The physician who uses a new drug that has not been "approved" for a specific indication or a specific age group frequently finds himself in a quandary. The physician using an "old" and time-honored drug usually neither consults the package insert nor searches for U.S. Food and Drug Administration 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.

**FDA and Federal Law**

Federal law requires that, before a new drug can be marketed in interstate commerce, it must be demonstrated safe and effective for its intended uses on the basis of substantial evidence submitted to the FDA. The law further mandates that the FDA approve the labeling of a new drug and the indications for which the manufacturer can advertise or otherwise promote it. This labeling includes the package insert and is intended to provide all information necessary for the drug to be used safely and effectively. Labeling and any promotional material must include the indications and recommended doses.

FDA approval of a new drug is based on the data submitted by the manufacturer. Special groups 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. Three fourths of the prescription drugs currently marketed in the United States lack full pediatric approval and are labeled with such disclaimers.

An "unapproved" use of an approved drug refers to a use which is not included or which is disclaimed in the approved labeling. Unapproved does not imply an improper use, and certainly not an illegal use. The word "unapproved" is merely to indicate lack of approval, not to imply disapproval or contraindication based on positive evidence of 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 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 less 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. However, if based on reasonable medical evidence, if done in good faith in the best interests of the patient, and if done without fraudulent intent, an unapproved use of a drug requires only that the same judgment and prudence be exercised in its use as are 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 best medical judgment in the interest of his patient, nor to impose liability for failure to comply with labeling restrictions. Indeed, a physician could conceivably be held liable (in a malpractice action) for a departure from accepted standards of medical care if he denied a patient something that was 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, calling for 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 per se determine whether or not treatment constitutes experimentation. The principal determinant of what is research appears to be the purpose or intent of the procedure, i.e., whether it is entirely or partially in the interest of other persons as contrasted to being solely 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 of 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 important to discuss with the patient or family.

There also appears to be confusion about whether an unapproved use requires FDA approval of an investigational new drug (IND) application. Neither an IND application nor reports to the FDA are required for a physician to use a noninvestigational drug that is already available to him, whether or not it is to be used in an unapproved way or for investigation. An IND classification is an exemption that permits the interstate shipment of a drug for investigation of unapproved use(s) in humans and not a “license” to perform drug research. The IND classification 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 consent of subjects (and/or parents), to submit reports of efficacy and adverse effects, and to account for the disposal of any unused drug after the study.

Development of Drug Information

It seems reasonable to suggest that the physician who chooses to prescribe a relatively untried 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 contact the FDA when they use drugs for unapproved uses or for clinical studies. This assists the FDA in its accumulation of the data needed for the eventual approval and proper labeling of the drug for the use in question.

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, these uses are frequently discovered through unapproved therapeutic use. In clinical practice, new usage or dosage frequently becomes 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 usage. Expanded indications and new dosage regimens may eventually be supportable by objective data acceptable to the FDA and be incorporated into the approved labeling (e.g., postapproval changes in labeling to include imipramine for enuresis, lidocaine for arrhythmias, furosemide in children, and naloxone in infants). Some approved uses may ultimately be shown to be unjustified, or even dangerous, by newer data, and may be deleted from the labeling.

Information about dosage, metabolism, half-life, and side effects of some drugs frequently is not available for pediatric patients when a drug is initially approved. The physician who prescribes this type of drug for an unapproved pediatric indication can thus best serve the pediatric population at large while still using the drug primarily “for the benefit of his patient” by collaborating with a clinical pharmacologist to obtain important data about the drug.

Use of Available Drugs

Lack of approval for a specific use should not prevent a physician from prescribing an available drug in the best interests of his patients. The decision to prescribe a drug rests with the physician; he must weigh the risks and benefits of the drug in question, whether it has full approval or
not. The decision to prescribe an unapproved use of an approved drug should be made by using all available data and 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.

COMMITTEE ON DRUGS

Sydney Segal, M.D., Chairman; Sanford N. Cohen, M.D.; John Freeman, M.D.; Reba M. Hill, M.D.; Benjamin M. Kagan, M.D.; Ralph E. Kauffman, M.D.; Albert W. Pruitt, M.D.; Lester F. Soyka, M.D.; Stanley M. Vickers, M.D.

REFERENCES


PROFESSIONAL REMUNERATION

... To me it now seems a simple anthropological fact of our culture that ever wider obvious fee-chasing reduces our status and consequently our autonomy and liberty of action in real social terms. The remedy is simple enough, to receive more of our remuneration by the displaced-in-time device of salary or session payment or capitation grant in various forms.

Now I know that it is argued by many that this could not increase our liberty but would reduce it by making us dependent on some potentially ill-disposed paymaster. There is no good evidence to support that view. One has only to look at the liberty of action and freedom from interference enjoyed by the judiciary, and also by academics, politicians and clergy, to realise that a salary is compatible with great professional freedom. And people actually want medicine in a way they don’t at all want judgement, learning, politics or God. ...

The fact is there are fewer and fewer countries left which allow the anarch and inequities involved in a laissez-faire market in health care resources and social services.

... Fees-for-service which so many doctors rationalise into a pre-requisite for freedom, are now I think going to be seen to be counterproductive of real professional liberty, though they could still provide relative riches for short periods here and there because of inconsistencies of administration and valuation.

E. HACKETT
Submitted by Student

Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the FDA

Pediatrics 1978;62;262

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