FDA aims to remove unapproved drugs from market Risk-based enforcement program focuses on removing potentially harmful products

Your patients may not be aware that all drugs dispensed from their pharmacy are not FDA approved. The Federal Food, Drug, and Cosmetic Act (FFDCA) generally requires that drugs marketed in the United States be shown to be both safe and effective prior to marketing and widespread use in the general population. FDA's evidence-based system of drug approval and the OTC monograph system play essential roles in ensuring that all drugs are both safe and effective. Drugs that are marketed without required FDA approval, however, may not meet modern standards for safety, effectiveness, quality, and labeling. Physicians and other health care practitioners, along with consumers, cannot assume that all marketed drugs have been determined by FDA to be safe and effective.

Background

For a variety of historical reasons, some drugs, mostly older products, continue to be marketed illegally in the United States without required FDA approval. Many older products introduced before FFDCA was passed in 1938 were tested in accordance with the 1906 Pure Food and Drug Act, which required only that drugs meet certain standards for strength and purity but not for safety. The FFDCA of 1938 required manufacturers to prove that the new drug was safe. Despite enactment of this legislation, some new drugs considered identical, related, or similar (IRS) to drugs already approved were not tested until the amendments to FFDCA in 1962. For the first time, drug manufacturers were required to prove to the agency the effectiveness of their products before marketing them. The newly amended act provided for a retroactive evaluation of the safety and the effectiveness of new drugs marketed between 1938 and 1962. This evaluation process was called the Drug Efficacy Study Implementation (DESI) review. Drugs entering the market between 1938 and 1962 that were approved for safety but not effectiveness are referred to as "DESI drugs." Drugs that are IRS to such drugs are also called DESI drugs.

In 1966, FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to expedite the evaluation of the effectiveness FDA still requires approved applications as a condition of continued marketing of the drug and all IRS drugs. Too often, people mistakenly claim that a product is a DESI drug and, therefore, does not require an approved application; this is inaccurate.

All drugs must have FDA approval or comply with an OTC drug monograph unless they fall into one of the following categories: DESI pending, OTC monograph pending, generally recognized as safe and effective (GRASE), or grandfathered.

DESI pending or

OTC monograph pending

Some unapproved marketed products are still undergoing DESI reviews and a final determination regarding efficacy has not yet been made. In virtually all these proceedings, FDA has made an initial

Table 1. Unapproved drugs FDA has moved against

Drug	Rationale
Carbinoxamine drug	Associated with 21 infant deaths
Quinine sulfate drug products	665 reports of adverse events, including 93 deaths; labeling lacked necessary warnings and safe dosing information
Ergotamine-containing drug products	Labeling omitted critical warnings about potential for serious, possibly fatal drug–drug interactions
Trimethobenzamide hydrochloride suppositories	Lacked evidence of effectiveness
Timed-release drug products containing quaifenesin	Directly competed with an approved drug
Hydrocodone products	Inadequate safety-related labeling or improperly suggested it was safe for young children
Injectable colchicine	50 reports of adverse events, including 23 deaths

of 4,000 drugs approved on the basis of safety alone between 1938 and 1962. If the final DESI review determination classifies a drug as ineffective, the product and all products IRS to it are no longer permitted to be marketed and are subject to enforcement action. Even if DESI (and IRS) products are found to be effective,

determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. The agency's longstanding policy is that products subject to an ongoing DESI proceeding may remain on the market while the proceeding is pending. OTC drugs awaiting the publication of a final OTC monograph may also remain on the market, subject to current enforcement policies.

GRASE

GRASE is a term used to describe certain old drugs that do not require prior approval from FDA in order to be marketed because they are generally recognized as safe and effective based on published scientific literature. FFDCA defines a new drug, which requires approval, as any drug "the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling."

Many firms that have marketed their products for a long time based on anecdotal data claim to be GRASE; this is incorrect. Only consensus among experts that the product is safe and effective based on published scientific literature regarding the finished drug product of the same quality and quantity needed to approve a drug can establish that a product is GRASE. It is unlikely that any currently marketed prescription drug is GRASE.

Grandfathered

Drugs that entered the market before the passage of the 1938 act or the 1962 amendments to the act are often referred to as grandfathered drugs. Under the 1962 grandfather clause, the FFDCA exempts a drug from the effectiveness requirements if its composition and labeling have not changed since 1962 and if, on the day before the 1962 amendments became effective, it was (1) used or sold commercially in the United States, (2) not a new drug as defined by the act at that time, and (3) not covered by an effective application.

Many older drugs without FDA approval claim to be grandfathered; however, FDA believes that very few drugs are on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, labeling, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion.

FDA's concerns

The FDA's drug approval process provides a review of product-specific information that is critical to ensuring the safety and efficacy of a finished drug product. For instance, the applicant must demonstrate that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. Furthermore, FDA's review of the applicant's labeling ensures that health care professionals and patients have the information necessary to understand a drug product's risks and its safe and effective use.

The manufacturers of drug products marketed illegally either have not received FDA approval or, in the case of OTC products, do not conform to the OTC drug monograph. These manufacturers

"FDA uses a risk-based enforcement program to concentrate its resources on those products that pose the greatest threat to public health, without imposing undue burdens on consumers or unnecessarily disrupting the market."

circumvent the FDA process of demonstrating that their products are safe and effective. Whether the unapproved drug predates 1938 or is a more recent addition to the market, the main concern with all unapproved drugs is the lack of evidence demonstrating that they are safe and effective.

Unapproved drugs initiative

Because several thousand unapproved drug products are marketed illegally, FDA uses a risk-based enforcement program to concentrate its resources on those products that pose the greatest threat to public health, without imposing undue burdens on consumers or unnecessarily disrupting the market.

In June 2006, FDA announced a new drug safety initiative to remove unapproved drugs from the market. The initiative included a final guidance titled Marketed Unapproved Drugs—Compliance Policy Guide (CPG, available at www.fda.gov/cder/guidance/6911fnl.pdf), which

outlined enforcement policies aimed at efficiently and rationally bringing all such drugs into the approval process. For all unapproved drugs, the CPG gives highest enforcement priority to the following:

- Drugs with potential safety concerns
- Drugs that lack evidence of effectiveness
- Fraudulent drugs
- Drugs that present challenges to the new drug approval and OTC drug monograph systems
- Unapproved new drugs that also violate the FFDCA in other ways
- Drugs with formulation changes made as a pretext to avoid enforcement
- Unapproved drugs that directly compete with an approved drug

Since publication of the CPG, the agency has taken enforcement actions against a number of firms with major violations of current good manufacturing practices (CGMPs) that also make large numbers of unapproved drugs. Table 1 shows various unapproved drugs against which FDA has taken action. FDA encourages voluntary compliance and creates incentives for manufacturers of marketed, unapproved drugs to seek approval of their products.

Importance to health care professionals

To find out if a drug is FDA approved, go to Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and type in the active ingredient or name of the drug. Names of the approved manufacturers of a drug will be displayed. FDA is taking steps to ensure that all marketed U.S. drugs have required approval. Because unapproved drugs are still on the market, however, pharmacists, other health care professionals, and patients should carefully consider the medical condition being treated, the patient's previous response to a drug, and the availability of approved alternatives for treatment.

—Janelle Derbis, PharmD; Brenda Evelyn; and Judy McMeekin, PharmD Contributing writers

Janelle Derbis and Brenda Evelyn are with FDA's Office of Special Health Issues. Judy McMeekin is with FDA's Center for Drug Evaluation and Research, Office of Compliance, Division of New Drugs and Labeling Compliance.