

## RISK MANAGEMENT

## CME

# Propofol Use Under the Direction of Trained Gastroenterologists: An Analysis of the Medicolegal Implications

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### GASTROENTEROLOGISTS, PROPOFOL, AND THE FEAR OF MALPRACTICE LIABILITY

During the past five years, propofol has gained popularity as a sedation agent for gastrointestinal (GI) endoscopy. A 2004 survey in the United States indicated that approximately one-quarter of all endoscopic procedures were performed with propofol (1). This growth reflects the potential benefits of propofol sedation: painless endoscopy, rapid recovery, and improved operational efficiency (2–4). The product label, approved by the U.S. Food and Drug Administration (FDA) in 1989 when propofol was first marketed, states that “propofol should be administered only by persons trained in the administration of general anesthesia” (5). Historically, therefore, propofol in most clinical settings has been administered by an anesthesiologist, and as interest in propofol use for endoscopy has grown, so too has the number of anesthesiologists participating in GI procedures (6). If the addition of an anesthesiologist during endoscopy were to become standard practice throughout the United States, the added cost would total \$5 billion annually; in the absence of evidence that patient safety is enhanced, economists, professional societies, and insurance carriers have justifiably challenged the cost-effectiveness of anesthesiologist-administered propofol (7).

Growing evidence suggests that with appropriate patient selection, equipment, staffing, and training, gastroenterologists can safely and effectively administer propofol during endoscopy (8–10). Gastroenterologists and anesthesiologists use different paradigms when giving propofol: gastroenterologists typically utilize small bolus doses of propofol (10–20 mg) and target moderate sedation (11); anesthesiologists use either larger bolus doses of propofol (20–70 mg) or an infusion, and target deep sedation. Evidence supporting “gastroenterologist-directed” propofol (“GD-P”)<sup>a</sup> comprises studies from around the world and from diverse

types of medical practices, and is endorsed (with appropriate caveats regarding implementation) by the three major professional GI societies in the United States (10). The use of propofol in well over 200,000 cases of GD-P worldwide has resulted in no sedation-related deaths (12). Because insurance carriers covering tens of millions of lives in the United States disallow reimbursement for anesthesiology services during routine endoscopy (13), for many patients, GD-P is their only access to propofol, unless they pay for an anesthesiologist’s services out-of-pocket. Nonetheless, GD-P has not been adopted by the majority of gastroenterologists. While the reasons for this are complex and include political and economic factors (1,7,14), the most important factor is gastroenterologists’ perceptions regarding malpractice liability (1).

Picture a malpractice trial involving a cardiopulmonary complication during endoscopy performed with GD-P. The plaintiff’s attorney establishes that the gastroenterologist could have chosen midazolam and fentanyl or anesthesiologist-administered sedation; reads aloud the FDA warning contained in the product label; produces an anesthesiologist-expert who equates the FDA label with the “standard of care,” and testifies that GD-P is irresponsible and hazardous (15); introduces an American Society of Anesthesiologists’ (ASA) consensus paper opposing GD-P (16); and implies that the gastroenterologist’s concerns for patient safety are eclipsed by other motivations (17). With this as a backdrop, it is not surprising that 67% of U.S. endoscopists responding to a recent survey indicated that they have not adopted GD-P because of medicolegal worries (1). Acknowledging this impact of the product label, the American College of Gastroenterology recently petitioned the FDA to remove the restrictive language cited above (18).

The purpose of the current article is to clarify for gastroenterologists the medicolegal weight of the propofol warning; to dispel the misperception that GD-P creates automatic provider liability for an adverse patient outcome; and to suggest strategies for GD-P that minimize medicolegal risk. To begin, a brief discussion of the legal and regulatory context is necessary.

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## THE “STANDARD OF CARE” AND THE “RESPECTABLE MINORITY”

Medical malpractice liability is governed by the law of negligence, which imposes on physicians a duty to comply with the “standard of care.” Although the precise legal formulation varies from state to state, the standard of care generally is defined as “that degree of skill and care possessed and employed by members of the profession in good standing” (19). Practically, courts interpret this standard to mean the skill and care exercised by competent physicians acting in circumstances similar to the defendant’s, and attempt to identify the treatment(s) that such competent physicians would find reasonable (20).

Because “jurors are not skilled in the practice of medicine and would find it difficult without the help of medical evidence to determine any lack of necessary scientific skill on the part of the physician” (21, 22), the plaintiff generally must establish the standard of care through expert witness testimony, in some instances supported by documentary materials. An expert “must demonstrate knowledge acquired from experience or study of the standards of the specialty of the defendant physician sufficient to enable him to give an expert opinion as to the conformity of the defendant’s conduct to those particular standards.” Documentary materials—peer-reviewed journal articles, consensus guidelines, FDA-approved drug labels, and other so-called “learned materials”—may also be introduced in most courts to establish the standard of care, but courts vary considerably on the circumstances and the manner in which they can be used (23, 24). Typically, courts allow attorneys to introduce learned materials to impeach or corroborate expert opinion.

The law in most jurisdictions recognizes that there may be more than one “right way” to approach a medical problem. Many states have adopted a “respectable minority rule,” which protects physicians who utilize a method of treatment that has been approved by a “substantial minority” of the medical community (25–27). Some jurisdictions utilize the “two schools of medicine” doctrine, which holds that lay jurors may not be called upon to resolve disputes within the medical community about complex medical matters (27). Accordingly, testimony by an expert that in the same clinical situation as the defendant he would opt for a different method of treatment is not a basis for imposing liability—indeed, in many courts, it is inadmissible (28).

## THE FDA AND PRESCRIPTION DRUG LABELING

According to its mission statement, the FDA “is responsible for protecting the public health by assuring the safety, efficacy, and security of human . . . drugs. . . (29).” To execute this mission, the FDA provides the public “accurate, science-based information they need to use medicines . . . to improve their health” (29). Before a manufacturer can legally market

a prescription drug in the United States, the FDA must conclude from scientific evidence that it is safe and effective for its intended use:

*“Most typically, the drug manufacturer drafts proposed labeling based on relevant available data. This includes data acquired during drug development, as well as publicly available data on the drug and other related drugs. FDA reviewers carefully scrutinize every phrase in the proposed label for completeness and fair balance and also to ensure that all statements are adequately supported by data. Scientific experts outside of the FDA and the general public may also be consulted for advice on labeling, particularly in the case of difficult or controversial issues.” (30)*

The FDA uses the product label to communicate information to physicians and the lay public. Regulations require the label to contain the essential scientific information needed for the safe and effective use; to be informative and accurate without being promotional, false, or misleading; and to be based on data providing substantial evidence of safety and effectiveness (31). The Physician’s Desk Reference (PDR) represents a compendium of FDA drug labeling information. Premarket data are analyzed to determine whether a risk should be classified on the product label as an “adverse reaction,” “warning,” “black box warning,” or “contraindication.” Evidence accruing after the drug is widely used can require the FDA to reclassify a risk—typically adding cautionary language when a new risk emerges.

The New Drug Application (NDA) for propofol, submitted in 1989, included only studies in which propofol was used for general anesthesia (32). Because “[l]abels are written to reflect the clinical trials that were performed to support them” (30), the FDA medical officer reviewing the propofol NDA had no basis upon which to evaluate the efficacy and safety of propofol targeted to moderate sedation by nonanesthesiologists. Accordingly, the FDA concluded only that “propofol is a safe and effective intravenous agent for the induction and maintenance of general anesthesia” (32). Thus, the warning in the initial propofol label recommending that it be administered only by persons trained in the administration of general anesthesia should be understood in the context of propofol’s original FDA approval for induction and maintenance of general anesthesia.

## OFF-LABEL PRESCRIPTION DRUG USE

“Off-label” use, defined by the Director of the Center for Drug Evaluation and Research (CDER) as “use for any indication, dosage form, population, or other use parameter not mentioned in the approved labeling” (33), is a vital part of the U.S. health system today: 80% of pediatric and more than 50% of oncology prescriptions are off-label (34); many drugs are prescribed more commonly off- than on-label (34, 35); in

instances, physicians who have *not* utilized a drug off-label have been accused of medical malpractice; and, third-party payors typically cover accepted off-label uses. The General Accounting Office has concluded that the FDA “could not review drugs in its lengthy testing process at a pace equal to that at which physicians discover beneficial off-label uses. . .” (35). Drug sponsors often lack a sufficient incentive to seek labeling changes because of the enormous costs associated with the process, especially when a drug is approaching patent expiration (34, 35). One court concluded: “Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses” (36).

At the same time, off-label use sacrifices some degree of patient protection because the safety and efficacy for the off-label use may not have been established by adequate and well-controlled clinical trials that satisfy the FDA’s rigorous standards. Restraints on off-label use that mitigate this downside include: restriction of off-label use to licensed physicians; non-FDA oversight organizations such as hospital peer review and credentialing committees; the FDA review that is triggered if an off-label use becomes prevalent; physicians’ apprehension of increased malpractice liability; adverse event reporting when off-label use causes injury; and the prohibition (without appropriate consent and Institutional Review Board [IRB] approval) of “experimental” use (in which a drug use is intended to test a hypothesis and/or benefit other patients) (37, 38).

A general consensus exists that off-label drug use promotes innovation in medical practice, physician autonomy, and flexibility in patient care, and that these benefits outweigh the loss of protection related to FDA oversight. The American Medical Association (AMA) has commented that “. . .the prescribing of FDA-approved medications for unlabeled uses is often necessary for optimal patient care” (30), while its formal policy states:

*“The AMA affirms. . .that a physician may lawfully use an FDA-approved drug product for an unlabelled indication when such use is based upon sound scientific evidence and sound medical opinion.”*(39)

FDA policy concurs:

*“The Food Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such . . .uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature.”* (40)

Put otherwise,

*“The FDA does not restrict a physician’s discretionary use of an approved drug, which is considered the practice of medicine. In fact, it is recognized that off-label use can be essential to medical care, that it is not always investigational or experimental, and that there is no legal or ethical obligation for physicians to discuss FDA regulatory status issues with their patients.”* (30)

Likewise, the courts generally recognize that

*“physicians may use approved drugs or devices in any way that they, in their professional judgment, believe will serve the best interest of their patients, regardless of whether the FDA has approved the drug or device for that particular use.”*(20)

## THE FDA LABEL AS EVIDENCE IN MALPRACTICE LITIGATION

In this context, what role could the FDA-approved propofol label play in a malpractice action against a gastroenterologist using propofol without an anesthetist? Reframed in legal parlance—is the FDA-approved propofol label admissible as evidence of the standard of care? If so, in what circumstances and subject to what limitations? And what weight would a jury give it?

No jurisdiction automatically imposes liability for prescribing a medication off-label, and all states allow the defendant to rebut the information contained in the label through personal and/or expert testimony. Furthermore, the plaintiff must still prove that the physician’s off-label use of the drug caused the plaintiff’s injury—in this hypothetical situation that the injury would have been avoided had an anesthesiologist been present (41). That said, the most common court ruling (the “majority rule”) regarding the place of a product label in a malpractice action is summarized in *Richardson v. Miller*:

*“Virtually every court . . . has concluded that the drug’s labeling and PDR reference are relevant to the standard of care issue. The primary dispute among the courts involves the weight to be given to this evidence. The great weight of authority is that a drug’s labeling or its parallel PDR reference is admissible, as long as it is accompanied by other expert evidence regarding the standard of care.”* (20)

In most jurisdictions, “the PDR, by itself, is insufficient to establish the standard of care” (42):

*“Neither [the FDA-approved drug labeling nor the parallel PDR reference], by themselves, are prima facie evidence of the prescribing physician’s standard of care. Thus, proof of a departure from the*

*recommendations in a drug's labeling or PDR reference is not alone sufficient to prove a breach of the standard of care."* (20)

The practical effect of this rule is that most courts allow the product label into evidence and allow the jury to consider it, along with the testimony of expert witnesses and other evidence as to the reasonableness or unreasonableness of the defendant's conduct. A minority of jurisdictions hold that the FDA-approved product label constitutes so called "*prima facie*" evidence of the standard of care—evidence that shifts the burden of proof to the defendant, who must then explain why his or her conduct was reasonable and in conformity with the standard of care (43).

When administering propofol without an anesthesiologist, the endoscopist gives the appearance of contravening a specific warning—and is therefore arguably "further" off-label than when administering a drug for an off-label indication, such as 6-mercaptopurine for ulcerative colitis. In "Package Inserts for Prescription Drugs as Evidence in Medical Malpractice Suits," James Bird argues that "Courts should differentiate between categories of information [in the package insert] and give warnings/contra-indications the greatest weight" (44). This emphasis could be contained in a judge's instructions to a jury, or in a jury's intuitive perception that contravening a warning is a bolder departure than other types of off-label use. Published legal cases that address this issue directly are rare, but generally support Bird's point of view. For example, in *Terrebonne v. Floyd*, the Louisiana Appellate Court held that deviation from a label warning was "evidence sufficient to make a *prima facie* case of negligence" (45). In *Ohligschlager v. Proctor Community Hospital*, the Illinois Supreme Court held that "the warning of the hazards accompanying its improper administration provide the proof of the proper professional standards which would ordinarily be shown by expert medical testimony" (46).

If giving the appearance of contravening a drug warning increases malpractice liability more than other types of off-label use, then those who choose to give GD-P must take strong measures to minimize risk.

### **RISK MINIMIZATION FOR GASTROENTEROLOGIST-DIRECTED PROPOFOL**

In *Mulder v. Parke Davis & Co.* the defendant prescribed chloramphenicol to the plaintiff on multiple occasions for an ear infection, despite a warning on the label that the drug could result in a fatal blood disorder (which killed the decedent) and therefore should only be used for serious infections and if no safer medication were available (43). At trial, the label was admitted as evidence without expert testimony, and the defendant provided no cogent explanation for his action; he testified that, although he was aware of the warning, he simply "chose not to be governed by it" (47). The Court held that, under such circumstances, it was "incumbent on the doc-

tor to disclose his reasons for departing from the procedure recommended by the manufacturer" (39).

In the Drug Manufacturers' Recommendations and the Common Knowledge Rule to Establish Medical Malpractice, Lawrence commented:

*"When a physician prescribes a drug for a use not in the approved labeling he invokes two responsibilities. One he has to be well-informed about the drug, and two, base his use of it on firm scientific rationale and sound medical studies."*(41)

In legal cases, this point of view has been echoed:

*The holding will require the physician to provide a sound reason for his deviating from the directions for its use, and will require corroborative evidence to determine whether the physician met or violated the standard of care."*

—*Thomson v. Carter*, 2001 (33).

*"Physicians may be found negligent if their decision to use a drug off-label is sufficiently careless, imprudent, or unprofessional."*(20)

As summarized by Bradford,

*"A physician who fails to document compliance with the drug manufacturer's warnings, cautions, and directions for use, would have the burden of persuasion to justify his prescribing to the jury."* (33)

As discussed earlier, "sound reasons" for using GD-P exist. The defense can select from the GI literature peer-reviewed studies, many conducted in ambulatory settings with patients representative of general practice, demonstrating safety and efficacy for GD-P (1, 48–50), and also pro-GD-P practice guidelines and editorials written by individual experts and the professional societies (51–53). Following the lead of several anesthesiology organizations (15, 54, 55), however, the plaintiff's attorneys will contend that gastroenterologists' vested interest in GD-P colors these recommendations (15). Thus, future risk minimization for GD-P ideally should include multidisciplinary support—studies, guidelines, and consensus statements published over the signatures jointly of gastroenterologists, anesthesiologists, and experts from other disciplines.

Physicians undertaking GD-P must have adequate knowledge and training to administer the drug safely and effectively. When a physician prescribes off-label, he cannot rely on FDA-approved, sponsor-written instructions for safe and effective drug use, and courts have highlighted this risk (20). Where can the gastroenterologist turn in order to acquire this knowledge? Authoritative instructions for GD-P must be published elsewhere. Ideally, as the AMA has stated, non-FDA prescription guidelines should reflect peer-reviewed National Library of Medicine-indexed research studies; acknowledge authorial conflicts of interest; be supported by professional

organizations; be well disseminated to the medical community; be investigator rather than sponsor driven; and be subject to expert reviewers representing a variety of perspectives (56). Anesthesiologists have published general guidelines for safe use of propofol (55, 57, 58). For their part, gastroenterologists have published protocols and offer instructional courses (some cotaught by anesthesiologists) in safe and effective GD-P (8, 50, 51). The two specialties agree on most points: Appropriate resuscitation and monitoring equipment must be available; one advanced cardiac life support (ACLS)-certified individual should be dedicated solely to administering the sedation; high-risk patients require an anesthesiologist; the provider must be knowledgeable regarding the pharmacology of propofol and the agents needed to provide hemodynamic support.

The ASA recommends that when using propofol “the administering physician” be “trained in the administration of general anesthesia” (54). Working together, anesthesiologists and gastroenterologists must clarify what “general anesthesia training” is necessary for GD-P (*e.g.*, patient risk assessment, positive pressure ventilation) and what is not (*e.g.*, cardiac anesthesia, inhalational anesthesia) and then cooperatively devise programs to teach, maintain, and certify these skills. Most specifically, such a program must specify the details of the upper airway management training required to permit safe GD-P. GD-P skills can then be taught to gastroenterologists through didactic presentations and hands-on training in simulation labs, or one-on-one preceptorships. The training period should involve a time commitment that is compatible with midcareer practice, much in the way that surgeons take midcareer training courses to learn new operative techniques. GD-P training can be integrated into GI fellowships, as is already being done at several institutions within the United States. Such programs (which can be adapted on an institutional level to serve other subspecialties—such as cardiology—where “non-anesthesiologist” propofol is also advantageous) certify and re-certify providers and include on-going quality assurance and carry weight in court.

Risk minimization further requires that the gastroenterologist adhere to the authoritative guidelines. This implies appropriate training, facilities, equipment, staffing, patient selection, drug titration, quality assurance, adherence to institutional policies and privileging, informed consent, and preprocedure and postprocedure monitoring (59, 60). As the courts have highlighted, this compliance must be carefully documented: “If a physician uses a device in the practice of medicine for an indication not in the approved labeling, he or she has the responsibility to . . . maintain records of the product’s use and effects” (61).

Although open-access endoscopy may discourage thoughtful preprocedure patient–doctor discussion, “the best defense a physician has is proof of complete informed consent” (41). It is appropriate for gastroenterologist and patient specifically to discuss the risks and benefits of the sedation as well

as of the procedural component of the endoscopy. The risks of sedation and the discussion regarding sedation should be documented in the signed informed consent. It is generally held that “There is no legal or ethical obligation for physicians to discuss FDA regulatory status issues with their patients” (30). Nor generally do malpractice policies require the physician to disclose off-label use to his or her carrier. In reviewing the completeness of an informed consent discussion, most courts ask what information a “reasonable physician” would provide and/or what information a “reasonable patient” would want to know (62).

Risk management also requires an understanding of the local environment. Certain states give the product label greater legal weight (47), certain state nursing boards prohibit nurses from administering propofol (63), and some endoscopy facilities restrict GD-P. These venues are less friendly to the study and implementation of GD-P. Conversely, environments in which anesthesiologists are unavailable to give propofol during endoscopy (*e.g.*, because payors disallow reimbursement for it) and in which physicians already have pioneered GD-P are legally and logistically more favorable.

## CONCLUSION

In most courts, a product label may be used alongside expert testimony to establish the standard of care. It is widely agreed that the FDA does not regulate the practice of medicine, and that a product label only reflects the evidence submitted to the FDA at the time of an NDA, often does not evolve in response to postmarket data, and may be rebutted by expert testimony or a defendant’s explanation of his action. Also, the “respectable minority” rule and other similar rules hold that there may be multiple ways to practice medicine within the standard of care. In the event of a malpractice action related to an adverse outcome involving propofol administration by a gastroenterologist, establishing causation would require proof that the presence of an anesthesiologist would have prevented the adverse outcome—in itself a high hurdle. Thus, although GD-P (like other innovations in medical practice) may raise malpractice liability risk, undertaken responsibly, it is medicolegally reasonable. The popular title “Nurse-Administered Propofol Sedation” (50) notwithstanding, the gastroenterologist is legally responsible for giving the drug when an anesthesiologist is not present. Many gastroenterologists will decide, reasonably, that they do not want to undertake the training and changes in practice necessary to adopt GD-P. However, because patients and endoscopists prefer propofol to conventional sedation (3, 64), and because insurance companies are increasingly disallowing reimbursement for anesthesia providers for most endoscopies, an increase in size of the “respectable minority” who undertake GD-P is likely. To enhance patient safety and practitioner legal protection, leaders in gastroenterology and anesthesiology must work cooperatively to develop training, certification, and quality assurance

programs, as well as authoritative practice guidelines for GD-P.

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- a. Several groups utilize the title “nurse-administered propofol” or “nurse-administered propofol sedation” to describe propofol given for endoscopy without an anesthesiologist present. Because the physician bears the ultimate medicolegal responsibility, the term “gastroenterologist-directed propofol” will be utilized throughout this paper.

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