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Committee on Drugs

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ABSTRACT. New regulatory initiatives have been designed to ensure that new drugs and biologicals include adequate pediatric labeling for the claimed indications at the time of, or soon after, approval. However, because such labeling may not immediately be available, off-label use (or use that is not included in the approved label) of therapeutic agents is likely to remain common in the practice of pediatrics. This policy statement was written to address questions practitioners have regarding off-label use. The purpose of off-label use is to benefit the individual patient. Practitioners may use their professional judgment to determine these uses. Practitioners should understand that the Food and Drug Administration does not regulate off-label use.

ABBREVIATIONS. FDA, Food and Drug Administration; IND, investigational new drug; FDAMA, Food and Drug Administration Modernization Act of 1997.

OFF-LABEL USE OF APPROVED DRUGS

Off-label use of an approved drug refers to a use that is not included in the approved label.* Omission of uses for a specific age group or a specific disorder from the approved label means that the evidence required by law to allow their inclusion in the label has not been submitted to the Food and Drug Administration (FDA). This circumstance is often reflected in statements such as "safety and efficacy in pediatric patients have not been established" in the product label. Off-label use does not imply an improper use and certainly does not imply an illegal use or a contraindication based on evidence. Explicit evidence-based warnings and contraindications are provided in product labels. The distinction between lack of FDA approval of a use or dosing regimen and explicit warnings or contraindications against uses is important medically and legally.

The package insert (label) is intended to provide all of the information judged to be necessary for the drug or biological to be used safely and effectively for the approved indication(s). Special groups, how-

ever, such as children and pregnant women, have commonly been excluded by disclaimers in the label because substantial evidence of safety and efficacy has not been submitted to the FDA. Three fourths of the prescription drugs currently marketed in the United States lack pediatric use information and are labeled with such disclaimers.^{1,2} Most drugs have not been adequately studied in the pediatric population. Recent regulations and legislation have been introduced to improve this situation. A description of these is provided in Appendix 1.

THE FDA AND FEDERAL LAW

The FDA regulates the manufacture, labeling, and promotion of drugs; it does not regulate the use of drugs by physicians (ie, the practice of medicine). The FDA's approval of a new drug is based on data submitted by the manufacturer. The Food, Drug, and Cosmetic Act³ 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 of use prescribed, recommended, or suggested in the proposed labeling," be submitted to and reviewed and approved by the FDA before the drug is marketed in interstate commerce. For biologicals (eg, vaccines) proof of effectiveness consists of "adequate and well-controlled studies" as defined for new drugs in the Code of Federal Regulations.⁴ Biologicals are approved under the Public Health Service Act.⁵ Given these requirements as well as the rapid pace of medical discovery, it is not surprising that labels do not reflect all possible uses of an agent.

PRACTITIONER RESPONSIBILITY

The practitioner who prescribes a drug is responsible for deciding which drug and dosing regimen the patient will receive and for what purposes. This decision is made on the basis of the information contained in the drug's label or other data available to the prescriber. The off-label use of a drug should be based on sound scientific evidence, expert medical judgment, or published literature. New uses, doses, or indications will not be approved by the FDA until substantial evidence of safety and effectiveness for that indication or age group is submitted to the FDA. This may take years or may never occur, because until recently, there has been little incentive for manufacturers to conduct trials and submit data for new uses in pediatric patients. Practitioners may be concerned that the off-label use of an approved drug may invite a variety of legal actions. To con-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

*See also Title 21 Section 201.56 (21 CFS 201.56)—General requirements on content and format of labeling for human prescription drugs. The labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug. The labeling shall be informative and accurate and neither promotional in tone nor false or misleading in any particular. The labeling shall be based whenever possible on data derived from human experience.

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form to accepted professional standards, the off-label use of a drug should be done in good faith, in the best interest of the patient, and without fraudulent intent.

A practitioner may be accountable for the negligent use of any drug in a civil action whether or not the FDA has approved the use of that drug. Labeling is not intended to preclude the practitioner from using his or her best medical judgment in the interest of patients or to impose liability for off-label use. Indeed, the practice of medicine may require a practitioner to use drugs off-label to provide the most appropriate treatment for a patient.

EXPERIMENTATION AND RESEARCH

One frequently asked question is whether an off-label use of an approved drug should be viewed as experimentation requiring formalized institutional review and informed consent. This question reflects a misunderstanding of what constitutes research. The FDA approval process does not determine whether treatment constitutes experimentation and research. According to federal regulations, "Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice."⁶ In most situations, off-label use of medications is neither experimentation nor research. 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 in the individual patient's best interest. However, discussion about the off-label status of a drug may, as a matter of professional judgment, be part of the information provided to the patient or parents. Similarly, the degree of acceptance among physicians of an off-label drug treatment may be an important issue to discuss with a patient or family.

There seems to be confusion also about whether an off-label use requires submission of an investigational new drug (IND) application to the FDA. Use of approved drugs in an off-label manner to treat an individual patient does not require an IND application. The IND regulations "do not apply to the use in the practice of medicine for an unlabeled indication."⁷ In fact, the IND process regulates interstate shipment of the drug for investigation of an unapproved use in humans. For further description of the IND process, see Appendix 2.

DEVELOPMENT OF DRUG INFORMATION

Physicians who choose to prescribe a medication with limited pediatric data have a public and a professional responsibility to assist in the systematic development of the information about that drug for

the benefit of other patients. Practitioners are encouraged to publish experiences that result from such off-label uses of drugs. It is also important that information about adverse events be reported to the drug manufacturer or directly to the FDA. Physicians or other practitioners should report serious adverse events via the FDA's MedWatch program by mail, phone, or Internet (<http://www.fda.gov/medwatch>). The law requires manufacturers to report all adverse experience reports they receive or are aware of (eg, published literature) to the FDA. Promising new uses for approved drugs might best be reported to the drug sponsor to encourage formal investigation. The full and ultimate role of a drug is rarely evident at the time of its initial approval and labeling. Many of the most important uses and toxicities emerge from postmarketing clinical experience. Although these uses are often discovered through off-label therapeutic use, confirmation of efficacy and safety in formal studies is usually required. In clinical practice, new uses or dosing regimens often become widespread and well accepted long before they are reflected in the labeling.

Expanded indications and new dosing regimens may eventually be supported by objective data that may be incorporated into the approved labeling. For example, postapproval changes in labeling include imipramine hydrochloride for the treatment of enuresis, lidocaine hydrochloride for the treatment of arrhythmias in children, furosemide for use in children, and naloxone hydrochloride for use in infants. Postmarketing safety experience may ultimately lead to restriction of labeled or off-label uses of the drug or eventual withdrawal from the market. Information about the dosage, metabolism, elimination, and adverse effects of drugs in pediatric patients is often not available when the drugs are approved initially. The decision to prescribe an approved drug for an off-label use should be based on all available data.

APPENDICES

Appendix 1. Recent Regulations and Legislation to Increase the Study of Drugs in Pediatric Patients

A regulation published in 1994 (the "1994 Pediatric Final Rule"⁸) that recognizes several methods of establishing substantial evidence to support pediatric labeling remains in effect. These methods include relying in certain cases on efficacy studies performed in adults and other supporting information to adequately label the product for safe and effective use in the pediatric population. The FDA has issued a new regulation (the "1998 Pediatric Final Rule"⁹), which became effective April 1, 1999, that requires pediatric studies of certain new and marketed drugs and biologicals. This rule establishes a presumption that new drugs and biologicals will be studied in pediatric patients unless the requirement is waived. The 1998 Pediatric Final Rule is designed to ensure that new drugs and biologicals contain adequate pediatric labeling for the claimed indications at the time of, or soon after, approval. Under this rule, the FDA can require studies to assess the safe and effective use of the drug or biological in the pediatric population for the claimed indications. This rule also authorizes the FDA to require pediatric studies of marketed drugs and biologicals when there is a compelling need for studies (ie, the product is used in a substantial number of pediatric patients or the product provides a meaningful therapeutic benefit over existing treatments for pediatric patients and, in either case, the absence of adequate labeling could pose significant risks for pediatric patients).

In 1997, a law was enacted (the Food and Drug Administration

Modernization Act of 1997 [FDAMA]¹⁰) that contains provisions establishing economic incentives to drug manufacturers for conducting pediatric studies of drugs for which exclusivity or patent protection is still available.⁹ A manufacturer that conducts pediatric studies required by the 1998 Pediatric Final Rule may qualify for economic incentives provided by FDAMA.

All these changes respond to concerns that drugs and biologicals have not been adequately studied in the pediatric population or if studied, the information required to meet the statutory requirement for the product to be declared safe and effective in this population has not been submitted to the FDA. Whereas current prescription product labels do not include adequate pediatric use information, these regulatory measures have been instituted to improve our knowledge base to provide better prescribing information for practitioners who care for pediatric patients.

Appendix 2. The IND Process

An IND application requires submission of a study protocol, labeling of the drug as investigational, submission of drug and investigator information, and an agreement to obtain the consent of subjects (and/or parents), to submit reports of adverse events, and to account for any unused drug after the study. After receipt of an IND application, the FDA reviews the application to determine whether proceeding with the study is safe. Investigational trials involving marketed 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 significant change in the labeling; 2) the investigation is not intended to support a significant change in the product's advertising; 3) the investigation does not involve a route of administration, dosing 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.⁷

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ADDITIONAL RESOURCE

Beck JM, Azari ED. FDA, off-label use, and informed consent: debunking myths and misconceptions. *Food Drug Law J.* 1998;53:71–104

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