abstract

The passage of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act has collectively resulted in an improvement in rational prescribing for children, including more than 500 labeling changes. However, off-label drug use remains an important public health issue for infants, children, and adolescents, because an overwhelming number of drugs still have no information in the labeling for use in pediatrics. The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term “off-label” does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient. *Pediatrics* 2014;133:563–567

INTRODUCTION

The purpose of this statement is to further define and discuss the status of off-label use of medications in children. Since publication of the 2002 statement from the American Academy of Pediatrics on the off-label use of drugs, the number of drugs approved by the US Food and Drug Administration (FDA) with pediatric indications or expanded labeling that informs drug use in pediatric patients (eg, pharmacokinetic/pharmacodynamic data, safety data) has substantially increased. The passage of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) has resulted in more than 500 pediatric labeling changes. However, despite this success and advances in both basic science and clinical trials in pediatrics, off-label drug use remains a common and important issue for children and adolescents. Moreover, off-label use of drugs presents an even larger and more complex issue in preterm and full-term neonates, infants and in children younger than 2 years, and children with chronic and/or rare diseases.

DEFINING OFF-LABEL USE

The term “off-label” use refers to use of a drug that is not included in the package insert (approved labeling) for that drug. The purpose of off-label use is to benefit an individual patient. It is important to note that the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use. To approve a drug for sale and marketing within the United States, the FDA requires substantial
evidence for efficacy and safety, usually in the form of 2 well-controlled trials. Subsequent requests by a sponsor to add a new indication to drug labeling must also be accompanied by additional evidence in support of that indication. If the FDA finds that such evidence supports approval, the new indication is added to the product labeling. If the evidence is deemed insufficient or if the sponsor chooses not to submit evidence, the indication is not added.

According to the Code of Federal Regulations, a sponsor is the entity that holds an investigational new drug application and that both takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. A sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual who uses 1 or more of his or her own employees to conduct an investigation that he or she has initiated is considered to be a sponsor, not a sponsor-investigator. In this case, the employees are investigators. Sponsor-investigators both initiate and conduct an investigation and direct the administration or dispensing of the investigational drug. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor: It is important to note that sponsors are not allowed to promote or even speak to off-label use. If a physician speaks on behalf of a sponsor, the same rule applies. It is acceptable to use drugs off label and to publish results related to off-label use, but it is not acceptable to receive remuneration from the sponsor for these uses.

The absence of labeling for a specific age group or for a specific disorder does not necessarily mean that the drug’s use is improper for that age or disorder. Rather, it only means that the evidence required by law to allow inclusion in the label has not been approved by the FDA. Additionally, in no way does a lack of labeling signify that therapy is unsupported by clinical experience or data in children. Instead, it specifically means that evidence for drug efficacy and safety in the pediatric population has not been submitted to FDA for review or has not met the regulatory standards of “substantial evidence” for FDA approval. In contrast to the absence of pediatric-specific information on some medications, other drug labels contain statements such as “the safety and efficacy in pediatric patients have not been established,” and explicit evidence-based warnings and contraindications are included on the label where indicated.

Understanding the distinction between the lack of FDA approval for a particular use or dosing regimen in the former case versus explicit warnings or contraindications against use in the latter is essential for the pediatric practitioner. In addition, when considering best practices for therapeutic decision-making, it is essential to understand that the FDA does not regulate the use of drugs as they pertain to the practice of medicine.

THE ROLE OF THE FDA

The FDA is the federal government agency charged with overseeing responsibility for the manufacturing, labeling, advertisement, and safety of therapeutic drugs and biological products. The 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 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 drugs and biological agents (eg, vaccines, antibodies), proof of effectiveness consists of “adequate and well-controlled studies” as defined for new drugs in the Code of Federal Regulations. Biological agents are approved under the Public Health Service Act. Given these requirements as well as the rapid pace of medical discovery, it is not surprising that labeling does not reflect all possible uses of an agent. Off-label use of drugs in children is not overseen by the FDA, because the FDA does not regulate the prescription practices of individual practitioners.

The FDA maintains a system for postmarketing drug surveillance, compiling and analyzing information about the incidence and severity of adverse events reported by practitioners, sponsors, hospitals, and other health care facilities. It is important to note that this postmarket surveillance system is passive and that the total number of adverse event reports in pediatrics relative to adults is small. To address this issue, the BPCA provides for a systematized review of adverse event reports in pediatric patients through the FDA Pediatric Advisory Committee. When the FDA notes an apparent association between use of a drug and an adverse event, the FDA may choose from several actions: to request further focused study of the drug, to add a contraindication or warning to the drug labeling, to issue a warning about use of the drug, or to seek voluntary or compulsory removal of the drug from the market. Therefore, although the FDA does not regulate the practice of medicine, practitioners should be aware of new information brought forward by the FDA, because it can serve as a valuable resource for information regarding the potential or proven adverse effects of drugs (see www.fda.gov).
THERAPEUTIC DECISION-MAKING

Therapeutic decision-making should always be guided by the best available evidence and the importance of the benefit for the individual patient. Practitioners are in agreement regarding the importance of practicing evidence-based medicine. However, for the pediatric population, gold standard clinical trials are often not available, so practitioners must rely on either less definitive information, such as expert opinion for the age group that they are treating, or use evidence from a different population to guide practice. There are now many resources available to help assess the quality of evidence-based medicine, including but not restricted to articles in peer-reviewed journals, American Academy of Pediatrics practice guidelines and policy statements, consensus statements, and handbooks and databases (ie, Cochrane, Lexicomp, and Harriet Lane). At times, there may be little or no published information to guide therapy. This situation is especially true when treating rare diseases or sparse populations such as neonates. In such situations, the practicing physician can play an important role in adding to therapeutic information by publishing his or her experience with off-label uses of drugs. These reports can serve as the basis of more formal efficacy and safety studies and can serve as a therapeutic decision-making resource for other physicians. The practicing physician also has a responsibility to report adverse events to the FDA through the Medwatch program (www.fda.gov/Safety/MedWatch).

In most situations, off-label use of medications is neither experimentation nor research. The administration of an approved drug for a use that is not approved by the FDA is not considered research and does not warrant special consent or review if it is deemed to be in the individual patient’s best interest.6 In general, if existing evidence supports the use of a drug for a specific indication in a particular patient, the usual informed-consent conversations should be conducted, including anticipated risks, benefits, and alternatives. If the off-label use is based on sound medical evidence, no additional informed consent beyond that routinely used in therapeutic decision-making is needed.10 However, if the off-label use is experimental, then the patient (or parent) should be informed of its experimental status.11 It would be prudent for pediatricians to know and abide by the appropriate informed consent laws in their respective states. In addition, particular risk-benefit ratios presented by the unproven therapies must be carefully considered and disclosed, and standard of care practices should be reviewed. When use of a drug is truly investigational, drug use should be performed in conjunction with a well-designed clinical trial whenever possible. This is especially true when the physician proposes to treat a group of patients rather than a single individual. Patients and/or their legal guardians should be specifically informed that the proposed therapy is investigational, and their consent to proceed despite the risks of investigational therapy should be carefully documented. Whether institutional review, consultation, or written consent are required for a given intervention depends on the degree of risk or departure from standard practices and the extent to which research, rather than individual patient care, is involved.

Practitioners may be concerned that the off-label use of an approved drug may invite a variety of legal actions. To conform 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, regardless of whether 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 will more than likely require a practitioner to use drugs off label to provide the most appropriate treatment of a patient. However, because the use of drugs in an off-label capacity can increase the liability risk for a practitioner should an adverse event or poor outcome ensue, it is essential that practitioners document the decision-making process to use a drug off label in the patient’s medical record.

FEDERAL LEGISLATION TO INCREASE DRUG TESTING IN CHILDREN

The BPCA and the PREA are 2 complementary federal laws that have substantially increased clinical evaluation and labeling of drugs in children both by the pharmaceutical industry and through government-sponsored trials.8 The PREA mandates that almost all new drugs and certain approved drugs must be studied in children for approved uses of the product if there is potential for use of that drug in children and that the application for new drug approval include the results of adequate pediatric studies unless the studies are deferred or waived by the FDA. The BPCA allows sponsors to qualify for an additional 6 months of market exclusivity if the sponsor completes and submits pediatric studies to the FDA, as outlined in an FDA-issued written request. A written request may include off-label as well as approved uses of a drug. In addition, the BPCA authorizes the National Institutes of Health, in conjunction with the FDA.
and physicians from clinical disciplines, to work together to assign priority for testing of specific drugs in children. The National Institutes of Health, acting through the Eunice Kennedy Shriver National Institute of Child Health and Human Development, then solicits proposals for pediatric drug testing concordant with the drug prioritization recommendations and funds clinical studies that are judged meritorious by external review. The ratification of these 2 laws has been considered a significant success, because there have been more than 500 pediatric labeling changes. Also as a result of these laws, increased prospective pediatric drug testing has occurred via industry-sponsored studies, investigator-initiated studies, and consortia, such as the National Institute of Child Health and Human Development–funded Pediatric Trials Network. The net result has been an expansion of both pediatric labeling information and the knowledge base from which practitioners can draw to make informed therapeutic decisions.\(^\text{12,13}\)

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act,\(^\text{14}\) reauthorizing and strengthening the BPCA and PREA. The legislation aims to ensure that pediatric evaluations under PREA are conducted earlier in the drug development process to improve the quality of and accountability for completion of such studies and to advance the neonatal drug studies under the BPCA and PREA. The legislation also makes both the BPCA and PREA permanent law.

### CONCLUSIONS

Off-label drug use remains an important public health issue, especially for infants, young children, and children with rare diseases. Evidence, not label indication, remains the gold standard from which practitioners should draw when making therapeutic decisions for their patients. The PREA and BPCA have been extremely successful and represent an essential first step in expanding this evidence as a means of achieving the ultimate goal that any and all drugs used to treat children will have age-appropriate evidence sufficient to provide information for labeling. However, labeling with pediatric information still exists in less than 50% of products,\(^\text{15}\) such that much work remains to be done to ensure the best possible practice for therapeutic decision-making in pediatrics.

### RECOMMENDATIONS

1. The practitioner who prescribes a drug is responsible for deciding which drug and dosing regimen the patient will receive and for what purpose.
   a. This decision should be made on the basis of the information contained in the drug’s labeling (when available) or other data available to the prescriber.
   b. The use of a drug, whether off or on label, should be based on sound scientific evidence, expert medical judgment, or published literature whenever possible.
   c. Off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature.

2. Pediatricians should continue to advocate for necessary incentives and requirements to promote the study of drugs in children.

3. Physician researchers are encouraged to continue the rational and critical study of drugs in children through conducting and/or collaborating in well-designed pediatric drug studies, including national consortium studies.

4. Journals should be encouraged to publish the results of all well-designed investigations, including negative studies.

5. Institutions and payers should not use labeling status as the sole criterion that determines the availability on formulary or reimbursement status for medications in children. Similarly, less expensive therapeutic alternatives considered appropriate for adults should not automatically be considered appropriate first-line treatment in children. Finally, off-label uses of drugs should be considered when addressing various drug-related concerns, such as drug shortages.

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