Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration: Subject Review

Committee on Drugs

ABSTRACT. Physicians who prescribe a new drug that has not been approved for a specific indication or a specific age group frequently find themselves in a quandary. Physicians who prescribe “old,” time-honored drugs usually do not consult the package insert or search for US Food and Drug Administration (FDA) approval. This statement was written to clarify the legal and informational status of the package insert and the role of the FDA in approving or not approving drugs for specific indications or specific age groups. The unapproved use of approved drugs, or so-called “off-label” use, is extremely prevalent among physicians who care for children. It is important that such use of compounds be brought up to date with current FDA policies and to emphasize the responsibility of the prescribing physician in the use of these compounds.

THE FDA AND FEDERAL LAW

FDA approval of a new drug is based on the data submitted by the manufacturer. The Federal Food, Drug, and Cosmetic Act requires that “substantial evidence” resulting from “adequate and well-controlled investigations” demonstrating that a new drug “will have the effect it purports or is represented to have under the conditions or use prescribed, recommended or suggested in the proposed labeling” be submitted to the FDA and reviewed and approved by the FDA before the drug is marketed in interstate commerce. The manufacturer can advertise or otherwise promote the drug only for the indications for which FDA approval is obtained, and all promotion must be based on information that is approved by the FDA for inclusion in the labeling of the drug. Labeling includes the package insert and is intended to provide all of the information known to be necessary for the drug to be used safely and effectively for the approved indication(s). Special groups, however, such as children and pregnant women, for whom substantial evidence of safety and efficacy has not been submitted to the FDA but for whom such an implication might otherwise be drawn, are excluded by disclaimers. FDA regulations pertaining to the specific content and format of prescription drug labeling stipulate that pediatric labeling be based on adequate, well-controlled studies involving children (Federal Register, June 26, 1979). The intention of these regulations was to encourage drug labeling that would regularly provide adequate information about the use of drugs in children. However, the result was not more adequately labeled drugs; labels now simply state that the drug’s safety and effectiveness in children have not been established. Three fourths of the prescription drugs currently marketed in the United States lack full pediatric approval and are labeled with such disclaimers. Consequently, the FDA published regulations that recognize several methods of establishing substantial evidence to support pediatric labeling claims, including relying in certain cases on studies performed in adults and in other cases permitting sponsors to characterize the available data on pediatric use of the drug or to indicate that no data are available (Federal Register, December 13, 1994). The regulations respond to concerns that current prescription drug labeling too often does not contain adequate information about the use of drugs in children and are meant to allow inclusion of more and better information to promote the safe and effective use of prescription drugs in children.

UNAPPROVED USE OF APPROVED DRUGS

An unapproved use of an approved drug refers to a use that is not included or that is disclaimed in the approved labeling. Unapproved use does not imply an improper use and certainly does not imply an illegal use. The word unapproved is used merely to indicate lack of approval, not to imply disapproval or contraindication based on positive evidence of a lack of safety or efficacy. The distinction between the lack of FDA approval of a use or dosage regimen and positive or explicit warnings or contraindications is important medically and legally.

PRESCRIPTION RESPONSIBILITY

The physician who prescribes a drug is responsible for the decision as to which drug and dosage his or her patient will receive and for what purposes. This decision is made in light of either the information contained in the drug’s labeling or other data available to the prescriber. New uses, doses, or indications will not be approved by the FDA until “substantial” evidence of safety and efficacy for that indication or age group is submitted to the FDA. This may take years or may never occur, because there is little incentive to gather and submit data for new uses after a drug has been approved for marketing. Physicians and hospitals are understandably concerned that the unapproved use of an approved drug...
may invite a variety of legal actions. The unapproved use of a drug, however, if based on reasonable medical evidence, done in good faith in the best interests of the patient, and done without fraudulent intent, requires only that the same judgment and prudence be exercised in its use as exercised in medical practice in general for it to conform to accepted professional standards.

A physician may be accountable for the negligent use of any drug in a civil action whether or not the drug has been approved. Labeling is intended neither to preclude the physician from using his or her best medical judgment in the interest of patients nor to impose liability for failure to comply with labeling restrictions. Indeed, a physician could be subject to a claim of malpractice if he or she denied a patient potentially the best treatment solely because the use was not included in the official labeling of the drug.

**EXPERIMENTATION AND RESEARCH**

One frequently raised question is whether an unapproved use of an approved drug should be viewed as experimentation requiring formalized institutional review and special consent. This question reflects a misunderstanding of what constitutes research and the status and meaning of the drug approval process. The FDA approval process regulates industry, not physicians; it does not determine per se whether treatment constitutes experimentation. The principal determinant of what is research seems to be the purpose or intent of the procedure, ie, whether it is entirely or partially in the interest of other persons compared with being solely used to meet the medical needs of the individual patient. Any medical intervention is based on consent, albeit implied in many instances. Whether institutional review, consultation, or written consent is required for a given intervention depends on the degree of risk or deviation from standard practices and the extent to which research rather than individual patient care is involved. The administration of an approved drug in a way that is not approved by the FDA is not research and does not call for special consent or review if it is given solely in the patient’s interest. However, information about the approval status of the drug for the indication prescribed may be a part of the full disclosure to which the patient or parents are entitled, just as its degree of acceptance among physicians generally may be an important issue to discuss with the patient or family.

There also seems to be confusion about whether an unapproved use requires FDA approval of an investigational new drug (IND) application. Neither an IND application nor a report to the FDA is required for a physician to use a noninvestigational drug that is already available. An IND application exempts a drug from approval requirements and permits interstate shipment of the drug for investigation of an unapproved use(s) in humans; it is not a license to perform drug research. An IND application requires prior FDA approval of the study plan, labeling of the drug (if not approved) as experimental, submission of drug and investigator information, and an agreement to obtain the consent of subjects (and/or par-ents), to submit reports of efficacy and adverse effects, and to account for the disposal of any unused drug after the study. Investigational trials involving approved drugs do not require IND applications if all of the following apply: (1) the investigation is not intended to be reported to the FDA as a well-controlled study to support a new indication or to support any other substantial change in the labeling; (2) the investigation is not intended to support a substantial change in the product’s advertising; (3) the investigation does not involve a route of administration, dose level, or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug; (4) the investigation is conducted in compliance with the requirements for institutional review and informed consent; and (5) the investigation is conducted in compliance with the requirements concerning promotion and charging for investigational drugs. An example of this would be studying the effect of carbamazepine (an anticonvulsant) on behavioral symptoms in children.

**DEVELOPMENT OF DRUG INFORMATION**

It seems reasonable to suggest that the physician who chooses to prescribe a relatively untired medication of potential importance has both a public and a professional responsibility to assist in the development of information about that drug for the benefit of other patients. Physicians are encouraged to report experiences that result from the use of drugs for unapproved uses or from clinical studies. It is especially important that information about adverse events be reported to the drug manufacturer or directly to the FDA. The law requires manufacturers to report all adverse experience reports they receive or are aware of (ie, published literature) to the FDA. Promising new uses for approved drugs might best be reported to the drug sponsor to encourage formal investigation and ultimate approval of the new indication. The full and ultimate role of a drug is rarely evident at the time of its initial approval, and many of the most important uses emerge from postmarketing clinical experience. Although these uses usually require confirmation or proof in formalized studies, they are frequently discovered through unapproved therapeutic use. In clinical practice, new uses or dosages frequently become widespread and well accepted long before they are reflected in the labeling. Manufacturers are not permitted to promote a drug for uses not approved for labeling, but after a drug is approved and available in a local pharmacy, the medical profession determines its reasonable use. Expanded indications and new dosage regimens may eventually be supportable by objective data that are acceptable to the FDA and may be incorporated into the approved labeling (eg, postapproval changes in labeling to include imipramine for enuresis, lidocaine for arrhythmias, furosemide in children, and naloxone in infants). Some approved uses ultimately may be shown to be unjustified, or even dangerous, by newer data and may be deleted from the labeling. Information about the dosage, metabolism, half-life, and side effects of some drugs in pediatric patients
frequently is not available when the drugs are initially approved. A physician who prescribes such a drug for unapproved pediatric indications can best serve the pediatric population at large while still using the drug primarily for the benefit of the patient by consulting with appropriate physicians experienced in the use of such a drug to obtain important data about the drug.

USE OF AVAILABLE DRUGS

Lack of approval for a specific use should not prevent physicians from prescribing an available drug in the best interests of their patients. The decision to prescribe a drug rests with the physician; he or she must weigh the risks and benefits of the drug in question whether or not it has full approval. The decision to prescribe an approved drug for an unapproved use should be based on all available data and should be made with the knowledge that lack of a wider approval status is usually based on the fact that the FDA has not received sufficient data from the drug’s sponsor, according to its statutory mandate, to approve labeling for such a use.

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