Phony pharm

Counterfeit products are challenging the ability of the FDA and others to ensure safe and effective drugs.

BY CHARLES W. SCHMIDT

Recently, Colombian officials from Bogota raided a crude laboratory and busted a criminal gang that was busy processing illegal drugs. Sound familiar? Sure, you're probably thinking cocaine. Think again. The group caught by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos, or INVIMA, the Colombian equivalent of the FDA, was making counterfeit prescription drugs—in some cases simply by adding colored dye to powdered cement. The material was being used to fill gelcaps that would then be packaged and sent off to local pharmacies.

"It's just outrageous," says Tom Kubic, executive director of the Pharmaceutical Security Institute in Virginia, who is assisting in the Colombian investigation. "Some of these drugs were undoubtedly sold to people who were seriously ill." Kubic, previously with the U.S. Federal Bureau of Investigation, says that up to 40% of prescription drugs sold in Colombia are counterfeit. Indeed, the problem of counterfeit or substandard drugs is endemic throughout Latin America and much of the developing world. The World Health Organization estimates that as much as 7–10% of the global supply of pharmaceuticals may be phony, leading to worldwide losses to the pharmaceutical industry in the range of $20–40 billion.

Using inert or even toxic substances in place of legitimate formulations, as in the Colombian example, is only one in a wide range of counterfeiting practices. Counterfeiters also refill new containers with expired pills, sell expired drugs with fabricated labels bearing new dates, produce dilute medications with little or no active ingredient, and sell older-generation drugs packaged in new-generation containers.

These adulterated products are increasingly being detected in the United States. As of July 2002, the FDA's Office of Criminal Investigations has opened 16 cases of drug counterfeit and made 12 arrests leading to 7 convictions. Among the more recent cases are those involving Zyprexa, a leading antipsychotic with annual sales of $1.8 billion; Epogen, a treatment for anemia in patients with renal failure, with annual sales of $2 billion; and Combivir and Serostim, two HIV medications. The potential health consequences of taking counterfeit drugs are serious, and in some cases, deadly. In the case of Combivir, the drug was swapped with another HIV medication called Ziagen, which is half the price of Combivir and causes a life-threatening reaction in 5% of people who take it.

Evidence of harm

There is little information documenting the health impacts of drug counterfeits on U.S. consumers, although most known instances of counterfeit in the United States have been detected before patients were harmed (see box, "Harm at home?"). But patients in developing countries have not been so lucky. In Haiti and Bangladesh, hundreds of children have died after consuming what was ostensibly paracetamol syrup (used to treat fever) but was actually made of antifreeze. And commonly faked drugs are used to treat some of the developing world's leading killers, including HIV and malaria. A recent study (*Lancet* **2001,** *357,* 1948–1950) found that 38% of tested antimalarials purchased in Southeast Asia, all of which purported to contain artesunate, a pivotal compound used in areas with rampant multidrug resistance, contained no active ingredient.

Lewis Kontnik, a principal with Reconnaissance International, an anticounterfeiting consultancy in Greenwood Village, CO, says a globalized marketplace and the lure of rising drug prices combine to attract counterfeiters here and abroad. "The crooks are catching on," he says. "They know they can make a lot of money with these high-value, hot-demand products." According to Kubic, counterfeiters are a diverse group—many of them possess highly sophisticated technology for making duplicate packaging and medical formulations. The Pharmaceutical Security Institute has recently identified drug counterfeiters with links to organized crime in Italy, some of them operating on a multinational basis throughout Western Europe. There is also growing evidence, he says, of counterfeiters in Latin America working with gangs involved in the narcotics trade.

The gray markets

Counterfeit drugs in the United States often move through murky channels in a

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booming "gray market". In these secondary markets, free samples and deeply discounted drugs intended for nonprofit hospitals and charities are diverted and resold—providing a portal through which adulterated, expired, and counterfeit pharmaceuticals enter the drug distribution system. "Drugs in the gray market change hands so many times it's hard to follow them," says Marv Shepard, director of the Center for Pharmacoeconomic Studies at the University of Texas. "The criminals are sophisticated. They have all the right paperwork, so it's hard for pharmacies to know that what they're buying is fake."

A particularly egregious gray market strategy is the so-called U-boat diversion, through which exported drugs are intercepted by criminals, repackaged, and returned for resale in the United States. In many cases, these discounted drugs are destined for people in developing countries who desperately need them. Citing research published by the Pharmaceutical Research and Manufacturers of America, Shepard says, "Up to 50% of the drugs shipped to South Africa never reach the South African bloodstream."

An open U.S. border

Stopping counterfeit drugs at the U.S. borders is a nearly insurmountable challenge. Customs inspectors with limited resources cannot check the authenticity or the origin of most prescription drugs. Perhaps the most porous barrier of all is the mail system, through which 2 million parcels containing FDA-regulated products enter the United States annually. In recent years, the mail has become inundated with drug imports bought by consumers in America on the Internet. According to the U.S. General Accounting Office, nearly half of the 300 to 400 Internet pharmacies operating today are based in countries outside the United States. Most countries, particularly developing ones, do not require pharmaceutical licensing—anyone with the money can set up shop and sell prescription drugs.

Those who sell counterfeits are apt to pick the most expensive, best-selling drugs. Viagra is a prime example: The pills are in hot demand, and they cost up to $6 apiece. Online consumers looking for Viagra want a deal, and counterfeiters are willing to provide it. In April 2002, a 17-month investigation by the Manhattan District Attorney's office in New York snagged a rare prize: the culprits behind an Internet pharmacy selling counterfeit Viagra imported from India and China. In this case, the consumers got more or less what they wanted—the pills, priced at $0.50 each, contained the active ingredient of Viagra, even though chemical analysis indicated the formulation was not identical to the real product.

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Other consumers may not fare so well, however. And those who suffer adverse reactions from counterfeit drugs bought online have little recourse available to them; the sellers are almost always incognito and beyond reach. "FDA has no ability to take effective action against these foreign operators on behalf of U.S. citizens," said William K. Hubbard, the FDA's senior associate commissioner for policy, planning, and legislation, during a Senate committee hearing on July 9, 2002.

Also at risk are consumers who purchase prescription drugs overseas, particularly in Mexico. In recent years, Tijuana has become an important entry point for counterfeit drugs into the United States. With prices soaring beyond the reach of the elderly, the poor, and the middle class, Americans are heading to Tijuana in droves searching for a bargain, despite the fact that it is illegal to do so. Some of them arrive in tour buses advertising "Mexican Drug Runs". But what they buy may not be what they expect. Citing data gathered by the U.S. Customs Office in 2001, Kubic says that up to 25% of the drugs purchased by Americans in Tijuana are likely to be counterfeit. "This is something people should be aware of," he warns. "You get what you pay for."

Despite the evidence, the FDA is reluctant to confirm that the volume of counterfeit drugs is increasing in the United States. Benjamin England, regulatory counsel to the associate commissioner for regulatory affairs at the FDA, says the recent spike in investigations may only indicate more reporting of counterfeit discoveries by drug companies. "This could give the appearance of an increase," he explains. "But I don't know that we have enough data to say for sure." England does, however, acknowledge that drug imports are a growing problem that may increase the potential for counterfeit exposure among Americans.

Working with industry to deal with the problem is a high priority at the FDA, he says. As part of this effort, England is working with other U.S. government agencies, drug companies, customs officials, and U.S. mail representatives on a project designed to identify priorities and targets for mitigation. "We're looking to develop anticounterfeiting technologies," he says. "It's an issue of public health, so it's very important to us."

Harm at home?

Unlike the situation in developing countries, documented reports of injury caused by counterfeit drugs in the United States are rare. Among the most highly publicized cases is that of Robert Courtney, a Kansas City, MO-based pharmacist, who earlier this year confessed to diluting nearly 100,000 drug prescriptions—including cancer medications—over the past decade to increase his personal profits. The extent of physical harm caused by these bogus prescriptions is not yet known. There is currently no mechanism for linking injuries to counterfeit drugs in the United States. In most cases, counterfeit drugs are filled with innocuous compounds or substandard doses that do not cause immediate adverse effects.

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