Facilities (www.aaaasf.org)

American College of Gastroenterology (www.acg.gi.org)

American Gastroenterological Association (www.gastro.org)

American Society for Gastrointestinal Endoscopy (www.asge.org)

Society of Gastroenterology Nurses and Associates (www.sgna.org)

Notes


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The Patient Safety Authority is an independent state agency created by Act 13 of 2002, the Medical Care Availability and Reduction of Error ("Mcare") Act. Consistent with Act 13, ECRI, as contractor for the PA-PSRS program, is issuing this newsletter to advise medical facilities of immediate changes that can be instituted to reduce serious events and incidents. For more information about the PA-PSRS program or the Patient Safety Authority, see the Authority’s website at www.psa.state.pa.us.

ECRI is an independent, nonprofit health services research agency dedicated to improving the safety, efficacy and cost-effectiveness of healthcare. ECRI’s focus is healthcare technology, healthcare risk and quality management and healthcare environmental management. ECRI provides information services and technical assistance to more than 5,000 hospitals, healthcare organizations, ministries of health, government and planning agencies, and other organizations worldwide.

The Institute for Safe Medication Practices (ISMP) is an independent, nonprofit organization dedicated solely to medication error prevention and safe medication use. ISMP provides recommendations for the safe use of medications to the healthcare community including healthcare professionals, government agencies, accrediting organizations, and consumers. ISMP’s efforts are built on a non-punitive approach and systems-based solutions.