

## The FDA Takes Action Against Unapproved Drugs

*By Michelle Meadows*

Most prescription drugs marketed in the United States have been reviewed and approved by the Food and Drug Administration as required by law. Thousands of unapproved prescription drugs, however, are still being prescribed and sold. The FDA, as part of its drug safety efforts, is bolstering its efforts against unapproved drugs in the United States.

"Although we estimate that less than 2 percent of prescribed drugs are unapproved, we believe that some unapproved products raise safety concerns that warrant regulatory action," says Deborah Autor, director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research (CDER).

There are several reasons why an unapproved drug may be available. One example is when only one company may have approval to market a drug, but other companies are illegally marketing their versions of the drug without having gone through the FDA's approval process. Another scenario is that a combination of ingredients is approved by the FDA, but a company is marketing a single ingredient without approval.

Some older products continue to be marketed illegally for historical reasons. "Many drugs were marketed before Congress made changes to the law requiring drugs to undergo FDA review," Autor says. There are unapproved drugs whose makers claim the drugs are "grandfathered" under older standards and therefore don't require approval under the current regulatory framework. "But the truly 'grandfathered' drugs represent only a few, at most, of all the unapproved drugs being marketed," Autor says. "Most unapproved drugs do require FDA approval."

Some drugs have been sold for so many years that physicians and pharmacists may not know they are unapproved. They even may be unaware that unapproved drugs are advertised in medical journals and listed in the Physicians' Desk Reference (PDR) and other reference books. These practices give the false impression that the drugs were reviewed and approved by the FDA.

"Consumers who discover that they are taking an unapproved drug shouldn't stop treatment without talking to their doctor first," Autor says. The FDA advises consumers and health professionals to carefully consider the medical condition being treated, the patient's previous response to the drug, and the availability of approved alternatives as part of discussing the benefits and risks of any unapproved treatment.

The major categories in which unapproved drugs exist include certain cough and cold preparations with antihistamines, some narcotics, and some types of sedatives. Examples include

- unapproved prescription cough and cold preparations with antihistamines, such as Pheniramine maleate and Dexbrompheniramine maleate
- unapproved prescription single-ingredient narcotics such as Codeine phosphate and Oxycodone HCL 5mg
- unapproved prescription sedatives such as Phenobarbital and Chloral hydrate.

## Enforcement

In June 2006, the FDA issued a guidance called Marketed Unapproved Drugs—Compliance Policy Guide, which describes plans for enforcement in this area.

"The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market," Autor says. "Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

A patient or physician may believe a drug is safe based on individual experience, but the FDA relies on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with taking a placebo or another accepted therapy. FDA approval means not only that the product has been reviewed for safety and effectiveness, but that the agency has reviewed manufacturing quality and product labeling to ensure that it adequately conveys the drug's risks and benefits. FDA approval also means that a drug's safety and effectiveness is still monitored after marketing.

Before pursuing regulatory action against unapproved drugs, the FDA plans to consider the effects on the public health, including whether the product is medically necessary. The agency recognizes that some unapproved therapies offer benefits. An example is Phenobarbital, a drug used to control seizures. In some cases, FDA action requiring drug approvals will be gradual to avoid shortages of medically necessary products.

The guidance explains that the FDA will continue to focus enforcement actions on unapproved drugs that carry potential safety risks, lack evidence of effectiveness, and constitute health fraud. For example, the FDA has ordered all manufacturers of unapproved carbinoxamine-containing products to stop making them because of safety concerns regarding their use in children younger than 2 years. Carbinoxamine is a sedating antihistamine. Manufacturers will need to obtain FDA approval to continue marketing these products.

The FDA has received 21 reports of death associated with carbinoxamine-containing drugs in children younger than 2 years. While it is not clear that the carbinoxamine caused these deaths, the FDA is concerned about the risks. Some of the unapproved products are being promoted for infants and young children, an age group in which carbinoxamine has never been studied. And young children are more susceptible to drug-related adverse events.

Some of these unapproved products are labeled for treatment of cough and cold symptoms, an indication for which carbinoxamine has not been found safe by the FDA. The two carbinoxamine-containing products approved by the FDA are indicated for treating allergic reactions or their symptoms, and are manufactured by Atlanta-based Mikart Inc. The products contain carbinoxamine maleate as the active ingredient without any additional active ingredients.

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