

Testimony submitted by Roger Bate, Resident Fellow American Enterprise Institute, and Richard Tren, Director Africa Fighting Malaria, to the Senate Committee on Health, Education, Labor, and Pensions Hearing on 'Restoring FDA's Ability to Keep America's Families Safe'; Thursday, April 24, 9:30 a.m.

Thank you Chairman Kennedy, Senator Enzi, and Members of the Committee for the opportunity of submitting testimony for this important hearing. Keeping American families safe, improving medical care and health outcomes is immensely important. Our testimony highlights the growing dangers of counterfeit and substandard medicines in the United States and around the world. We believe that in restoring the FDA's ability to keep American families safe, the U.S. Congress will not only save lives at home, but will help to improve standards of medical care and drug quality for many millions of people around the world, particularly the poor and vulnerable in Africa.

Introduction

The tragic deaths of 81 patients from tainted heparin treatment highlight the potential danger of cheaply produced, often counterfeit, medicine imported from abroad. Congress is indeed paying attention, as this hearing follows closely on Chairman Dingell's House hearing on April 22: yet we fear it may miss the point.

Importing finished medicines and the active pharmaceutical ingredients (API) used to make them, reduces price. And India and China have some of the cheapest production around. All three presidential candidates—Senators Clinton, Obama, and McCain—support making drug importation easier.

What they, and others, seldom acknowledge however, is the risk inherent in such importation, especially when done by individuals outside the secure supply chain. The WHO estimates that over half the drugs bought from Internet sites that conceal their actual physical address are counterfeit. At least one North American death has been linked to drugs purchased in this way.

This episode exposes the ugly little secret that in the quest to produce cheap drugs, quality is sometimes sacrificed. Substandard and counterfeit drugs are prolific in many countries in Africa, Asia, and elsewhere, where government regulatory agencies are not as adept as the FDA, and businesses are not as vigilant as U.S. companies (such as Baxter, Covidien and B. Braun), all of which took the initiative by issuing precautionary recalls of heparin. In some European countries, notably Finland, incidence of counterfeit products may be as high as 8% of total pharmaceutical sales, although in the United Kingdom, like the United States, it is under 1%.

Companies are better positioned to source and import drugs than are patients, since they have experience, expertise—and reputations to maintain. Western governments and agencies, such as the World Customs Organization and Interpol, should continue to encourage vigilance in exporting countries; the FDA should send more inspectors to randomly check on drug production in China and India.

In the United States, high commercial and regulatory standards have limited counterfeits in the

market. But this has led to complacency, and political opinion is now leaning towards allowing more third-party intermediaries to import drugs from overseas. This may reduce costs in the short run, but may also introduce more counterfeits. While regulators can oversee legitimate companies, they have very little defense against the myriad actors that importation encourages, including criminal operators. An unchecked drive for the cheapest drugs will increase the risk of more heparin-type incidents.

U.S. companies already import 40% of API from India and China, and this is expected to rise to 80% within a decade. While a few companies in both countries have the technical capacity to make good drugs and API, regulatory structures are weak, and their markets are plagued by counterfeit and substandard medicines which annually kill tens, maybe hundreds, of thousands of their residents.

American consumers benefit when U.S. companies import API from Asia, assuming these companies pass cost savings on to consumers. This system should continue. But there is a risk, and to deny it, or leave individuals to make the decisions, is folly.

Defining the Problem

What constitutes a “counterfeit” drug varies from country to country. WHO broadly defines a fake or counterfeit drug as “a medicine which is deliberately and fraudulently mislabeled with respect to identity and source. Counterfeiting can apply to both branded and generic products, and may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.” For the most part, “originator pharmaceuticals,” also known as branded pharmaceuticals, are the main target of counterfeiters, since they promise high profit margins.

As with any illegal activity, the scope of the problem is impossible to define with precision. Unofficial estimates from researchers on the proportion of counterfeit drugs in the pharmaceutical markets across the world range from a high of 50 percent to a low of 1 percent, with other estimates from reputable researchers at 40, 30, and 17 percent. WHO reported in 2006 that the fake drug industry has annual revenues of over \$40 billion—a figure sure to increase as more cases of counterfeit drugs are investigated and reported. The U.S. Food and Drug Administration (FDA) reports that the number of open investigations into domestic counterfeit drugs jumped from about five per year in the 1990s to more than twenty by 2000; in 2004 alone, there were fifty-eight documented investigations. WHO cites the Center for Medicine in the Public Interest’s prediction that counterfeit drug sales will reach \$75 billion globally in 2010—an increase of more than 90 percent from 2005.

This Rolex Might Kill You

Counterfeit drugs are commonly made and distributed by criminal gangs, who are attracted by the high profit margins of the trade. Many counterfeiters use fake Western addresses to impress patients and doctors in poor countries. These gangs also peddle other illicit items, such as narcotics, arms, and fake jewelry. Like fake Rolexes, fake drugs are often hard to identify. A fake Rolex will probably tell time, but when examined closely, most people can tell it is a fake.

The ineffectiveness of fake drugs may be revealed only when a life has been put at risk. Fake drugs also undermine confidence in branded products and even entire health-care systems.

Counterfeit drugs contain little or none of the active ingredients of legitimate drugs, with varying consequences depending on the disease. An outright lack of active ingredients may cause death, particularly in infants. In some cases, the material substituted for the authentic active ingredient may be toxic, leading to allergic reactions or death. In July 2007, a 57-year-old Canadian woman died after ingesting counterfeit antidepressants and acetaminophen that contained toxic levels of aluminum, phosphorus, titanium, tin, strontium, arsenic, and other heavy metals. In the heparin case, the component substituted for heparin was not approved for medical use because it causes severe allergic reactions.

Too little active ingredient poses another problem. Low-strength medicines will only knock out the weaker strains of the parasite or disease, leaving the stronger ones to thrive and develop resistance to the drug. This means that even the genuine drug will be rendered useless to the patient; his or her only option will be to try to get access to vastly more expensive second-line drugs. If the disease develops population-level resistance, a whole drug class will be lost.

Dora Akunyili, the director general of the Nigerian National Agency for Food and Drug Administration and Control, astutely analyzes the situation in her country and elsewhere: “The evil of fake drugs is worse than the combined scourge of malaria and HIV/AIDS put together. . . . Whereas HIV/AIDS can be avoided, and malaria can be prevented, fake drugs kill en masse, and anyone can be a victim.”

Yet counterfeiting pharmaceuticals usually carries far lower penalties than producing and selling narcotics—and because it is just as lucrative, it is becoming a booming business. The extent of the problem is shocking: counterfeit drugs manufactured by South American narcotics gangs or unregistered chemical works in China have infiltrated legitimate supply chains and ended up in pharmacies, clinics, and hospitals all over the world. Even well-respected, high-quality pharmacies such as CVS and Rite Aid have been fooled in the past; the recent infiltration of fake heparin was effected through established, here-before reliable supply channels.

At present count, 81 deaths have been associated with violent allergic reactions to a heparin-like substitute introduced into active pharmaceutical ingredients manufactured in China and imported into the U.S. and other western countries, where it was used to manufacture medicines. The adulterated product passed standard quality tests and only after suspicious symptoms and deaths had occurred was the product tested further. FDA scientists determined that suspicious lots of API used to make the drug were imported from China and appeared to contain 5 to 20 percent of a heparin-like compound which mimicked heparin activity so closely that it was not recognized by routine testing.

Raw heparin is normally sourced from the intestines of pigs, while the contaminant—oversulfated-chondroitin sulfate—comes from the cartilage of the animal. It is more abundant and cheaper than raw heparin, and not registered for medical use because it causes severe allergic reactions. The FDA was careful to avoid the word “counterfeiting,” when pressed by reporters, but Dr. Janet Woodcock, its Director of the Center for Drug Evaluation and Research, noted that

the Agency was “99% sure [the contaminant] is not a natural component that got in there as part of the purification process.”

FDA inspection of the Changzhou, China facility of Scientific Protein Laboratories LLC (SPL), the company responsible for producing the suspect API, revealed insufficient standard-setting and a lack of good record keeping. On Monday, when the Chinese Government suggested that the problem may have originated within the U.S., the FDA quickly responded by issuing a warning to SPL (and indirectly criticizing the Chinese Government) citing "significant deviations" from good manufacturing processes at its Changzhou facility and recommending disapproval of applications to manufacture other active pharmaceutical ingredients.

The FDA and affected companies appear to be managing the incident well, minimizing American exposure to suspect lots while ensuring that patients are guaranteed supplies of genuine drugs. On January 17, Baxter International voluntarily recalled nine lots of its injection multi-dose vials of the drug, and in late February, expanded the recall to all remaining lots and doses of the multi-dose product. Meanwhile, FDA investigated both the Wisconsin and Changzhou, China facilities of SPL; shortly thereafter, SPL's Wisconsin facility announced it was recalling the heparin it had distributed to a number of companies. The FDA also investigated a New Jersey facility to find out whether the heparin could have been contaminated by its packaging. The diligence appears to be paying off: no new deaths associated with the suspicious allergic reaction since the end of February have been reported (although the FDA has revised the total number of deaths attributed to the allergic reaction several times since then, probably earlier deaths now attributed to the contaminated product).

Tracking Counterfeit Medicines around the Globe

The problem of counterfeiting drugs is rampant in both developed and developing countries. In wealthier developed countries, counterfeiting most frequently affects “lifestyle drugs” such as hormones, steroids, erectile dysfunction, and anti-allergy medicines. In the 1990s, several deaths associated with the use of a fake version of the antibiotic gentamicin occurred in the United States. More recently, in May 2003, nearly 20 million doses of fake Lipitor, a cholesterol-lowering medication, had to be pulled from U.S. pharmacies. Altogether, because wealthy countries have stricter regulatory mechanisms, and since most patients in wealthy countries can afford branded medicines, counterfeits account for less than 1 percent of the market value—although 50 percent of Internet sales are estimated to be counterfeit.

In developing countries, the scale of the problem is disproportionately worse. The latest joint estimates by WHO, the Organisation for Economic Co-operation and Development, and the Pharmaceutical Security Institute show that more than 30 percent of medicines in some areas of Latin America, Southeast Asia, and sub-Saharan Africa are counterfeit. For Africa, data are scarcer, but the situation is similarly bad. In 2005, a random survey by Kenya's National Quality Control Laboratories and the Pharmacy and Poisons Board found that almost 30 percent of the drugs in Kenya were counterfeit. Some of the drugs were no more than chalk or water.

In poor countries, essential and life-saving drugs used to treat infectious disease such as tuberculosis and malaria are often the drugs threatened by counterfeiting. Since the burden of

these diseases is greatest in these countries, and because people tend to be disproportionately poor, they will often buy counterfeit drugs on the black market, despite poor quality and even appearance. In our anecdotal experience—poor family members of the very sick often buy anything they can afford rather than do nothing.

Malaria: A Critical Example

A field survey from 2002 to 2003 showed that 53 percent of artemisinin-based antimalarials—the most effective treatment available—bought in several Southeast Asian countries were counterfeit and contained incorrect levels of the active ingredient. The authors noted that the problem seemed to have increased significantly compared with their previous survey in 1999–2000.

In 2006, researchers conducted a quality-control study of antimalarial tablet samples purchased on the black market in Angola, Burundi, and the Democratic Republic of the Congo. The results identify a variety of problems: dubious packaging, low content of the active ingredient, and substandard technological properties (including very low dissolution profiles). In a 2003 survey, researchers found that the active ingredient content in at least one of three formulations of counterfeit drugs tested in seven African countries was below the minimum level recommended for the product.

Malaria claims over 1 million lives every year, mostly among children in Africa. The disease is entirely curable, but urgent treatment is necessary because the disease can progress very quickly, particularly in young children or pregnant women. In most of Africa, people procure their malaria treatment from the private sector, frequently paying out-of-pocket for poor quality medicines and sometimes for fakes. While most African countries have officially changed their malaria drug treatment policies to the new, effective artemisinin-based combination therapies (ACTs), most have not removed the less effective artemisinin monotherapies from their drug registries. Untested, unregulated and potentially dangerous medicines are frequently sold and are widely used. The problem of substandard treatment of malaria is of particular concern due to the dangers of drug resistance. No new classes of malaria treatment will be available within at least 10 years making it imperative to ensure the highest standards of treatment and care with the existing drug regimen.

The failure to improve treatment standards for malaria exposes the deficiencies in drug regulation policies in many poor countries. Yet instead of focusing on better policing and ensuring higher standards of imported drugs, industrial policies in many malarial countries favor local production of malaria medicines. These policies, often supported by donor nations, will further burden the regulatory agencies in malaria countries. There is little evidence that local production of medicines produces cheaper, high quality drugs.

Targeting Best-Known Diseases

HIV/AIDS and bird flu treatments are also being jeopardized. In a 2004 study, one researcher discovered counterfeit antiretrovirals (stavudine-lamivudine-nevirapine and lamivudine-zidovudine) in central Africa. This is alarming because the previously effective first-line therapy

for treating HIV could soon be rendered defunct as the virus develops resistance. The bird flu scare led to an increased demand for the antiviral drug Tamiflu, one of the proven remedies for the disease. Soon thereafter, fake versions of the drug were flooding the Internet.

Developing countries are not only markets for counterfeit drugs—they also produce the fakes, according to a report from the International Policy Network (IPN). The chief culprits are Asian countries like China and India, where oversight is weakest. According to figures cited in the *British Medical Journal*, China had five hundred illegal medicine factories in 2001; in the same year, the *San Francisco Examiner* reported that the Chinese government closed 1,300 factories while investigating 480,000 cases of counterfeit drugs.

According to the IPN report, about 15,000 manufacturers of copies operate in India, and while the majority are legitimate (even if their drugs are substandard), “a small minority are ‘fly-by-night’ operations that do not comply with proper regulatory standards.” Most of the counterfeit medicines in Nigeria, for example, originate in India, which led Nigerian authorities to threaten to ban the import of all drugs from India in 2003. With an influx of legitimate Chinese investment in Africa, however, informed sources say that China may soon take the lead in this odious trade. The manufacture of fake medicines also flourishes in Latin American countries like Argentina, Brazil, Mexico, and Venezuela.

The production of counterfeit medicine often occurs through a multi-national chain of production and sale that originates in countries that either do not recognize or loosely enforce patent laws, where the drugs can be synthesized or their component parts bought. A copy manufacturer operating in Argentina, Greece, or Mexico purchases the ingredients from a country such as India or Thailand, then presses the tablets or makes the pills and prints counterfeit labels.

Wilfrid Roge, a former French Customs official who is now director of corporate economic security at the French pharmaceutical company Sanofi-Aventis, describes a typical path for counterfeits: “The products are transported to free trade zones in Dubai in the Middle East and are exported to Latin American countries like Panama. The products are then re-exported to North America and Europe through the United Kingdom and some north European countries”. The fake drugs eventually make their way through several cut-rate brokers to a pharmaceutical distributor.

These findings suggest that massive amounts of fake drugs are circulating in drug distribution chains. Even more worrisome, many patients are taking incorrect doses or compositions of drugs—with potentially lethal outcomes.

Cashing In on Death

In studies all over the world, counterfeit medicines, which contain little or no active ingredients, have no therapeutic benefits to patients. During the Niger meningitis epidemic of 1995, for example, 2,500 people died as a result of fake vaccines. In Haiti, Nigeria, Bangladesh, India, and Argentina, throughout the 1990s, more than 500 patients (mostly children) died after ingesting diethylene glycol (a chemical commonly used as antifreeze) offered as paracetamol syrup.

Today, due in part to lax regulatory standards in China, we are seeing contaminated toothpaste from China containing the same ingredient.

WHO estimates that 1 million deaths occur from malaria every year. It is logical to conclude that this chilling estimate could be significantly reduced if the medicines available were effective, of good quality, and used correctly. WHO suggests that an astonishing 200,000 malaria deaths per year would be prevented absent fakes and poorly prescribed medicines. In 1999, at least thirty people died in Cambodia after taking counterfeit antimalarials prepared with sulphadoxine-pyrimethamine (an older, less effective antimalarial), which were marketed as the more advanced artesunate. A study conducted in Southeast Asia in 2001 revealed that 38 percent of 104 antimalarial drugs on sale in pharmacies did not contain any active ingredients and had led to several preventable deaths.

Perhaps one of the most worrying implications of the counterfeit boom is the acceleration of new, drug-resistant pathogens, parasites, and bacteria. The IPN report found this especially true of malaria and HIV/AIDS. Scientists have begun to observe resistant strains of bird flu, which could indicate that fakes are already penetrating the market for bird flu drugs. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) says that “drug resistance resulting from the use of counterfeit medicines is among key factors contributing to the upsurge of major infectious diseases in developing countries.”

Aside from their hefty death toll, counterfeit drugs undermine incentives to invest in further research and development. The use of fake drugs also undermines confidence in health-care systems, health professionals, pharmaceutical manufacturers, and distributors. It deprives pharmaceutical companies of significant financial resources and places financial burdens on patients and governments with two major consequences: money is wasted on drugs that do not work, and additional funds must be spent on purchasing genuine products to deal with the ensuing devastation that toxic or under-strength products cause. This is particularly damaging in developing countries, where disposable income for health care is significantly constrained.

Fighting Counterfeiting Drugs

Since its inception in 1946, WHO has often attempted to quell the spread of counterfeit drugs. Article 2 of the WHO Constitution establishes its obligation to set standards for pharmaceutical products. WHO initiated programs for the prevention and detection of counterfeit drugs, and in 1982 established a Counterfeit Drug Database. In 1992, WHO joined forces with IFPMA to settle on a working definition of a counterfeit drug. More recently, in 2000, WHO convened a working group on drug quality and counterfeiting. Made up of WHO officials and organizations representing patients, pharmacists, and medical professionals, the group hopes to raise awareness about the problem of counterfeiting while promoting effective regulatory safeguards to ensure that patients are protected from the hazardous effects of these medications. WHO is also promoting its International Medical Products Anti-Counterfeiting Taskforce, which is slowly mobilizing resources on a multilateral basis.

At the national level, some countries are taking steps to tackle this problem. Nigeria, which has a major problem with counterfeits, issues bulletins and maintains a website with information on

counterfeit drugs and food to educate consumers. In 1996, the Philippines enacted a law permitting random sampling and monitoring of drug quality in pharmacies and hospitals and punishment of offenders with long prison sentences or hefty fines. The government in China, where many products are fraudulently manufactured, has taken the drastic step of sentencing an official formerly in charge of food and drug safety, Zheng Xiaoyu, to death for accepting bribes to approve counterfeit products. More punitive sentencing for those peddling fake drugs is certainly warranted, but it is only part of the solution. According to the legal literature, increasing the potential punitive cost (judicial sentences) of illegal activity often does not lower the activity significantly, but rather just increases the level of brutality involved. Stricter penalties must be combined with increased monitoring activity by technically qualified laboratories and concerted policing.

Fighting Substandard Drugs

Although WHO has done much to prevent the spread of fake drugs, it has actually encouraged the use of substandard drugs through the promotion of products it classifies as generics—but whose quality has not been verified by a stringent regulatory authority. As widely documented, this has been a significant problem for HIV drugs. Unfortunately, the Global Fund to Fight AIDS, Tuberculosis and Malaria has exacerbated the problem by listing generic drugs on its approved antimalarial compliance list that have not demonstrated bioequivalence therapies by registering with a competent agency. Sources inform us that nearly 20 percent of total purchases by the Global Fund—well over 450 transactions—are for non-approved drugs. European and Indian companies have also exploited loopholes in domestic legislation, which have allowed them to copy drugs for export without undertaking significant quality testing. Belgium and Italy in particular have allowed drugs produced in their countries to compete for Global Fund awards without having them fully tested.

It is uncertain how damaging substandard, pseudo-generic drugs may be for patient safety. Their use—and hence impact—is set to grow even faster than the market for fake drugs. This is disquieting, since the Global Fund does not see this as a problem. It continues to use funds from the Bill and Melinda Gates Foundation and the G8 countries to purchase such drugs. The Global Fund mistakenly assumes that because the drugs are cheaper, more lives will be saved, which is only true if the copies are bioequivalent to the originals. Meanwhile, the Fund continues to show antipathy toward the research-based pharmaceutical industry. The recent Board decision to increase access to antimalarials of unproven quality was the desire to prevent Novartis, the producer of Coartem, the best drug on the market, from increasing its dominance, even though Novartis sells the drug at cost.

When the new head of the Global Fund was asked about this issue in Washington in May 2007, he brushed it off. Only when tragedy strikes will action be taken. Action is vital because substandard drugs can be more dangerous than fakes—especially at the population level. Since they contain active ingredients, but at sub-lethal levels for the bacteria/parasite, they breed resistance.

Approval of poor copy drugs also provides cover for the broader acceptance of total fakes. When doctors and patients are inundated with new copy drugs, it is more difficult for doctors to discern total fakes, making drug policing more complicated and expensive.

Looking Ahead

The problem of counterfeiting requires a concerted effort from all stakeholders. As one top health official from the Philippines noted, “The fight [against counterfeit medicines] is a cooperative undertaking.” As the IPN paper notes, to contain the global counterfeiting scourge, it is crucial “to address those lacunae of governance which allow LDC counterfeiters to ply their trade with relative impunity.” Most importantly, it is essential that intellectual property rights and the rule of law be upheld in the countries where the majority of these drugs are produced. In South American countries, the penalty for illicit cocaine and heroin dealing is fifteen years of jail time. The penalty for the production and sale of fake drugs is only six months; the perpetrator may be out on bail in only days. These sentencing incongruities should be rectified. Stiff penalties are needed because counterfeiting offers high profits, with comparatively low risks. In 2003, an expert committee in India recommended that the maximum penalty for the sale or manufacture of fake medicines be changed from life imprisonment to the death penalty and that the minimum prison sentence for these offenses be increased from five to ten years. But as noted above, increasing sentencing without massively increasing policing will have little impact on the fake drug market.

Promoting generics as an alternative to tackling drug counterfeiting is not a viable option unless the recognized international standards—including the bioequivalence requirement—are in place to ensure the quality of product. Unless such standards are set, aid agencies will continue to exacerbate and tolerate bad medicine in the market.

Summary

Counterfeit and substandard medicines are an insidious threat to the United States and to global health more broadly, and the risks they pose have been largely underestimated to date. Counterfeits containing no active ingredient will fail to cure disease; those with wrong ingredients may cause mental and physical damage—and even death. Counterfeits containing insufficient active ingredients breed resistance, which can make authentic drugs useless. No area of the world is unaffected, as exposed by the recent deaths in the United States from tainted heparin. Mounting evidence shows that the problem is disproportionately severe in developing and emerging-market countries, which also have the highest burden of infectious diseases. National governments have the primary responsibility—both in stopping criminal manufacturing and distribution and in protecting their citizens from counterfeit products. The Food & Drug Administration (FDA) is highly active in fulfilling this responsibility, but this is not true in many other countries in the world. Multilateral organizations such as the World Health Organization (WHO), the World Customs Organization (WCO), and the International Criminal Police Organization (Interpol) must do more to expose the problem and help countries tighten regulatory controls. Companies affected by counterfeiting in developing countries are expending private resources to perform roles which should be carried out by police and regulators, including assisting multilateral organizations in building capacity among local customs and regulatory officials.