

DRUG QUALITY, SAFETY ISSUES AND THREATS OF DRUG IMPORTATION

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ABSTRACT

Until the last decade, the U.S. Food and Drug Administration (FDA) had tight control over drug importation; principally, drug manufacturers were the only entities which could legally import pharmaceuticals. However, in the last ten years, the FDA's tight control has weakened. The number of U.S. residents who personally import prescription medications has increased dramatically. For example, in 2004, over two million U.S. residents purchased over twelve million prescriptions from Canada alone. The number of prescriptions purchased from other countries is unknown, but it is estimated that Americans buy \$800 million in drugs from Mexico. Additionally, drug products are entering the United States from across the globe. Drug importation not only affects the economy; importation presents serious drug safety issues for the public. One problem is that some pharmacy Web sites where individuals obtain their prescription drugs are rogue, fraudulent sites, with many selling substandard, counterfeit drug products. Furthermore, many pharmacy Web sites do not require a prescription and thus some sites are shipping a plethora of narcotic and non-narcotic drugs to Americans. Thus, medical supervision by licensed health care practitioners is missing. Some imported products are of poor quality and are counterfeit. The imported drugs have no active ingredients, wrong active ingredients, or are poorly labeled and packaged. However, some imported drug products are FDA-approved and are the same quality as products from U.S. pharmacies. The problem is distinguishing the "good" products from the substandard products. However, documentation of the adverse effects from imported,

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substandard medications, including hospitalizations and deaths associated with imported drug products, is lacking. Furthermore, information is lacking regarding the type of drugs being purchased, quantities and frequency of drug purchases via the Internet or by people crossing the border, demographic characteristics of the purchasers, and the outcomes of imported drugs on our health care system. This information is essential to better determine the risks, and how to address the risks, of imported drugs. Policy makers need to take a careful look at the information and investigate the potential impact of drug importation before setting policy. At this time, drug importation is not the answer to the U.S. problem of drug access.

INTRODUCTION

Until the 1990s, importation of prescription drugs was very limited in the United States. If it occurred, it was primarily by people who lived near either the Mexican or Canadian border. Individuals living in border communities have been purchasing pharmaceuticals from Mexico and Canada for decades. In addition, U.S. residents returning home from travels abroad would return with foreign pharmaceuticals.

Other than these instances, the U.S. Food and Drug Administration (FDA) has had a tight grip on the importation of pharmaceuticals. The only entities that can legally import pharmaceuticals are drug manufacturers. It is illegal for wholesalers, hospitals, and pharmacies to import pharmaceuticals for commercial sale. Moreover, it is illegal for a U.S. resident to import prescription drug products.¹

Today the situation has changed dramatically. The FDA's tight "barbwire" hold now has gaping holes and drug products are entering the United States from all corners of the world. The FDA's grip on preventing drug wholesalers, community pharmacies, and hospitals from importing pharmaceuticals still exists. It is the U.S. resident that has escaped the FDA's containment. Millions of U.S. residents are now purchasing pharmaceuticals from foreign pharmacies. In fact, it is estimated that four percent of the U.S. population purchased drugs from a foreign pharmacy last year.

The development of the World Wide Web and the personal computer has facilitated this change. From their homes, U.S. residents can order pharmaceuticals from all parts of the globe and have the drug

1. See Federal Food, Drug, and Cosmetic Act 21 U.S.C. §§ 301-399 (2005).

delivered to their home. Many times no prescription is needed; all one needs is a credit card number and a mailing address.²

The driving force pushing U.S. consumers to foreign pharmacies is the relatively high cost for U.S. brand name pharmaceuticals when compared to other countries, especially from those countries where governmental price controls have lowered drug costs.³ Another driving force behind this movement is the easy access to drugs because in many parts of the world, "you don't need no stinkin' prescription." You can purchase a variety of pharmaceuticals, including controlled substances such as narcotics, antipsychotic, and antidepressant medications, via the Internet without a prescription.⁴ Thus, one avoids the cost associated with seeing a physician to obtain the prescription.

Importantly, some imported drug products are very high quality; some are FDA-approved and essentially have the same quality as products found in a U.S. community pharmacy. However, some imported drug products are substandard and poor quality, some are fakes, and some do not have FDA approval. Some have no active ingredient, wrong active ingredients, or wrong quantities of the correct active ingredient. Some have no labels or are poorly labeled. The problem is that it is extremely difficult to differentiate between the good quality products and the substandard products.⁵

EXTENT OF DRUG IMPORTATION

Easy access to foreign Internet pharmacies has increased the number of drug products entering the United States dramatically in recent years. From 2003 to 2004, there has been a 1000% increase in the number of drug packages destined for U.S. residents. The Miami international mail facility at the Miami International Airport is receiving up to 30,000 drug-containing packages a day. Chicago O'Hare International Airport receives over 4000 drug packages a day, while JFK Airport in New York receives over 40,000 parcels a day.⁶ Packages

2. U.S. GEN. ACCOUNTING OFFICE, INTERNET PHARMACIES: SOME POSE SAFETY RISKS FOR CONSUMERS, GAO DOC. NO. 04-820, at 1, 11 (2004), available at <http://www.gao.gov/new.items/d04820.pdf>.

3. *Buyer Beware: The Danger of Purchasing Pharmaceuticals Over the Internet: Hearings Before the Permanent Subcomm. on Investigations of the S. Comm. on Governmental Affairs*, 108th Cong. 5, 7 (2004) [hereinafter *Buyer Beware Hearings*] (opening statement of Sen. Carl Levin).

4. U.S. GEN. ACCOUNTING OFFICE, *supra* note 2, at 11.

5. *See id.* at 6-7.

6. *Buyer Beware Hearings*, *supra* note 3, at 2-3 (opening statement of Sen. Norm Coleman).

are coming from Brazil, India, Pakistan, the Netherlands, Spain, China, Portugal, Canada, the United Kingdom, Ireland, Mexico, Costa Rica, Belize, Colombia, the Bahamas, and Honduras, in addition to many other countries. Clearly, drug products are entering the United States from across the world.

The United States has fourteen International Mail Branches that handle all of the U.S. international mail. In addition to these mail facilities, there are twenty-nine consignment ports and 312 ports of entry, all of which handle imported pharmaceuticals. Based on the above numbers, it is estimated that 20 million packages containing drug products enter the United States yearly. However, when you include the number of people crossing the U.S. border, the number may be much higher. In 2004, it is estimated that close to a billion dollars worth of drugs were shipped from Canada alone into the United States, and an estimated \$800 million in pharmaceutical sales along the U.S.-Mexico border.

Since personal importation of a pharmaceutical product is illegal, the FDA realizes that there may be situations when importation of an unapproved drug may be necessary and thus the FDA has established some guidelines for when to enforce the law. These guidelines are now being followed by Immigration and Customs Enforcement (ICE). The guidelines suggest not taking action against personal importation when all of the following are met:

- When the intended use of the unapproved product is “for a serious condition for which effective treatment” is not available in the United States.
- “[T]here is no . . . commercialization or promotion to persons residing in the United States by those” distributing the product.
- The product does not “represent an unreasonable risk.”
- The patient has exhausted U.S. treatments and the product is NOT available in the United States. This is essentially a last attempt to treat the condition.
- The patient is under a doctor’s care for the drug, or started the treatment outside the United States and is continuing therapy upon returning to the United States.
- The product is for personal use, not for commercial use.⁷

Foreign made versions of U.S. drugs are not intended to be covered by these guidance variances. The FDA views unapproved for-

7. MARVIN A. BLUMBERG, FDA, INFORMATION ON IMPORTATION OF DRUGS, Apr. 3, 1998, <http://www.fda.gov/ora/import/pipinfo.htm>.

foreign made versions of U.S.-approved drugs as an unreasonable risk. The guidelines express elements of leniency; for example, visitors to the United States should be allowed to bring their medications with them when they come to the United States.

Today, these variances have become much broader, and people are now allowed to import a ninety-day supply of a non-controlled prescription drug product and fifty units (fifty capsules or tablets) of a Schedule II through V product. Scheduled or controlled drug products are narcotic or psychotropic products, products which have a potential for abuse or are addictive.

Various testimonies at congressional hearings show that many times the quantities of drug products per package coming in from foreign sources exceeds the ninety-day supply limitation. Examples include huge boxes containing many plastic bags, each filled with different colored capsules or tablets; in one instance, none of the bags had a product identification label. Some of the boxes had thousands of drug doses, while other parcels only had one drug product that met the ninety-day supply requirement.

The Bureau of Customs and Border Protection, the FDA, the Drug Enforcement Administration, ICE, the U.S. Postal Inspection Service, the Office of National Drug Control Policy, and the Department of Justice formed a working group to address the issues revolving around drug importation. This working group investigated the type, volume, and quality of pharmaceuticals being imported into the United States. The project was titled "Operation Safeguard," and it was a three-year investigation ending in 2003. The first "blitz" operation examined imported mailed drug shipments in Miami, New York, San Francisco, and Carson, California. In this operation, a total of 1153 shipments of imported drug products were examined. A second series of blitz operations occurred in November of 2003; this blitz occurred at the International Mail Branches in Buffalo, Dallas, Chicago, and Seattle. A total of 3375 drug products were examined from both blitzes. The operation "found the volume of pharmaceuticals shipped through international mail to be enormous." A summary of the results from both investigations follows:

- "[A] significant number of [products] [did] not contain an active pharmaceutical ingredient. . . ."
- Some products were expired.
- Some products did not have FDA approval.
- Some products had improper directions for use.
- Some products were from "facilities not under proper regulation."

- Some products were “gray” market or foreign versions of U.S. approved and patented drug products.
- Some products were unlabeled.
- Some products were improperly packaged. Products requiring refrigeration were not properly packaged.
- Some products were withdrawn from the U.S. market.
- Some products had labels written in a foreign language.⁸

Obviously, some imported drug products pose health risks to the American public. The FDA has issued several warnings to the U.S. public via public announcements and the FDA Web site about the risks of purchasing prescription drug products from foreign Web sites. The FDA’s stance is that it is a “buyers beware” market.⁹

ROGUE PHARMACY WEB SITES AND “BAIT AND SWITCH” TACTICS

There are over a million pharmacy Web sites worldwide where one can order prescription drug products. Some of these Web sites are licensed U.S. pharmacies, with some U.S. sites being certified as a Verified Internet Pharmacy Practice Site (VIPPS). VIPPS certificates are granted by the U.S. National Association of Boards of Pharmacy and are only given to those pharmacies that meet stringent certification requirements. VIPPS certification seals can be found prominently displayed on the opening Web page of the pharmacy.¹⁰ VIPPS certification offers consumers added quality assurance.

Many Web-based pharmacies are not located in the United States, and at times it is very difficult for consumers to determine if the pharmacy is legitimate and where the pharmacy is located. Rogue, fraudulent pharmacy Web sites are abundant; additionally, many Web sites have cascading affiliate Web sites that makes it more difficult to determine the legitimacy of the pharmacy.

Many Web-based pharmacies do not include an address or a telephone number on the Web site and many use deceptive domain names. That is, the domain name deceives one to think that the pharmacy is a legitimate operation located in the United States or another

8. *Buyer Beware Hearings*, *supra* note 3, at 220-24 (statement of Jayson P. Ahern, Assistant Comm’r, Office of Field Operations, Bureau of Customs and Border Protection).

9. See FDA, BUYING MEDICINES AND MEDICAL PRODUCTS ONLINE, <http://www.fda.gov/buyonline/> (last visited Aug. 13, 2005); JOHN HENKEL, FDA, BUYING DRUGS ONLINE: IT’S CONVENIENT AND PRIVATE, BUT BEWARE OF “ROGUE SITES,” FDA CONSUMER, Jan.-Feb. 2000, available at http://www.fda.gov/fdac/features/2000/100_online.html.

10. NAT’L ASS’N OF BOARDS OF PHARMACY, VIPPS, <http://www.nabp.net/vipps/intro.asp?styletag=default> (last visited Aug. 13, 2005).

country, when in fact, it may not be legitimate and it is not located in the country designated by its domain name. For example, a report released in June 2005, prepared for the FDA by Cyveillance, a firm which specializes in online risk management, reported that out of approximately 11,000 pharmacy Web sites designated Canadian, only 1009 of the sites actually sold prescription drugs, and out of this total only 214 were located in Canada.¹¹ Another study examining the misrepresentation issue, conducted by Global Options, found *supposedly* Canadian pharmacy Web sites to be located in Mexico City, Barbados, and the United States.¹² Thus, U.S. residents thinking they are getting a medication from Canada may be getting drug products from another country. It is the classic “bait and switch” tactic.

What further complicates the issue is that more and more Canadian pharmacy Web sites are transferring U.S. prescriptions to pharmacies located outside of Canada. The Canadian Web-pharmacy *Canadameds.com* recently reported that it was transferring 10,000 prescriptions a week to pharmacies located in thirty different countries including New Zealand, Germany, Israel, and the United Kingdom.¹³ Thus, even when the site is located in Canada, the drug may come from another country.

DOCUMENTING PROBLEMS

Documenting the hazards of substandard imported pharmaceuticals is a very difficult task. Deaths and injury from imported pharmaceuticals have occurred, but the evidence is anecdotal. When death or injury does occur, it is usually a special case, such as an overdose of a narcotic or adverse reaction to the drug.

One must understand that a medication that does not have an active ingredient—a fake drug—usually does not kill people, especially if the product is a treatment for an asymptomatic disease. Another common problem with fake drugs is the “placebo effect.” This occurs when people believe they are improving because they are taking a drug product. Many times counterfeit drug makers take advantage of both factors because they make fake drugs for asymptomatic condi-

11. Press Release, Cyveillance, Cyveillance Helps U.S. Food and Drug Administration Identify Online Pharmacy Misrepresentation (June 13, 2005), *available at* http://www.cyveillance.com/web/newsroom/press_rel/2005/2005-06-13.htm.

12. GLOBAL OPTIONS, INC., AN ANALYSIS OF TERRORIST THREATS TO AMERICA'S MEDICINE SUPPLY 145 (2003).

13. *Canadameds.com Now Filling Half of All Scripts Overseas*, SCRIP WORLD NEWS: WORLD PHARMACEUTICAL NEWS, Feb. 11, 2005, at 18.

tions. Examples of this latter category are prophylactic medicinal products used to lower cholesterol levels or medications to treat high blood pressure. Many times patients do not feel the illness or the condition. Thus, it may take months, or over a year, before one realizes that the product to lower cholesterol levels or hypertension medication was substandard.

In addition, if the patient does not show any improvement, the physician will either raise the dose of the existing drug or prescribe a different drug. The possibility that the patient is taking a fake or substandard drug is seldom raised. As mentioned, this can occur with a wide range of products, and in fact recently occurred with counterfeit Lipitor. This drug, which controls cholesterol levels, was being purchased by Americans in Mexico's border towns and was found to be counterfeit after tests showed that it had little effect on the patients' cholesterol levels.¹⁴

Furthermore, if death or morbidity occurs, the result is usually blamed on the disease. Very seldom is the drug product suspected. Seldom does one investigate the drugs the patient is taking; they are assumed to be FDA-approved products. In this sense, it is a perfect crime. An example of the difficulty of investigating deaths due to a fake drug is the counterfeit drug case that occurred in June 2005 in Hamilton, Ontario.¹⁵ Counterfeit Norvasc, a drug used to treat high blood pressure and angina, was dispensed from a community pharmacy. A consumer discovered the fake product by noting a slight color and shape difference in the tablet. Seven people who had prescriptions filled for Norvasc at the pharmacy are dead, leaving little evidence behind. Six were already buried, one was cremated, and an autopsy was only done on one person. This case will be a "major forensic challenge" in determining if the fake drug was the cause of death.¹⁶

Unless someone suspects foul play, no determination is made as to whether or not a drug product was involved; the death is conveniently blamed on the disease. It is true the death may be due to the disease, but by not taking the appropriate drug product, the substandard medication may have contributed to the death. The problem is that no one knows; the data is not being collected.

14. Nick D'Amore, *Fake Drugs Sold in Mexico*, 24 MED. AD. NEWS 68, 68 (2005).

15. *Counterfeit Heart Medication Seized From Hamilton Pharmacy by Police*, CANADIAN PRESS, June 16, 2005.

16. Luma Muhtadie, *Fake Drug Case: Huge Forensic Challenge*, HAMILTON SPECTATOR, July 16, 2005, at A01.

Despite the problems of the lack of data, documentation, and problems with investigating cases involving substandard or fake pharmaceuticals, deaths and hospitalizations have been reported in the press due to the imported medication. However, most of these are either due to a narcotic drug overdose or the patient had a severe adverse reaction to the product. With the high number of reported counterfeit and substandard drugs being imported, it is difficult to believe that some Americans have not been affected. The problem lies with the lack of investigating and documenting the use of imported pharmaceuticals.

OTHER SAFETY ISSUES WITH DRUG IMPORTATION

Since it takes one to two weeks or even longer to receive an imported medication, most imported drug products are used to treat chronic conditions, such as arthritis, diabetes, heart conditions, high cholesterol levels, etc. Importation of medicinal products for acute care needs is impractical. For acute conditions, people need the medication now, and they cannot wait two weeks for the therapy. Normally, patients will use a local community pharmacy to obtain prescription drugs for acute care needs, such as an antibiotic medication.

If this same person purchases his or her chronic care drugs from a foreign pharmacy, then an added health risk is present. The purchasing of acute care drugs from one pharmacy and chronic care drugs from a different pharmacy presents added health risks because now neither pharmacy has a complete record of all the drug products the patient is taking. Thus, the risk of taking two contraindicated drugs or the risk of taking a drug that is contraindicated for a disease is much higher and may result in serious problems for patients. Local community pharmacists do maintain an electronic record of all drugs the patient is taking and pharmacists do use computer programs to help them screen for drug interactions. Splitting drug therapies between two or more pharmacies raises the risk of a drug misadventure.

There are other risks associated with purchasing prescription drug therapies from foreign pharmacies. These include:

- Who does the monitoring of the patient's therapy?
- Who does the patient call if they have drug therapy questions?
- Who is monitoring the patient's drug compliance?
- Who checks on prescription drug refills and calls the physician for a refill?
- Who checks for inappropriate therapies?

- Who is monitoring for duplicate or multiple therapies?

All of the above are critical questions, especially for those patients who are on multiple drug therapies, including the elderly. The safest approach for patients is to use one pharmacy and develop a trusting relationship with the pharmacist. A pharmacy, which has a complete record of all medications and who can monitor for drug and disease interactions, can reduce risks and improve the patient's health.

Another safety issue is with the same drug names, but different ingredients by country. The same drug names may be used in different countries, but the active ingredients may be different. For example, the U.S. product named Flomax (tamsulosin) is for the treatment of benign prostate cancer; but in Italy, the product named Flomax contains morniflumate and is a treatment for inflammation, pain, and fever. Another example is the U.S. product named Norpramin (desipramine), used for the treatment of depression in the United States. However, in Spain the product called Norpramin contains omeprazole and is the treatment for peptic ulcers.¹⁷ It does raise a concern when a patient wants a cancer treatment product and receives an entirely different product, but it is not realized because it has the same name. The name for brand name drugs may differ by country because of language translations and negative connotations, or slang used by the culture.

Lastly, physicians rarely ask where patients obtain their drug products, assuming patients use FDA-approved products and get their products from a U.S. pharmacy. Today, physicians must increase their awareness and ask where their patients are obtaining their drugs, especially if they see a lack of progress in the patient. What makes this more difficult is that many patients do not want to admit they are getting their prescription drugs from a foreign source and thus, they may not tell the physician they are getting their drugs from Mexico or somewhere else.

LACK OF DATA ON THE SAFETY AND OUTCOMES OF IMPORTED PHARMACEUTICALS

The problem is not that imported drugs do not cause problems. There is enough documentation on the amount of substandard and counterfeit medications being imported by U.S. residents to realize that there must be some health consequences. The problem is getting

17. Michael R. Cohen, *Drug Trade Names; Something's Lost in Translation*, 35 NURSING 12 (2005).

access to the outcome information and collecting data to document the problems. This is a tremendous challenge and one that is currently being exploited by the drug importation businesses.

Foreign drug providers are very reluctant to release drug use data on the clientele or patient level. Some have released aggregate data, but this does not address the issues. Even if the data are redacted, foreign pharmacy providers will not release the information. Thus, no information is available as to the type and amount of imported drug products being purchased by U.S. residents. There is little or no information as to therapeutic outcomes of people who use foreign-sourced drug products. There is no information available on the type of drugs being purchased, broken down by demographic characteristic of the purchaser. For example, critical questions include:

- What is the average age of the purchasers?
- What is the distribution of drug products by quantity of drugs or by number of prescriptions dispensed per patient?
- What is the drug product distribution by age or gender?
- What is the geographic location where the purchasers reside?
- What is the drug expenditure per prescription, by drug, or by therapeutic category?
- How many prescriptions are being filled annually per person from a foreign site?
- What are the drug expenditures per person annually?
- What is the repeat business?
- Do Internet drug buyers stay with one provider or do they shop for drugs worldwide?

Obviously, more research questions can be generated. The point is that the information is essential to understand drug importation and its risks, but currently it is unattainable from foreign pharmacies, including Canada.

CONCLUSION

Drug importation is a very difficult policy concern. It is not just an economic issue. There are political issues, international trade concerns, patient liability and legal issues, as well as health concerns, intellectual property protection issues, and the financial implications expressed by the pharmaceutical industry, community pharmacies, and the health insurance industry. The legalization of drug importation will have a huge impact on many U.S. industries. Clearly the situation is complex. The demand for cheaper prescription drugs will continue.

For many, lower drug costs have a higher priority than finding affordable and safe medications. This country needs to address drug access and drug pricing directly, rather than using drug importation. Drug importation is not a long-term solution to the drug access problem. With the proposed legalization of drug importation, we are not importing drugs—we are importing price controls set by another country. In addition, we may be importing more public health problems. That is not a sustainable solution to the problem of access to safe, affordable medications for the citizens of this country.