
COMMENTARY

Counterfeit and substandard drugs

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When a patient does not respond to a drug product or has an adverse reaction to a drug product, is it because the product is substandard or even counterfeit? Here are some case reports to illustrate the problem.

CASE REPORTS

Case 1. A 63-year-old man who was the co-owner of a clothing manufacturing company based in New York traveled two to three times a year to Asia to visit clothing factories. The patient had a history of coronary artery disease, hypertension, and hypercholesterolemia. The patient's blood pressure was in the normotensive range while the patient was taking 25 mg of Maxide (Bertek) (triamterene and hydrochlorothiazide) daily, and his cholesterol profile improved (total cholesterol, 201; high-density lipoprotein cholesterol, 43) while the patient was taking 20 mg of Mevacor (Merck) (lovastatin). Repeatedly elevated blood pressure readings and elevated cholesterol levels were noted during several office visits in 1995. The patient reported obtaining his

medications from pharmacies during his trips to Indonesia and India. When the patient was apprised of the possibility of substandard or counterfeit medication and adhered to prescribed medication obtained at United States pharmacies, his blood pressure came under control and his cholesterol levels improved.

Case 2. A 64-year-old cleric with history of extensive foreign travel, primarily to Africa and Latin America, had been treated for mild bouts of diverticulitis previously with Cipro (Bayer) (ciprofloxacin). During a trip to Haiti and Cuba in November 1997 he had a flare-up of left lower quadrant abdominal pain and obtained Cipro at a pharmacy in Haiti. On his return to the United States, his symptoms had progressed, with left lower quadrant tenderness and mild leukocytosis. He was switched to domestically produced ciprofloxacin and metronidazole. Prompt resolution of symptoms and normalization of white counts occurred. Although it is unclear whether the ciprofloxacin he received in Haiti was substandard, his previous prompt response to quinolones alone suggested that it was.

Case 3. A 51-year-old health care worker who was a native of the Netherlands reported working in family health clinics in Indonesia in the 1970s. The health care worker placed intrauterine devices that were all subsequently found to be defective. He was advised to switch all women to oral contraceptives that had been donated to the family health clinic by European companies.

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Many pregnancies resulted in women who were taking these "birth control pills."

Case 4. A 38-year-old French national jazz musician traveled to West Africa in October 1999. He was provided with pre-travel inoculations and a prescription written for Lariam (Roche) (mefloquine). He only filled the prescription for the first 3 doses of this weekly medication because the cost was too high; he expected to fill the remainder of the prescription for his 3-month stay while he was in Africa. He went to a pharmacy in Dakar, Senegal, and asked for mefloquine (Lariam is a scored white tablet) and was given small white tablets that he took faithfully each week. Approximately 2 weeks after beginning this medication he developed fever and shaking chills and was diagnosed as having falciparum malaria at a hospital in Senegal. It is unlikely that the tablets he obtained in Dakar contained the proper amount of mefloquine.

Case 5. A number of United States citizens working in Bangkok were taking local diet pills. This was several months after fenfluramine and dexfenfluramine had been removed from the United States market because of cardiac valve toxicity. The physicians in Thailand were all well aware of the phen-fen problem. The local diet pills were all being dispensed at a particular clinic in Bangkok. The "Swedish-trained" physician in the clinic stated that the pills were herbal, entirely natural, and safe but refused to divulge the actual composition of the pills, claiming that the information was proprietary. "Samples of 7 different pills from that clinic given me by a patient were sent to the FDA in the US. Report of the analysis stated that 2 of the pills were fenfluramine, 1 was diethyl-pro hydrochloride (diethylpropion [INN, amfepramone], a sympathomimetic drug?), 1 was methoazole (methazole, an herbicide?), and 3 were herbal plant material." (N. J. Riesland, MD, personal communication, June 8, 2000.)

Case 6. A 72-year-old American with refractory rheumatoid arthritis complicated by nonsteroidal anti-inflammatory drug-related gastrointestinal bleeding traveled to China seeking traditional Chinese medicine for these problems.

Five days after receiving treatment, he presented to my clinic in Shanghai with abdominal pain and melena. He showed me the "traditional medications" dispensed at one of the local clinics. Although the box was exotically labeled in Chinese, inside were pills of Clinoril [sulindac; Merck], an NSAID [nonsteroidal anti-inflammatory drug] from the West being passed off as traditional medicine. (Joseph Kolars, MD, FACP, personal communication, June 7, 2000.)

COUNTERFEIT DRUGS

The subject of overall drug quality has been addressed recently in several World Health Organization (WHO) publications.¹⁻³ A substandard drug product is one that does not meet the official specifications for what it is claimed to be. One special class of substandard drugs is the class of counterfeit drugs. The WHO defined a counterfeit medicine as one "which is deliberately and fraudulently mislabeled with respect to identity and/or source."⁴ A counterfeit medicine is not one that is innocently but incompetently prepared. It is a product that is intentionally mislabeled to deceive the sick and profit from them. The WHO has a database about counterfeit drugs, and as of 1997, the database contained approximately 700 reports of detected counterfeit drug products.⁵

Dr Yasuhiro Suzuki, WHO Executive Director in charge of Health Technology and Pharmaceuticals, stated at the World Health Assembly in Geneva on May 17, 2000, that "no country is immune from the threat of counterfeit drugs but those with weakly regulated pharmaceutical markets suffer most." Because the least developed countries have some of the weakest drug regulatory programs, the poorest and most vulnerable people on earth are at the greatest risk of being harmed by the criminals who sell counterfeit drugs. However, any person from an industrialized country who purchases medicine in a poorly regulated market, such as when traveling, through mail order, or by means of the Internet, is also at risk.

An accurate measure of the extent of the problem has been impossible to obtain. Pharmaceutical companies are reluctant to make information about counterfeiting of their products public, and there is no way to know how much counterfeiting of drug products is undetected.

EXAMPLES OF SUBSTANDARD AND COUNTERFEIT MEDICINES

A scandal in Brazil in 1998 led to reports of 200 suspected unwanted pregnancies caused by a dummy contraceptive pill, and several deaths were attributed to a false anticancer drug.⁶ A workshop on fake drugs in Nigeria was held in Nigeria in 1987. A study was reported in which drug products were purchased from street markets and vendors. The percentage of samples that were substandard, worthless, or dangerous were as follows: antibiotics, 40%; antimalarials, 47%; antipsychotics, 50%; and benzodiazepines, 23%.⁷

L. Salako, Director-General of the Nigerian Institute of Medical Research, did a study of the quality of 50 brands of chloroquine tablets purchased in Nigeria in 1990 (personal communication, September 8, 1999).

Twenty percent were substandard; some tablets had less than 50% of the labeled amount of chloroquine in the tablets. Shakoor et al⁸ assayed drug products from Nigeria and Thailand. They found that 2 of 32 chloroquine products from Nigeria and 3 of 5 from Thailand contained no chloroquine at all. One of 9 amoxicillin (INN, amoxicilline) products from Nigeria also contained no amoxicillin.⁸

Petralanda⁹ studied antimalarial drugs in the Amazon region of South America. Twelve samples from 9 manufacturers of primaquine had 19% to 168% of the labeled amount in the dosage form. Those outside the United States Pharmacopoeia range were clearly substandard, but whether some with very low drug content were intentionally fraudulent products or incompetently made cannot be determined from the data alone.⁹

A WHO study of drug product quality in 3 countries (Cameroon, Madagascar, and Chad) found that 12 of 157 major antibiotic formulations contained none of the labeled antibiotic. The same was true of 4 of 138 antiparasitic products. These were clearly fraudulent. Another 28 antibiotics and 18 antiparasitic drug products were substandard by WHO criteria but not necessarily intentionally fraudulent (WHO/DAP/95.3).

Another study of anti-infective drug products in Cambodia found that 36 of 128 were substandard; 6 of those had no active ingredient in the product.¹⁰

Centrale Médico Humanitaire Pharmaceutique, set up within Pharmaciens Sans Frontières, supplies drug products to humanitarian organizations. In a list of substandard samples analyzed by their laboratory in 1 year, there were 30 batches of antimicrobial drug products that had significantly less of the drug in them than was on the label (J. Y. Videau, Pharmacien Responsable, personal communication, August 20, 1999). These manufacturers were located in several countries and presumably were selling their drug products to other purchasers who did not have independent testing facilities.

In a paper presented at the 27th International Seminar of the French Society of Pharmaceutical Sciences and Techniques in 1995, a report of 229 cases of counterfeiting was presented in which the type of counterfeiting was described. Fifty-one percent of the drugs contained no active ingredient, and 17% contained the wrong ingredient (M. Thomas, MD, personal communication, August 20, 1999.)

Following are some examples from a paper presented by Agathe Wehrli, Chief Division of Drug Management and Policies, WHO, at the PIC-PIC/S Seminar in Finland (June 10-12, 1997). (The paper is available on request from WHO, Geneva.)

Bulk sulfamethizole that had been partially substituted with sugar milled to the same particle size as the sulfa drug was delivered to an Australian company.

Inferior grade, including rejected, bulk active pharmaceutical ingredients were placed in that bottom of drums.

Bulk antibiotics were given false batch code information in the United States in 1991 so that the antibiotic in the containers had not been tested and certified as claimed on the label. The United States company doing this was caught and fined, and 1 individual was sentenced to 24 months in jail.

Ethylene glycol has been known for a long time to be highly toxic. It was used instead of glycerin (INN, glycerol), which led to the deaths of more than 500 patients in Argentina, Bangladesh, India, Nigeria, and Haiti in recent years.

ENFORCEMENT

The report of the 27th International Seminar of the French Society of Pharmaceutical Sciences and Techniques states the following:

What is the attraction of counterfeit medicines for criminals? There are three basic explanations: they are difficult to detect; a small consignment may have a high market value; current legislative provisions make traffic in them safer than in hard drugs. (M. Thomas, MD, personal communication, December 23, 1999.)

Does enforcement make a difference? A letter dated December 13, 1999, from J. C. Onwudinjo for the Director-General of the Nigerian Agency for Food and Drug Administration and Control (NAFDAC) was sent in response to an inquiry about the status of counterfeit drugs in Nigeria. After describing the laws passed in 1989 to 1993, more recent decrees of 1999, and the more vigorous enforcement since 1994, Onwudinjo wrote the following:

Indeed the impact of enforcement of these legislations has been encouraging. Prosecution and conviction of offenders have been on the increase while the prevalence of counterfeit and fake drugs is now on the decrease.

Experience has however shown that substandard medicines are being exported into this country by unscrupulous people and that such medicines are most often not consumed in the country of origin.

NAFDAC is therefore of the view that a more permanent solution to the issue of drug faking would be for developed countries to consider the need to approve legislation that would apply the same measure of quality standard to medicines consumed locally with those intended for export.

Once the proposed measure is enforced by overseas Regulatory Agencies, it would to a large extent reduce the availability of fake drugs in developing countries like Nigeria.

In Australia, 41 people or companies were charged with 577 crimes involving counterfeit drugs over a period of 5 years (1992-1997). Thirty-four people or companies were convicted during that time. The Head of Surveillance of the Therapeutic Goods Administration of Australia added an interpretation of a detailed report of counterfeit drug activity that was mostly related to catching counterfeit drugs at the port of entry into the country.

The import offences detected do reflect a concentration of effort in that area and to some extent could be said to be self created. What is important however, is that each of those offenses detected, generally involved the seizure and ultimate destruction, of large quantities of unlawful drug products. Those drugs seized have been prevented from entering Australia's domestic market, and from entering Australia's pharmaceutical export markets.

The result, in my experience, has been that the amount of unlawful product being supplied in Australia has reduced to roughly half what it was six years ago, even though more crime is being reported to and detected by the TGA. (S. Howells, Head of Surveillance, Therapeutic Goods Administration, Australia, personal communication, August 20, 1999.)

OVERVIEW AND CONCLUSIONS

There are multiple examples of counterfeit or substandard drugs that were mislabeled with respect to source in addition to the mislabeling with respect to content that is described in this article. We have focused this article on the problem of fraudulent products that are inert and lead to no treatment or, as in the example of ethylene glycol, that are toxic and directly kill sick people.

In the past, this has been viewed by many as a problem for people in underdeveloped countries and of little direct relevance to most people in industrialized countries. Yet travelers from countries with strong drug regulation who purchase medications in areas with little drug regulation and enforcement are at risk, as some of our case reports indicate. People who travel abroad to

purchase medications because the medications are cheaper, such as Americans who cross the Texas border to purchase drugs in Mexican border towns, are at risk.^{11,12} People who purchase drugs from Internet Web sites that are able to evade strict regulation are also at risk. Thirteen of 46 Web sites that offered prescription drugs included in one study were based outside of the United States.¹³ We are fortunate in the United States to have a drug distribution system that is structured, organized, and regulated. We also have strong laws and a strong Food and Drug Administration and Customs Service to enforce the regulations. These federal agencies provide substantial, but not perfect,¹⁴ protection for Americans from both counterfeit and substandard drugs.

If a drug product contains no active drug, clearly the manufacturer should be considered criminally negligent even if one cannot prove intentional fraud. How much intent rather than negligence is involved in products that contain little but some active drug is usually impossible to determine. Certainly, there should be a level of negligence at which intent should be inferred—criminal negligence and not merely incompetence.

It has been very difficult to obtain citable factual information about the extent of the problem of counterfeit drugs. Drug companies keep the information they have strictly confidential. The reasons given for this secrecy are that companies are afraid that if it becomes known that one of their products has been counterfeited, people will stop buying it and purchase a competitor's product even after the counterfeit product has been destroyed. Anecdotal examples of this occurring were described to one of the authors (MMR) by a representative of a major United States international drug company. Another reason is that this is serious criminal activity and companies want to protect the people who discover and report the counterfeit activities from criminal retribution.

The international pharmaceutical industry has set up the not-for-profit Pharmaceutical Security Institute, a counterfeit intelligence forum that conducts world-wide investigations. The Pharmaceutical Security Institute has established, and intends to maintain, a database of information obtained in collective inquiries into counterfeiting. It provides information on illegal activities to governments and international agencies, which are responsible for proceeding against counterfeiters. This Institute supplied us with many publicly available documents, usually reports from the lay press, about counterfeit drug activities, but none with analytical data and nothing that was not already public.

It is not clear how much the introduction of counterfeit drug products is facilitated by corrupt govern-

ment officials. Informal comments by knowledgeable people suggest that in some places corrupt government officials do facilitate the entrance of counterfeit drugs into the market place. None of the people making these statements would permit us to cite their names for attribution. The reasons for their reluctance to be named as accusers of government officials (some rather high in their governments) of being corrupt are self-evident.

The problem of counterfeit drugs will not disappear unless there is sufficient public outcry so that governments pay attention. The fact that there are people, criminals, who intentionally make inert products to sell to sick people in need of medicine is thoroughly repugnant. The fact that these products enter the distribution system means that some health care professionals somewhere permit these products to enter the system. It is hard to imagine that every one of these professionals is innocent and unknowing.

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