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What's in a Label? A Guide for the Anesthesia Practitioner

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Basis of Drug Labeling

DRUG labeling is of vital importance in guiding the safe and effective use of approved drugs. Drug labels represent the most visible expression of months or years of scientific review by physicians and scientists at the U.S. Food and Drug Administration (FDA), and they are also fundamental to the purpose and mission of the FDA. Creation of the FDA dates to the 1906 passage of the Food and Drugs Act, which prohibited the manufacture and interstate shipment of adulterated and misbranded foods and drugs.† A 1937 disaster, in which more than 100 people died after ingestion of Elixir Sulfanilamide, precipitated the Federal Food, Drug, and Cosmetic Act of 1938, which, for the first time in U.S. history, required demonstration of safety before marketing new drugs. Elixir Sulfanilamide contained diethylene glycol and had never been tested for safety. In 1960, a marketing application for the drug thalidomide was submitted to the FDA. Withstanding enormous pressure from the applicant, FDA reviewers, including Frances Kelsey, M.D., Ph.D., a medical officer at the Center for Drug Evaluation and Research at the FDA (Washington D.C.),‡ determined that inadequate data were available to support the safety of the drug product despite its already widespread use throughout the rest of the world. The application was not approved. After thousands of children in 46 countries were born with deformities as a consequence of thalidomide use, leaving the United States relatively unscathed, a political movement for tighter drug controls in the United States gained popular support. The Drug Amendments of 1962 were the first to require demonstration of effectiveness before marketing, recognizing that the assessment of safety must also consider benefit. Since 1962, more than a thousand prescription drugs have had their labeling changed or have been taken off the market to reflect the scientific evidence (or lack thereof) documenting their safety and/or effectiveness.§ Section 505 of the Federal Food, Drug, and Cosmetic Act (21 USC 355)‖ currently specifies that approved drugs must be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.

Current regulations stipulate the following labeling requirements[1]:

1. Labeling shall contain the essential scientific information needed for the safe and effective use of the drug.
2. Labeling shall be informative and accurate without being promotional, false, or misleading.
3. The labeling shall be based on data providing substantial evidence of safety and effectiveness.

The Code of Federal Regulations provides the basic skeleton for drug labels,# specifying the section headings and content, as well as the order in which these sections should appear. Regulations have been proposed to improve on the current system of labeling by changing the format of drug labeling to make the information more useful and accessible to practitioners.[2] This proposal would partition the label into three parts: a Highlights section, an Index, and Comprehensive Prescribing Information.

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 sup-

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† http://www.fda.gov/oc/history/default.htm. Posting date December 27, 2001. Accessed January 4, 2005.

‡ http://www.fda.gov/fdac/features/2001/201_kelsey.html. Posting date March 5, 2001. Accessed January 4, 2005.

§ http://www.fda.gov/cder/about/history/Histext.htm. Posting date December 21, 1999. Accessed January 4, 2005.

‖ http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=browse_usc&docid=Cite:+21USC355. Accessed January 4, 2005.

Note that the Food, Drug and Cosmetic Act defines labeling as "all labels and other written, printed, or graphic matter . . . accompanying such article." This definition would include such items as price lists, catalogs, and advertising. In some contexts, *label* is used only to describe the information printed on the drug article itself. For the current discussion, except as otherwise indicated, the terms *label* and *labeling* refer primarily to the information contained in the product package insert.

ported 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. Commonly, labels undergo one or more rounds of revisions before final approval.

Generally, new indications for a drug require evidence of effectiveness based on data submitted from adequate and well-controlled studies (*i.e.*, generally more than one) conducted in humans under an Investigational New Drug application, under defined standards for data quality and integrity and the reporting of adverse events.†† All relevant data must be submitted to a new drug application (NDA), including data from failed trials, along with complete protocols and protocol revisions. Supporting chemistry, pharmacokinetic, and preclinical (*in vitro* and animal) data are usually required as well. FDA grants indications only after its own internal review and analyses of these data by physicians, statisticians, chemists, clinical pharmacologists, toxicologists, and other relevant scientific and regulatory disciplines within the FDA. In addition, experts external to the FDA, including members of FDA advisory committees, may be consulted as needed. Medical literature, on which much off-label use is based, is usually not accepted as the sole basis for approval of a new drug indication. There are several reasons for this. First, the raw data, along with complete protocols and revisions, are usually unavailable for review. Second, the standards for data quality, integrity, monitoring, and adverse events reporting are often unknown. Last, the study sites are unavailable for inspection. The FDA must also consider the possibility that published literature may present a skewed or incomplete profile of the efficacy and safety of a drug for human use.

This regulatory process can be illustrated using the examples of levobupivacaine (Chirocaine; Purdue Pharma LP, Stamford, CT) and of dexmedetomidine hydrochloride (Precedex; Hospira, Lake Forest, IL).‡‡

Levobupivacaine (Chirocaine) was approved in 1999 for adult patients for the production of local or regional anesthesia for surgery and obstetrics, and for postoperative pain management. The NDA applicant studied more than 1,400 patients in a total of 27 clinical studies in the United States and Europe. These included 2 pharmacokinetic studies, 4 phase I pharmacodynamic studies examining neurologic and cardiovascular endpoints, 2 studies of epidural administration for cesarean delivery, 2 studies of epidural administration for labor analgesia, 2 studies of epidural infusion for operative procedures, 1 study of intrathecal injection for lower limb surgery, 4 studies of epidural infusion for postoperative pain, 7 studies of peripheral nerve blocks, and 3 pediatric studies, 2 of which were still ongoing at the time of NDA submission. Much of the preclinical support for this application was in the form of animal studies of levobupivacaine and bupivacaine (approved in 1972) that were available in the published literature. Before its approval, the FDA consulted the Anesthetic and Life Support Drugs Advisory Committee, which included a guest cardiac electrophysiology consultant, to discuss the relative safety of levobupivacaine compared with bupivacaine and how the product should be labeled with respect to cardiotoxicity. In addition, FDA chemists and microbiologists reviewed data and information related to the product chemistry, manufacturing, and quality before approval.

Dexmedetomidine hydrochloride (Precedex), an α_2-adrenoceptor agonist, was approved in 1999 for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. It is to be administered by continuous infusion for not more than 24 h. The NDA applicant submitted full reports of animal pharmacokinetic, toxicology, and teratogenicity studies; two placebo-controlled human studies demonstrating the efficacy of dexmedetomidine; and a total human safety database of more than 3,038 subjects, of whom 1,473 were intensive care unit patients who received the drug by continuous infusion. Only 78 patients received dexmedetomidine for longer than 24 h, and no patient received the drug for longer than 40 h. No safety data in pediatric patients were submitted, and more than 500 patients older than 65 yr were studied, 129 of whom were aged 75 yr or older. Human pharmacokinetic data included evaluation in patients with renal failure after single administration and evaluation of pharmacokinetics with hepatic impairment, as well as analysis of the effects of age on pharmacokinetics in adults. In addition, the FDA inspected clinical trial sites and reviewed information related to the product chemistry, manufacturing, and quality before approval. The NDA applicant also agreed to seven phase IV commitments to address areas in which the FDA desired additional information that might be used to inform future labeling. These included (1) dog studies to evaluate general toxicology, effects on the hypothalamic-pituitary axis, and changes in drug metabolism after 2 weeks of drug infusion; (2) an animal study to evaluate the effects of the three major human metabolites of dexmedetomidine that are absent in rats and dogs; (3) preclinical mutagenicity studies to elucidate findings from studies submitted before approval; and (4) long-term continuous infusion studies in patients to evaluate the pharmacokinetics, safety, and extended effectiveness of dexmedetomidine in the intensive care unit setting and to evaluate the use of long-term infusions in patients with renal failure. To date, these commitments have not been deemed fulfilled in

** http://www.fda.gov/cder/regulatory/applications/default.htm. Posting date May 27, 1999. Accessed January 4, 2005.

†† http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf. Accessed January 4, 2005.

‡‡ http://www.fda.gov/cder/approval/index.htm. Accessed January 4, 2005.

their entirety, and there have not been any labeling changes for dexmedetomidine (Precedex) that are based on these postmarketing commitments.

After a drug has been approved for marketing, a supplemental application to the FDA is required to change the labeling to reflect a new indication. The supplemental application must present data to support the safety and effectiveness of the new indication. The data requirements for a supplemental application might not be as extensive as would be expected for a novel NDA application, depending on the nature of the supplement and the indication sought.

For example, a supplemental application for ropivacaine (Naropin; AstraZeneca, Wilmington, DE) was approved in 2000 for changes in the labeling, including (1) use of the 0.75% concentration for major nerve block and for epidural administration for cesarean delivery (previously approved concentrations for these indications were 0.2% and 0.5%, respectively); (2) use of 0.2% ropivacaine (Naropin) for up to 72 h for postoperative pain (previously approved for up to 24 h only); and (3) a change in the recommended infusion range for thoracic epidural administration for postoperative pain from 4–8 ml/h of 0.2% ropivacaine (Naropin) to 6–14 ml/h. To support the new labeling recommendations, the NDA sponsor submitted the results of clinical trials in which 324 women received 0.75% ropivacaine by the lumbar epidural route for cesarean delivery, 119 patients received 0.75% ropivacaine for brachial plexus block, and 441 patients received epidural infusions of 0.2% ropivacaine for postoperative pain. Pharmacokinetic data were obtained in 8 of the 20 submitted clinical studies. The FDA also reviewed preclinical (*in vitro* and animal) studies investigating acute, subchronic, and chronic toxicity; pharmacokinetics; cardiovascular toxicity; reproductive toxicology; and genotoxicology before approval of the supplement.

Generally, the FDA requires that indications reflect the likely clinical use of a drug to ensure that a drug is not approved for unrealistically narrow indications. For example, drug company XYZ might propose to develop a novel general anesthetic agent only for "general anesthesia for left foot bunionectomies" and submit data supporting only this indication. In such a case, the company might be asked for more data to support a broader indication that would realistically reflect the likely clinical use, or they would be asked to provide adequate justification that such a limited indication is appropriate. As a corollary, a very broad indication for "maintenance of general anesthesia" would not be supportable by submission of data only from healthy patients undergoing bunionectomy procedures.

Food and Drug Administration guidance to industry states that "in general, drugs should be studied prior to approval in subjects representing a full range of patients likely to receive the drug once it is marketed. . . ."[3] Therefore, to the extent possible, sponsors are expected to study the full range of patients likely to receive drug for the desired indications. Further, recent legislation stipulates that new drug applications are specifically required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.[4] In addition, drug product sponsors are generally expected to study elderly patients, and to investigate the effects of metabolic and renal impairment and drug–drug interactions when relevant.[5–7] In a new drug application, sponsors are also required to present effectiveness and safety data for important demographic subgroups, specifically sex, age, and racial subgroups.

Current regulations also require specific labeling in the following subpopulations as applicable: pregnant women (including use during labor and delivery), nursing mothers, pediatric patients, and elderly patients.[8]

However, with the exception of those few special populations defined by regulation or guidance, unless there are data to indicate a need for special study or labeling, it is generally not required, feasible, or even scientifically meaningful, to discuss all potential subpopulations in the label.

Therefore, industry is encouraged to study drugs in the range of settings and populations reflecting their likely clinical use, including the range of likely comedications and comorbidities. Labels, in turn, are written to reflect the clinical trials that were performed to support them. However, these clinical trials cannot anticipate or thoroughly study all of the ways that a drug may be used after it is approved. Because every patient and clinical situation is unique in some way, this would truly be an impossible task. In spite of the best efforts of the FDA and the drug industry, neither labels nor the supporting clinical trials can comprehensively describe all potential labeled or off-label uses.

Off-label Use

What Is Off-label Use?

What exactly is off-label use, and what are the implications for the anesthesia practitioner? Any use of a drug for a condition or in a manner not appearing in the drug's approved label is considered off-label. This lack of approval is most commonly because data have not been submitted to the FDA to support the safety and efficacy of that use, not necessarily because there has been an adverse finding with respect to safety or efficacy. Off-label use most often describes a deviation from the labeled indication, dosage form, dose regimen, or patient population. However, any significant departure from the approved labeling or any use that is not described in the approved label may be considered to be off-label. When off-label uses are associated with a particular safety hazard, they may be described in the Contraindications,

Warnings, or Precautions sections of the label. However, although all contraindicated uses are off-label uses, the Warnings and Precautions sections may discuss both labeled and off-label uses.

For example, dexmedetomidine (Precedex) is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. It is to be administered by continuous infusion for not more than 24 h. In this case, the use of dexmedetomidine outside an intensive care setting or in non–mechanically ventilated patients, such as for monitored anesthesia care sedation in the operating room, would be considered off-label. Similarly, infusions of dexmedetomidine lasting longer than 24 h are also off-label, as noted in the Indications and Usage, Precautions, and Dosage and Administration sections of the label. Data have not been submitted to the FDA to support the safe and effective use of dexmedetomidine outside the labeled indications, and for monitored anesthesia care sedation or long-term infusions to be reflected in the FDA-approved labeling, an application would need to be submitted to the FDA with adequate supporting data.

The following are additional examples of off-label uses in anesthesiology:

- Sufentanil (Sufenta; Akorn, Buffalo Grove, IL) is not approved for intrathecal use.
- Fentanyl (Sublimaze; Akorn) is approved for intravenous and intramuscular injection only. It is not approved for intrathecal or epidural use. Neither has fentanyl (Sublimaze) been approved for use in pediatric patients less than 2 yr of age.
- Infusing propofol (Diprivan; AstraZeneca) faster than 40 mg every 10 s (or 20 mg every 10 s in elderly, debilitated, or American Society of Anesthesiologists physical status classification III or IV patients) is considered off-label use.
- Ketamine (Ketalar; Parkdale, Briston, TN) is not approved for use in obstetric patients or in pediatric patients younger than 16 yr.
- Bupivacaine (Marcaine; Hospira) is not approved for use in pediatric patients younger than 12 yr.
- Lorazepam injection (Ativan; Baxter Healthcare Corporation, Deerfield, IL) is not approved for use in pediatric patients.

FDA Does Not Regulate the Practice of Medicine

Where does that leave the individual anesthesiologist who, based on his or her own knowledge of the medical literature, medical judgment, and experience, believes that a particular off-label use would be safe and effective for the patient at hand? Anesthesiology is unique among medical specialties in the methods by which practitioners administer drugs that they prescribe. Anesthesiologists administer drugs with their own hands and often do not conform to a fixed algorithm. Instead, drug use is tailored to effect and to the individual needs of the patient, as well as to surgical and medical conditions. Anesthesiology is a specialty that prides itself on innovation and resourcefulness. New routes and modes of administration, mixes, doses, and applications for medications are commonly used to solve complex problems.

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.[9] For example, many drugs used in anesthesia have never been approved for use in children. Restricting anesthesiologists only to labeled uses would have a devastating effect on the practice of pediatric anesthesia, and indeed, practitioners restricting their practice in such a way might well be accused of engaging in poor medical practice. It is the physician's prerogative to use legally marketed drugs in a way that he or she believes is best for the individual patient, according to his or her medical judgment (outside of medical research).

However, in this context, perhaps understandably, physicians are often unfamiliar with information available in drug labels and even are unaware of basic information about the labeling for drugs that they use, such as indications, dosage and administration information, and warnings.[10] There are many other reasons that physicians might not read labels. Physicians have many demands on their time, medical practice is increasingly complex, and labels may be viewed as cumbersome to read and interpret. Physicians often cannot find the information they are seeking in the label. Lastly, practitioners may view the information contained in the label with skepticism and uncertainty.[11]

A concerning example of the apparent disassociation between instructions for use found in drug labeling and actual physician practice is illustrated by the drug cisapride. In 1995, 2 yr after it was approved for marketing, a "boxed" warning was added to the cisapride label because of the risk of life-threatening dysrhythmias related to QT prolongation. The revised label contraindicated use in patients taking drugs that affect cisapride metabolism, and the labeling change was accompanied by the distribution of a "Dear Health Care Professional" letter. After the promulgation of these warnings, contraindicated use of cisapride in a sampling of practice sites was found to occur in 26–60% of users. In June 1998, the boxed warning was expanded to include other patient categories at risk. This change was accompanied by the circulation of a press release and distribution of another "Dear Health Care Professional" letter. Despite these efforts, the prevalence of contraindicated cisapride use remained essentially unchanged.[12] In recent history, several effective drugs such as cisapride have been with-

drawn from the market because labeling has been ineffective in modifying dangerous prescribing behavior and preventing avoidable serious adverse events.[13]

Off-label Use: Points to Consider

There are very good reasons for anesthesiologists to read and understand the contents of drug labels and to think carefully about contemplated off-label uses. The label contains much important information that can inform decisions about such use.

Most straightforward are the stated warnings, contraindications, and precautions. Practitioners should know what these are and the bases for them in order to inform decisions on when a particular patient may benefit despite an existing warning.

It is just as important to know where the label is silent, where a particular use is not stated because data demonstrating safety and effectiveness do not exist or have never been submitted to the FDA.

Is It Off-label? If there is no mention of diabetic amputees in the label of a general anesthetic drug, is use in this population off-label? For the individual physician who is not looking to study, market, or advertise a drug, the question of whether use in diabetic amputees is off-label may be largely irrelevant. The more relevant question is can the drug be used safely and effectively in diabetic amputees, and if so, how?

Labeled use represents a spectrum of risk for which the FDA has made a determination that the overall benefit justifies the risk in the labeled populations and settings.§§ However, for individual patients within that population, the range of risks and benefits may be quite variable, even to the extent that some individual patients within the indicated population may experience serious adverse events that are not counterbalanced by individual benefit. Off-label uses similarly represent a spectrum of risk and benefit where, unless known risk exists, as would be reflected in a specific labeled warning or contraindication, the FDA simply has not been presented with adequate data to make a determination of safety and efficacy for the given indication. The label is simply a tool to present those conditions in which safety and efficacy have been demonstrated and to summarize the trials and data that were used to support these findings. As required by regulation and as relevant, labeling describes specific conditions, populations, and coadministrations that may call for special consideration.

Unless use is contraindicated in this population, diabetic amputees might be considered a subset of the wider adult population that was studied to support the drug's indication. However, if diabetic amputees are not mentioned in the label, it is also likely that they did not represent a large enough portion of the total clinical database to make meaningful conclusions about whether appropriate use of the drug in this subpopulation should vary from the wider adult population. The label describes the important clinical trials and available information on pharmacokinetic, dosing, and safety considerations and special populations. Using this information, the clinician is expected to exercise clinical judgment in determining the best use of the drug in the individual patient at hand. Therefore, diabetic amputees may require individualization of dose based on dissimilarity from the general population in body weight and volume of distribution, renal function, autonomic dysfunction, and increased risk of ischemic events.

Of note, older drugs for which generic versions are available have limited financial incentives to develop new drug indications. Therefore, as the clinical use of these drugs evolves over time, clinical use may diverge from the approved labeling, and clinical judgment and ongoing medical research may take on an increasingly important role in guiding their appropriate use. An example of this is fentanyl (Sublimaze), the NDA for which was submitted to the FDA in the late 1960s. Fentanyl (Sublimaze) is approved only for intravenous and intramuscular injection in patients aged 2 yr and older. Despite the widespread use of fentanyl by intrathecal and epidural routes, and the routine use of this drug in pediatric patients younger than 2 yr, data demonstrating the safety and efficacy of these uses have never been submitted to the FDA to support the addition of these indications to the labeling.

Pharmacology/Toxicology Considerations. The anesthesiologist should consider several other points when contemplating off-label use of a drug. Dose–response data and pharmacokinetic data usually inform labeled dosing recommendations. Off-label populations and indications typically have less data to guide dosing strategies. Also, indications for new routes of administration and new populations are generally supported by toxicology studies in animal models. In these models, it is possible to more completely define the potential toxicity profile for drugs in ways that are not possible in humans, such as by histopathologic examination of tissues at doses approximating the proposed human doses and higher. Animal toxicology data are often unavailable to support the safety of off-label routes of administration or of systemic exposures of greater magnitude or longer duration than approved doses and routes of administration. A practitioner who wishes to administer a drug that is labeled only for intravenous use by the intranasal or intrathecal route should understand that the potential for local toxicity may not have been thoroughly evaluated in those tissues for that drug. Drugs that are being used by unapproved routes may also have very different patterns of systemic exposure than by the approved

§§ http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf. Accessed January 4, 2005.

route, a situation that may result in very different drug efficacy and safety profiles.

Labeled recommendations for duration of dosing are often defined by the clinical and preclinical trials conducted, from which safety and efficacy data are available only for a limited period. Duration of dosing may also be limited by specific concerns related to safety or efficacy, in which case these concerns are usually discussed in the label. Other considerations may also come into play. For example, assessment of safety for labeling takes into account the potential cumulative exposure to drug, impurities, and excipients. Some drugs that are approved only for short-term use may result in potentially toxic exposures to patients if given long-term. For example, etomidate (Amidate; Hospira) is approved only for induction of general anesthesia and for supplementation of anesthesia during short operative procedures. Prolonged infusion of etomidate is off-label and has been associated with adrenal suppression. In addition, many drugs used by anesthesiologists, pain specialists, and intensivists exhibit tachyphylaxis or tolerance with continued use. If continued use of these drugs is not evaluated in clinical trials, the practitioner may not have adequate information to guide dosing decisions with continued use and may not even be assured of the continued efficacy of the drug.

Chemistry. There are also a number of chemistry and formulation issues of particular relevance to anesthesia providers. For example, drugs approved for epidural or intrathecal use may be subject to different standards than intravenous medications with respect to potential exposure to impurities, endotoxins, and excipients (including preservatives). This is a critical point: Anesthesiologists commonly use drugs by neuraxial routes that are not approved for such use. The presence and concentrations of impurities and endotoxins are generally not stated in the product labeling and, if present, may cause harm if the drug is injected neuraxially above certain exposure limits. Although anesthesiologists may know to avoid preservative-containing solutions for epidural or intrathecal use, they may not always know which injectable drug formulations contain preservatives. For example, until recently, the container labels affixed to some smaller vials of midazolam did not state the benzyl alcohol content of these solutions. The physician had to read the package insert to find that information. In addition, generic drugs can differ from the branded product in the content of buffers, antioxidants, and preservatives provided that the generic applicant identifies and characterizes the differences and provides information that the differences do not affect the safety or efficacy of the drug product for the labeled uses.[14] Therefore, although the branded product may contain a certain preservative or no preservative, a generic version of that product may or may not contain that preservative, and it may or may not contain a different preservative altogether.

Anesthesiologists are often quite creative in the ways that they prepare and combine drugs for administration. If these are not specifically addressed in the label, these too may be considered off-label uses. The Dosage and Administration section of the label contains information about dilution, preparation, and administration of the dosage form. These directions are supported by data demonstrating chemical and physical compatibility of the drug in the final preparation. In addition, drugs are tested for stability and compatibility with container surfaces with which they come into contact. Anesthesiologists mixing and coadministering drugs off-label should be aware of the risks of chemical and physical incompatibility. After the FDA received reports of precipitation upon coadministration of thiopental with vecuronium,[15] the FDA initiated a label revision to warn practitioners. Before this change, the label was silent on coadministration of these drugs. Unfortunately, existing drug labels do not anticipate the entire range of clinical use. Another example is the practice of transferring propofol to plastic bags that contain di(2-ethylhexl)phthalate (DEHP). DEHP is a plasticizer that has been associated with dose-related adverse events in laboratory animals, particularly to male reproductive tract development in young animals.[16] Approved crystalloid products in DEHP containers have acceptably low DEHP concentrations under normal use and storage conditions. However, DEHP is known to leach out in higher amounts into solutions that contain lipids. The extent and time course for the leaching of DEHP out of bags into which propofol is injected and the potential for toxicity to humans related to such exposures have not been evaluated. Anesthesiologists should be cautious about transfer and storage of drugs outside their original containers if not described in the label. When mixing or coadministering drugs off-label, practitioners should be vigilant in monitoring for precipitate and for unexpected drug effects. When these events do occur, practitioners should report them.‖‖

Physicians are the best arbiters of risk *versus* benefit for an individual patient. However, without balanced information derived from prospective, randomized, controlled trials, the individual practitioner may be at a disadvantage in making this determination. Drug effects (and placebo effects) vary from patient to patient and from situation to situation in the same patient. In addition, relatively uncommon adverse events may not be appreciated as potential drug-related events in clinical practice. This potential is particularly true in the perioperative setting, where multiple comorbidities, comedications, and surgical stresses create an environment in which adverse events are common and in which there

‖‖ http://www.fda.gov/medwatch/index.html. Updated April 28, 2004. Accessed January 4, 2005.

are usually multiple potential alternative causes for adverse events.

It is incumbent on individual physicians to be aware of off-label use and to report adverse events when they occur in the context of both labeled and unlabeled use of medications. Postmarketing adverse event reporting is a major mechanism by which the FDA can obtain and disseminate safety information about off-label use of drugs. Detailed information about the patient, the clinical setting, dosing, comedications, and the clinical supporting data describing the event are critical to the effective analysis and interpretation of these adverse event data. Information on how to report adverse events, product problems, or medication errors can be found on the FDA Web site.|||| Reports may be submitted on-line or by fax, mail, or telephone, after which they are entered into a database where they undergo systematic FDA review.

Finally, labeling has implications for advertising and marketing of drugs. Drug advertising generally must conform to labeling and contain information about side effects, contraindications, and effectiveness as presented in the drug label. Drug sponsors are not allowed to advertise off-label uses of drugs, although they may distribute medical literature relevant to such uses under some restrictions, usually requiring previous submission or a commitment to submit an application for the off-label use. A prominent statement that the use is not FDA approved, along with the approved labeling for the drug, must also accompany such information.

Conclusions

The FDA itself has stated that "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. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations."[17] Optimal regulatory practices with respect to off-label uses of medications may be a subject of debate in the literature and in the press. However, it is clear that (1) the risks associated with off-label use represent a broad spectrum, (2) the benefits of certain off-label uses may clearly outweigh the associated risks in certain patients, and (3) off-label use plays a vital role in the practice and evolution of modern medicine.

Physicians have the responsibility to be well informed about the drugs they are prescribing and to base off-label use on firm scientific rationale or on sound medical advice. To best appreciate and consider the potential implications and hazards of off-label use, it is imperative that anesthesia practitioners be familiar with the labels for the drugs that they use and understand the bases and shortcomings of these labels.

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