# HHS TASK FORCE ON DRUG IMPORTATION

## Report on Prescription Drug Importation

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**Department of Health and Human Services**

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# HHS TASK FORCE ON DRUG IMPORTATION

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## LIST OF ABBREVIATIONS

Bioterrorism Act – Public Health Security and Bioterrorism Preparedness and Response Act of 2002
CBO – Congressional Budget Office
CBP – U.S. Customs and Border Protection
cGMP – Current Good Manufacturing Practice
CMRI – Center for Medicines Research International
CMS – Centers for Medicare and Medicaid Services
CSA – Controlled Substances Act
CSDD – Center for the Study of Drug Development
DEA – U.S. Drug Enforcement Administration
DOJ – U.S. Department of Justice
EC – European Commission
EMEA – European Medicines Agency
E.U. – European Union
FCC – Forensic Chemistry Center Laboratory
FD&C Act – Federal Food, Drug and Cosmetic Act
FDA – U.S. Food and Drug Administration
HHS – U.S. Department of Health and Human Services
HMO – Health Maintenance Organization
ICH – International Conference on Harmonization
IND – Investigational New Drug
IT – Information Technology
JFK – John F. Kennedy International Airport Mail Facility
MEDS Act – Medicine Equity and Drug Safety Act of 2000
MMA – Medicare Prescription Drug, Improvement and Modernization Act of 2003
MOU – Memoranda of Understanding
MRA – Mutual Recognition Agreement
NABP – National Association of Boards of Pharmacy
NAFTA – North American Free Trade Agreement
NASs – New Active Substances
NCE – New Chemical Entity
NDA – New Drug Application
OASIS – Operational and Administrative System for Import Support
OCI – Office of Criminal Investigations
ORA – Office of Regulatory Affairs
PDMA – Prescription Drug Marketing Act of 1987
PSW – Pharmacy Society of Wisconsin
R&D – Research and Development
RFID – Radio-Frequency Identification
SSRIs – Selective Serotonin Reuptake Inhibitors
SWID – Southwest Import District
TRIPS Agreement – Trade Related Aspects of Intellectual Property
U.K. – United Kingdom
U.S. – United States of America
USPS – U.S. Postal Service
USPTO – U.S. Patent and Trademark Office
VIPPS – Verified Internet Pharmacy Practice Site
WTO – World Trade Organization

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## OVERVIEW

### Introduction

In 2003, Congress passed the Medicare Prescription Drug, Improvement and Modernization Act of 2003, Pub. L. 108-173 (Medicare Modernization Act or MMA), which for the first time provided a prescription drug benefit for seniors and people with disabilities. The MMA also contained provisions that would permit the importation of prescription drugs into the U.S. if the Secretary of the Department of Health and Human Services (HHS) certifies that drugs imported from Canada pose no additional risk to public health and safety and that such imports would provide significant cost savings to American consumers. The MMA also requires the Secretary to conduct a study on the importation of drugs. The conference agreement for MMA included eleven issues for consideration. The Surgeon General of the U.S. Public Health Service, Dr. Richard H. Carmona, was charged with leading a task force of senior executives across the Federal government to conduct the analysis required by the MMA. The Task Force met with key constituencies numerous times throughout 2004 in public forums, received testimony from over one hundred presenters from around the world with all types of backgrounds, and received over one hundred written comments providing insight into these issues. This report is a summary of what the Task Force reviewed from the testimony and written comments for the specific questions posed in the MMA conference agreement and their findings based on this evaluation.

### Background

In the early years of the twentieth century, pharmaceuticals in the U.S. were characterized by a large number of ineffective, often dangerous, compounds, the principal ingredient of which was often alcohol. The invention of penicillin in the 1930s marked the beginning of the modern era of drug development, when scientists were able to create powerful new chemicals that were safe and effective in killing bacteria. Since then, the world's investment in research and development (R&D) has produced many more safe and effective treatments to reduce pain and inflammation, regulate the cardiovascular system, impede the growth of cancer cells, and provide a host of other effective therapies for disease. The resulting discovery of new medications has enabled doctors to offer comfort for the sick and to prescribe from an extensive array of drugs to treat most human afflictions.

As this innovation began in the 1930s, Congress recognized the need for a strong oversight body to ensure that drugs were properly tested before being given to patients. The manufacturing of drugs needed equally rigorous oversight to ensure that drugs were made in a safe and consistent way. The Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 and its 1962 amendments provided that oversight, by requiring that the U.S. Food and Drug Administration (FDA) approve each new drug as safe and effective before marketing and authorizing FDA to oversee the production of drugs, whether manufactured in a U.S. facility or imported from abroad.

By the 1980s, Congress recognized that some entities not subject to U.S. law were importing counterfeit drugs as well as improperly handled and stored drugs. For example, at that time, counterfeit birth control pills found their way into the U.S. drug distribution system. These types of activities posed significant risks to American consumers. Therefore, in 1987, Congress passed the Prescription Drug Marketing Act (PDMA), which, among other things, strengthened oversight of domestic wholesalers and added the "American goods returned" provision to the FD&C Act, which prohibits anyone

except a drug's manufacturer from importing into the U.S. a prescription drug that was originally manufactured in the U.S. and then sent abroad.

We recognize that there are different categories of "imported drugs" that potentially have different levels of associated risk. Currently, the only types of legally imported drugs are: 1) those that are manufactured in foreign FDA-inspected facilities and adhere to FDA-approval standards, or 2) those that are U.S.-approved and manufactured in the U.S., sent abroad, then imported back into the U.S. by the manufacturer under proper controls and in compliance with the FD&C Act. This latter category includes products that are truly re-imported. In both cases, the manufacturing process is subject to direct FDA oversight and the drug distribution system is "closed," and the manufacturer complies with FDA and other regulations to assure that the drug delivered to the pharmacy is of high quality.

Another category of imported drugs are those that are manufactured in a foreign facility that also manufactures the U.S.-approved version. In such a case, FDA would have inspected the U.S.-approved manufacturing process, but not the unapproved production lines; in this case, the foreign version may differ in certain respects from the U.S.-approved version. Although there may be significant similarities between the two versions, because of the potential differences and the fact that only the U.S.-approved drugs have been shown to meet U.S standards enforced by FDA, the foreign version cannot necessarily be considered equivalent to the U.S.-approved version.

A final category of imported drugs are unapproved drugs that are produced in foreign facilities that FDA has not inspected and, therefore, has no knowledge of, or experience with, the facility. Consequently, the safety and effectiveness of these drugs and the safety and security of their distribution systems are unknown. These drugs pose the greatest level of concern because they are not regulated within the U.S. drug safety system and little is known to U.S. regulators about the specifications to which they are made, the processes used to ensure their safety, and the integrity of their distribution. As the report describes, there is ample evidence that these are the types of drugs that consumers have received when they order prescription drugs from some international sources over the internet.

When a drug is imported into the U.S., FDA inspectors are required to confirm that the drug meets the necessary approval requirements. Such review of imported drugs is limited by the amount of resources available, given the substantial amount of legal and illegal prescription drugs that are imported daily. If there is a question of whether the drug can legally be imported and, thus, raises safety questions, FDA has the authority to detain the product and gives the importer several days to demonstrate the drug's acceptability (or, failing that, the drug is either refused admission and returned to its foreign source, if known, or destroyed.)

The conclusion of Congress reflected in current law is that the safety and effectiveness of imported drugs can only be assured for drugs legally imported into the U.S., as described above. In these cases, the chain of custody is known for a U.S.-approved drug manufactured in an FDA-inspected facility using FDA-approved methods as it travels through the U.S. distribution system. Much of the current public debate about the safety of broader importation comes down to issues regarding the additional oversight authorities, resources, and foreign government support that would be needed to assure the safety and effectiveness of other types of drugs, principally foreign drug purchases from international internet operations that are not subject to FDA's regulatory oversight.

Since the FD&C Act's passage in 1938, American citizens returning from overseas with foreign drugs have been advised that most of these drugs are not legal, but, as a matter of enforcement discretion, FDA has generally allowed those citizens to bring in small quantities for their personal use and advised them to consult with their physician. FDA created this enforcement discretion policy to allow American residents who became ill in another country to continue the treatment prescribed by a foreign healthcare practitioner until they could receive medical attention back home. That policy was not controversial until the latter part of the 1990's, when some citizens

began traveling regularly to other countries to fill their prescriptions, and especially when more Americans began ordering drugs via internet pharmacies located in other countries.

The Task Force understands what motivates more and more Americans to import drugs. Access to affordable prescription drugs, many of which are needed to treat life-threatening and serious conditions, is a daily concern and challenge for many Americans. As there has been a significant increase in drug utilization and in list prices for drugs in the U.S. over the last few years, spending by American consumers on prescription drugs has risen significantly. Over 40 percent of Americans take at least one prescription drug and, in an effort to lower their prescription drug bill, a relatively small but increasing number have turned to importing drugs.

Consequently, the Task Force believes that access to drugs that are safe and effective, as well as affordable, is a critical policy goal, and that all approaches to achieving this challenging goal should be explored thoroughly. Drugs that are affordable, but not safe and effective, could be more harmful to patients than not having the drugs at all. The difficult balance between the need for affordable prescription drugs and concerns over potential safety hazards that many imported drugs may pose is reflected in the public debate and controversies regarding drug importation policy in the U.S. The Task Force report presents a comprehensive overview of the evidence related to this balance, as well as a number of other critical issues, as requested by Congress, on the subject of prescription drug importation.

## THE REPORT IN BRIEF

### Chapter 1 –Scope, volume, and safety of unapproved drugs

The number of unapproved prescription drug products entering the U.S. is now very large. Nearly five million shipments, comprising about 12 million prescription drug products with a value of approximately $700 million, entered the U.S. from Canada alone in 2003, via internet sales and travel to Canada by American consumers. This report estimates that an equivalent amount of prescription drugs are currently coming in from the rest of the world, mostly through the mail and courier services.

Imported drugs are arriving from all corners of the world, including developed and emerging countries. Their scope is broad and includes tablets, capsules, inhalants, injectables, biologics, generics, brand name drugs, and controlled substances. Some of the arriving products appear to have been made in the U.S.; however, many are not. The majority of these currently imported drugs are unapproved by FDA and do not appear to conform in many aspects to the properly approved and manufactured products available in American pharmacies.

Numerous comments submitted to the Task Force described the current practice of internet purchases by American consumers who seek lower-priced drugs. Many state-licensed internet pharmacies provide a legitimate means for consumers to access safe and effective medicines, but others raise significant safety concerns.

Most of these drugs are purchased by individual consumers via internet, phone, or fax, from entities that focus on providing drugs to Americans and other long-distance purchasers. These entities generally are cross-border foreign pharmacies that may not primarily serve the citizens of the country in which they are located, and their methods for providing drug products may not be subject to the same oversight that foreign governments provide for drugs and pharmacies serving their own citizens. When consumers order prescription drugs over the internet from international sources, they generally receive drugs that do not have regulatory assurances of equivalence to U.S. products or of safety and security in the distribution process.

Some sellers of imported drugs are "rogue" internet pharmacies that pretend to be legitimate and operate behind facades. Many of the drugs sold over the internet claim to be interchangeable with the approved U.S. drug, but are not. Imported drugs include those that pose special concerns, such as drugs that require special handling, drugs with high

abuse potential, drugs that should be sterile, counterfeit drugs, improperly packaged drugs shipped loose in sandwich bags and envelopes, and drugs from countries that have differing and sometimes more limited regulatory authority to assure the safety of pharmaceuticals manufactured and exported from those countries. In sum, this report finds that American consumers currently purchasing drugs from overseas are generally doing so at significant risk.

## Chapter 2 – Limits on resources and authorities

The Federal law governing drug safety in the U.S. establishes the standards by which FDA determines whether a prescription drug is "safe and effective" for sale in the U.S. These standards govern the way in which prescription drugs are manufactured, packaged, labeled, held, and shipped. Many of the prescription drugs that are imported into the U.S. now by individual citizens, via mail and courier services, fail to comply with some or all of these Federal standards. To ensure that imported prescription drugs are as safe as those that are legally sold in the U.S., an importation program for U.S.-approved drugs would have to ensure that the imported drugs meet the current (or equivalent) Federal standards. This report determines that it would be extraordinarily difficult to ensure that drugs personally imported by individual consumers could meet the necessary standards for a certification of safety to be made, especially if consumers continue to import prescription drugs in the same or increased numbers. Meanwhile, a commercial importation program could be feasible but would require new legal authorities, substantial additional resources and significant restrictions on the type of drugs that could be imported, which could increase the costs of imported drugs.

## Chapter 3 – Impact on the pharmaceutical distribution system

The drug distribution network for legal prescription drugs in the U.S. is a "closed" system that involves several players (e.g., manufacturers, wholesalers, pharmacies) who move drug products from the point of manufacture to the end user, and provides the American public with multiple levels of protection against receiving unsafe, ineffective, or poor quality medications. This system evolved as a result of legislative requirements that drugs be treated as potentially dangerous consumer goods that require professional oversight to protect the public health. The result has been a level of safety for drug products that is widely recognized as the world's "gold standard." Legalized importation of drugs in such a way that creates an opening in the "closed" system will likely result in some increase in risk, as the evidence shows that weaknesses in the oversight of drug regulation and the distribution system have been exploited. For example, doing so would increase the opportunity for counterfeit and other substandard drugs to enter and be dispersed into the U.S. drug distribution system.

## Chapter 4 – Role of new technologies

There are a number of anti-counterfeiting technologies that show potential for effectively assuring the authenticity of drugs and, thus, for combating the counterfeiting of drugs. Some examples include holograms, color shifting inks, and watermarks currently employed for U.S. currency. So-called "track and trace" technologies, such as radio-frequency identification (RFID) and sophisticated bar coding, can provide effective monitoring of a drug's movement from the point of manufacture and through the U.S. distribution chain. Although these new and emerging technologies are promising, until they are fully adopted internationally they cannot be adequately relied upon to secure the safety, efficacy, and integrity of the global market to safely import prescription drugs into the U.S.

## Chapter 5 – Agency resources associated with drug importation activities

FDA currently has about 3,800 employees assigned to field activities (e.g., inspections) involved in protecting the many thousands of products that make up the Nation's food, drug, biologic, medical device, and veterinary drug supply. Of the 3,800 field staff, 450 are involved in investigative import activities. Only a limited number of FDA inspectors are available to staff the 14 international mail facilities in the U.S., where they historically have had to inspect a small number

of large commercial pharmaceutical imports. FDA managers have repeatedly noted that the large number of personal drug shipments coming into the international mail and courier facilities is overwhelming the available staff.

This report finds that despite significant efforts, including joint efforts with CBP and import alerts/bulletins, FDA currently does not have sufficient resources to ensure adequate inspection of current levels and categories of personal shipments of prescription drugs entering the U.S. With respect to commercial shipments, based on the information presented to the Task Force, FDA would need a meaningful investment, among other things, in new information technology and personnel, as well as appropriate standards to ensure adequate inspection of commercial quantities of drug products, if importation were legalized.

## Chapter 6 – Role of foreign health agencies

Just as the U.S. is responsible for the safety and effectiveness of drugs made available to its citizens, foreign governments give priority to ensuring the safety of drugs used by their citizens. Foreign governments have little incentive and limited resources to ensure the safety of drugs exported from their countries, particularly when those drugs are transshipped or are not intended for import. No country expressed any interest or willingness to ensure the safety and effectiveness of drugs exported from their country in any expansion of legal U.S. importation. Although we specifically solicited them, few comments were submitted by foreign governments, and none outlined a specific strategy for new steps to collaborate with the U.S. government on the effective oversight of importation, suggesting that they are not willing or do not have the means to ensure the safety of exported products and that the primary safety responsibilities would have to remain with the U.S.

## Chapter 7 – Effects of importation on prices and consumer savings

Consumers seek to import prescription drugs from other countries in part because they believe they can save money if they purchase their drugs from outside the U.S. In many instances, U.S. consumers have been able to purchase from abroad foreign versions of U.S.-approved brand name drugs at lower prices. However, based on an analysis of actual data on drug prices and volumes, this report finds that total savings to consumers from legalized importation under a commercial system would be a small percentage relative to total drug spending in the U.S. (about one to two percent). These savings are much smaller than some specific international comparisons of retail prices for certain drugs might suggest. Under any safe, legalized commercial importation program, when the scope is limited, intermediaries would likely capture a large part of the price differences. (This is based on evidence from European countries where some form of importation is legal.)

This report also finds that generic drugs are often cheaper in the U.S. compared to international prices for similar drugs. Other, independent studies have reached similar conclusions. The prices foreigners pay for generic drugs are on average 50 percent greater than the prices Americans pay for generic drugs. Furthermore, there is evidence that greater use of U.S.-approved generic drugs by Americans could reduce drug spending by billions of dollars annually. In addition, to the extent that prescription drugs are eligible for importation from the same company at a lower price than in the U.S., potential quantity constraints imposed by manufacturers or foreign governments would limit the eligible supply and the benefits to U.S. consumers.

## Chapter 8 – Impact of importation on research and development and consumer welfare

One of the most frequently debated issues surrounding drug importation is whether the legalization of importation would reduce research and development (R&D), including spending on discovery, development, and launching of new drugs. Based on both an empirical analysis of drug data and a review of previous studies, this report finds that, by shifting sales to countries with price controls for new drugs, importation would reduce overall U.S. pharmaceutical industry revenues. Since revenues would fall without a reduction in the cost to produce new medicines, prof-

its would likely fall, as well as spending on R&D. Consequently, legalized importation would likely adversely affect incentives for R&D, thereby slowing the flow of new drugs. This report also finds that since annual R&D spending would drop, importation could result in between four to eighteen fewer new drugs being introduced per decade at a substantial cost to society. Furthermore, if there were a likely reduction in innovative new drugs, then the foregone consumer benefits associated with loss or delay in new therapies may significantly offset any anticipated savings from legalized importation, depending on uncertainties.

### Chapter 9 – Impact on intellectual property rights

Intellectual property rights have evolved over many years to strike a balance between, on the one hand, providing incentives for innovation through grants of exclusive rights over new ideas or products and, on the other hand, ensuring that knowledge and products are widely disseminated and accessible to provide the maximum benefit to society now and in the future. As with most new ideas and products, inventors of pharmaceuticals may obtain patents and other intellectual property protections for their products that provide certain exclusive rights. The challenge policymakers face is to ensure that intellectual property protection for pharmaceuticals provides adequate economic incentives to develop new drugs while facilitating access to affordable medicines.

An exhaustive legal analysis of the implications of allowing importation of patented pharmaceuticals to which intellectual property protections apply would require further study. However, it is clear that importation could impact the intellectual property rights of developers of pharmaceutical products and could be subject to challenge under domestic law, including possibly the U.S. Constitution, and international intellectual property rules.

### Chapter 10 – Liability issues related to importation

This report identifies the liability issues raised if importation is legalized for entities within the pharmaceutical distribution system. This report notes that allowing prescription drug importation would have uncertain effects on the litigation exposure of manufacturers, distributors, doctors, and pharmacists. To deal with these likely increased risks, entities in the pharmaceutical distribution chain may take additional costly defensive actions. Perhaps the largest source of additional liability and/or litigation risk under a drug importation system would be an increase in the number of injuries and poor disease outcomes if imported drugs are, as a class, less safe and effective.

## KEY FINDINGS

This report details the diverse opinions expressed, the data collected, and Task Force findings based on the information presented. Some of the key findings of the Task Force are:

1) **The current system of drug regulation in the U.S. has been very effective in protecting public safety, but is facing new threats. It should be modified only with great care to ensure continued high standards of safety and effectiveness of the U.S. drug supply.** Americans have the benefit of one of the safest drug supplies in the world and generally have first access to the newest breakthrough drug treatments. Any legislation to permit the importation of foreign drugs should only be done in a way that provides the statutory authority and substantial resources needed to effectively regulate imported drugs and, most importantly, protect the public health by providing the same level of safety assurances available for drugs sold in the U.S.

2) **There are significant risks associated with the way individuals are currently importing drugs.** While some means of drug importation (e.g., traveling to Canada for certain brand name drugs available in both countries) may be relatively safe in specific instances, this is not the only way "importation" into the U.S. is occurring today. Many transactions are occurring via poorly-regulated and occasionally bogus internet operations that have been documented in some cases to provide consumers with inferior products that are not the same as the U.S.-approved ver-

sions. Also, treatment failures, which are not obvious adverse events, are a real concern with substandard drug products.

3) **It would be extraordinarily difficult and costly for "personal" importation to be implemented in a way that ensures the safety and effectiveness of the imported drugs.** While wholesalers and pharmacists purchase, transport, and dispense imported drugs within our regulatory framework, American consumers making individual purchases from foreign sources outside our regulatory system, in particular those making long-distance purchases from internet sites or by fax or phone, face safety hazards that would be extraordinarily difficult to effectively address and prevent.

4) **Overall national savings from legalized commercial importation will likely be a small percentage of total drug spending and developing and implementing such a program would incur significant costs and require significant additional authorities.** The public rightly expects that, under any legal importation program, the imported drugs will be safe and effective. To accomplish this, additional safety protections would need to be added that would increase the costs of the program in an additive way as more safety measures are put in place. Substantial resources would also be needed to ensure adequate inspection of imported drug products. In addition to other factors that are likely to reduce potential consumer savings, these increased regulatory and program costs will also impact potential savings to consumers. Furthermore, intermediaries will likely capture at least half of any savings between the U.S. and price-controlled countries and potential quantity constraints imposed by foreign governments and manufacturers will likely further limit the supply of these drugs to U.S. consumers.

5) **The public expectation that most imported drugs are less expensive than American drugs is not generally true.** Generic drugs account for most prescription drugs used in the U.S. and are usually less expensive in the U.S. than abroad. Shopping around for price comparisons, asking a doctor or pharmacist for a generic alternative to a prescribed brand name drug, or using a Medicare or other prescription drug discount card is a proven method to save American consumers money on domestic prescription drugs while retaining the protections of a comprehensive safety regime.

6) **Legalized importation will likely adversely affect the future development of new drugs for American consumers.** This report estimates that R&D incentives will be lowered by legalized importation, resulting in roughly between four and eighteen fewer new drugs introduced per decade.

7) **The effects of legalized importation on intellectual property rights are uncertain but likely to be significant.** A host of legal and constitutional challenges are probable, and the effects on enforcement of intellectual property rights and on agreements with foreign countries are likely to be problematic. These effects could create additional disincentives to develop breakthrough medicines and further limit any potential savings that might have been realized.

8) **Legalized importation raises liability concerns for consumers, manufacturers, distributors, pharmacies, and other entities.** Consumers harmed by imported drugs may not have legal recourse against foreign pharmacies, distributors, or others suppliers. Entities in the pharmaceutical supply chain may take actions to protect themselves from liability that could ultimately raise the cost of drugs.

# BACKGROUND

## I. WHY ARE WE ISSUING THIS REPORT?

### A. Medicare Modernization Act (MMA)

#### 1. Statutory Language

The Medicare Prescription Drug, Improvement and Modernization Act of 2003[1] (Medicare Modernization Act, or MMA) was signed into law on December 8, 2003. MMA primarily provides a new prescription drug benefit enabling Medicare beneficiaries to receive coverage for drugs not administered in a hospital setting. However, MMA also includes provisions aimed at providing lower cost drugs to consumers.

Title XI, Subtitle C of MMA amends 21 U.S.C. 384 (importation of covered products) in the Federal Food, Drug, and Cosmetic (FD&C) Act. Under section 384, the Secretary of the Department of Health and Human Services (HHS) is directed to promulgate regulations that would allow pharmacies and wholesalers to import certain FDA-approved prescription drug products from Canada. The section also requires the Secretary to promulgate regulations to grant individuals a waiver to import certain FDA-approved prescription drugs from Canada under certain circumstances and permits the Secretary to grant individuals, by regulation or on a case-by-case basis, a waiver to import other drugs under such conditions as the Secretary determines appropriate. By allowing individuals to import such drugs, the MMA expands the scope of section 384, as originally established by the Medicine Equity and Drug Safety Act of 2000[2] (MEDS Act) because the MEDS Act authorized only pharmacists and wholesalers to import drugs. Nevertheless, as with the MEDS Act, Congress conditioned the implementation of the MMA's importation program on an initial certification by the Secretary. Section 384 provides that drug importation shall become effective only if the Secretary of the HHS is able to certify that implementing the program will:

- pose no additional risk to public health and safety, and
- result in a significant reduction in the cost of drugs to the American consumer.

Regardless of whether the Secretary certifies safety and savings, however, MMA also requires the Secretary to submit a study to Congress within one year on the importation of drugs. This study is the subject of this report.

#### 2. MMA Conference Agreement

The MMA requires the Secretary of HHS, in consultation with appropriate government agencies, to provide a comprehensive study that identifies problems with implementation of existing law and examines a range of issues associated with the importation of drugs. The conference agreement[3] specifies eleven separate issues that Congress requested the Secretary address in the study:

- Identification of the limitations, including limitations in resources and, if applicable, in current law authorities that may inhibit the Secretary's ability to certify the safety of pharmaceutical products imported into the U.S.
- Assessment of the pharmaceutical distribution chain and the need for, and feasibility of, modifications, in order to assure the safety of products that may be imported into the U.S.
- Analysis of whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as those products that could be imported from foreign nations. This analysis shall identify the types of technologies, if available, and assess the limitations of these technologies to the distribution chain.*
- Estimate of costs borne by entities within the pharmaceutical distribution chain to utilize any new technologies identified.*

- Assess the scope, volume, and safety of unapproved drugs, including controlled substances, entering the U.S. via mail shipment. This assessment should include the percentage of drugs commercially available in other countries that conform in all respects to FDA requirements, and the limitations of visual inspection, sampling, and other testing methods to determine its quality.
- The extent to which foreign health agencies are willing and/or able to ensure the safety of drugs being exported from their country into the U.S., including drugs that are transshipped through their countries.
- Assessment of the potential short and long-term impacts on drug prices and prices for consumers and other system costs associated with importation of pharmaceuticals from Canada and other countries into the U.S.
- Assessment of the impact on the research and development of drugs—and the associated impact on consumers and patients—if importation were permitted.
- Estimation of agency resources, including additional field personnel, needed to adequately inspect the current amount of pharmaceutical products entering into the country. This estimate shall detail the number of field personnel needed in order to appropriately secure all ports of entry on a daily basis.
- Identification of liability protections, if any, that should be in place, if importation is permitted, for entities within the pharmaceutical distribution chain.
- Identify the ways in which importation could violate U.S. and international intellectual property rights and describe the additional legal protections and agency resources that would be needed to assure the effective enforcement of these rights.

* For purposes of this report, we combined the issues of anti-counterfeiting and new technologies to better communicate the intricate relationship between the two.

## B. The Task Force's Charge

On February 26, 2004, HHS Secretary Tommy G. Thompson announced the creation of a task force[4] to advise him on how to address the questions posed by Congress in the MMA conference report.

Surgeon General Richard H. Carmona serves as chairman of the Task Force. The other Task Force members are: Jayson P. Ahern (Assistant Commissioner for Field Operations, Customs and Border Protection); Alex M. Azar II (General Counsel, HHS); Josefina Carbonell (Assistant Secretary for Aging, HHS); Lester M. Crawford (Acting Commissioner, Food and Drug Administration); Elizabeth M. Duke (Administrator, Health Resources Services Administration); Tracey Hardin (Attorney, Department of Justice); Mark B. McClellan (Administrator, Centers for Medicare & Medicaid Services); Michael J. O'Grady (Assistant Secretary for Planning and Evaluation, HHS); William Raub (Deputy Assistant Secretary for Public Health Emergency Preparedness, HHS); Thomas M. Reilly (Public Health Branch Chief, Office of Management and Budget); Amit K. Sachdev (Deputy Commissioner for Policy, Food and Drug Administration); and Elizabeth A. Willis (Chief of Drug Operations Section, Drug Enforcement Administration).

## C. How did we address the issues?

As part of our fact-finding and information collection process to address the issues, we made great efforts to gather input, ideas, and expertise from the public to give us guidance.

### 1. Listening Sessions and Public Meeting

We held five listening sessions and a public meeting, bringing together a wide variety of stakeholders to present testimony and provide information relating to the questions posed in the MMA conference report. The public meeting was held on April 14, 2004 and everyone who wanted to speak was given an opportunity to be heard. We heard from over 100 individuals, including: consumer representatives; pharmaceutical industry representatives; international regulatory and industry representatives; academicians; health care purchasers; professional medical groups; government and elected officials; and members of the public. All of the listening sessions were open to the media.

### 2. Website

Immediately following the first listening session, HHS developed a website (http://www.hhs.gov/import-taskforce/) dedicated to Task Force activities. The website contains information about each stakeholder listening session, including: the agenda, the text of the speaker presentations, and a complete transcript of each meeting. In addition, the website provides a link for the public to submit and view comments.

### 3. Docket

We established a public docket to solicit and receive information and comments.[5] We announced the creation of the docket in the Federal Register.[6] To stimulate and focus the discussion, the Federal Register notice listed the broad questions that Congress posed in the MMA conference agreement and also asked more specific questions to seek additional input to assist us in preparing this report. We requested that all comments be submitted by June 1, 2004; however, we also considered comments submitted after this date. We received and considered more than 100 written comments to the docket before drafting this report.

### 4. Other Sources of Information

We supplemented the information presented during the listening sessions and submitted to the docket with information from other sources to be certain that we adequately addressed the questions posed by Congress. We obtained information relating to the volume of imported drugs and drug prices from IMS Health, a global data collection and analysis firm. For some issues, where the comments did not provide sufficient data or other information, we received information from the U.S. Customs and Border Protection (CBP), the U.S. Food and Drug Administration (FDA), and the Department of Justice (DOJ). Additionally, in June 2004, a group of Task Force members toured the international mail facility at John F. Kennedy (JFK) airport to observe how imported drugs are processed daily by CBP and FDA personnel. During this visit, we saw how drugs are processed by this facility and the types of drugs that are being imported.

## D. What is in this report?

This report contains our findings based on all of the information presented to us and expert views solicited from appropriate government agencies. The report is divided into chapters according to the issues posed by Congress in the MMA conference agreement.

### 1. Definitions

The terms "imported," "importation," "re-imported," and "re-importation," are commonly used throughout this report. For purposes of this report, imported drugs are drugs manufactured for sale inside and outside of the U.S., then brought into this country for use by U.S. consumers. Unless otherwise specified, the term "importation" includes a) *personal importation* (internet sales, foot traffic across the border, mail order) where the drugs are purchased by those who consume them, and b) *commercial importation* where the drugs are purchased by pharmacies and wholesalers for resale to the ultimate consumer.

"Re-imported" drugs refer to FDA-approved prescription drugs that were made in the U.S., sent abroad, and then brought back into the U.S. Currently, only the original manufacturer can legally re-import a prescription drug and only if the manufacturer ensures that the drug is authentic, properly handled, and relabeled for sale in the U.S., if necessary.

### 2. Types of Imported Drugs

We recognize that there are different categories of imported drugs that potentially have different levels of associated risk. Currently, the only types of legally imported drugs are: 1) those that are manufactured in foreign FDA-inspected facilities and adhere to FDA-approval standards, or 2) those that are U.S.-approved and manufactured in the U.S., sent abroad, then re-imported back into the U.S. by the manufacturer under proper controls and in compliance with the FD&C Act. This latter category includes products that are truly re-imported.

Another category of imported drugs are those that are manufactured in a foreign facility that also man-

ufactures the U.S.-approved version (in such a case FDA would have inspected the U.S.-approved manufacturing process, but not the unapproved production lines); however, the foreign version may be slightly different than the U.S.-approved version. Although there may be significant similarities between the two versions, because of the potential differences and the fact that FDA determined the U.S.-approved drugs meet U.S. standards, the foreign version cannot necessarily be considered equivalent to the U.S.-approved version.

A final category of imported drugs are unapproved drugs that are produced in foreign facilities that FDA has not inspected and, therefore, has no knowledge of, or experience with, the facility. Consequently, the safety and effectiveness of these drugs are unknown. These drugs pose the greatest level of concern because they are not regulated within the U.S. drug safety system and there is little known about the specifications to which they are made, the processes used to ensure their safety, and the integrity of their distribution. These are the types of drugs that consumers may receive when they order prescription drugs over the internet.

## E. Brief History of U.S. Importation

### 1. The Current U.S. System

The FD&C Act limits the types of drugs that may be imported into the U.S. The current drug distribution system is relatively "closed," which helps ensure that the domestic drug supply is safe and effective.

New drugs marketed in the U.S., regardless of whether they are manufactured in the U.S. or a foreign country, must be the subject of a New Drug Application (NDA) approved by FDA based on demonstrated safety and efficacy. The drug must be produced in plants that are inspected by FDA and are operated in accordance with the current Good Manufacturing Practice (cGMP) regulations.[7] Also, the drug's labeling must bear certain information required by the FD&C Act. Only a drug's manufacturer can re-import into the U.S. a U.S.-made prescription drug that was sent abroad, but the law clearly allows legal, FDA-approved drugs to be made abroad. In fact, many drugs now sold in the U.S. were made in foreign, FDA-inspected facilities to standards approved by FDA. When such drugs or active ingredients are offered for import into the U.S., FDA inspectors evaluate them as they would any other drug—they attempt to assess whether the drug is FDA-approved, whether it is properly labeled, and whether it otherwise complies with the FD&C Act.

Under sections 381 and 331, unapproved, misbranded, and adulterated drugs cannot be legally imported into the U.S. This includes unapproved "foreign versions" of FDA-approved medications. In addition, under the "American goods returned" provision, it is illegal for any person other than the original manufacturer of a drug to re-import into the U.S. a prescription drug that was originally manufactured in the U.S. and then exported to another country.[8] This provision was included in the Prescription Drug Marketing Act of 1987 (PDMA)[9] to ensure that prescription drug products purchased by consumers would be safe and effective and to avoid an unacceptable risk that counterfeit, adulterated, misbranded, subpotent, or expired drugs were being sold to American consumers. Congress determined that legislation was necessary because there were insufficient safeguards in the prescription drug distribution system to prevent the introduction and retail sale of substandard, ineffective, or counterfeit drugs and that a wholesale drug diversion submarket had developed that prevented effective control over, or even routine knowledge of, the true sources of drugs. Congress limited access to reimported drugs because of these safety concerns.

Thus, in order to comply with the FD&C Act, any entity that intends to import prescription drugs into the U.S. must ensure that each drug is FDA-approved, meets all the U.S. manufacturing and labeling requirements, and that the importation does not violate section 381.

FDA drug approvals are manufacturer-specific, product-specific, and include requirements relating to the product, such as manufacturing location, formulation, source and specifications of active ingredients, processing methods, manufacturing controls, container/closure system, and appearance.[10] Drugs sold to

wholesale or retail establishments outside the U.S. may comply with the foreign country's specifications, but may not be manufactured pursuant to an FDA approval at all.

Even if a manufacturer has FDA approval for a drug, the version produced for foreign markets may not meet all of the requirements of the FDA approval, and thus it may be considered to be unapproved in the U.S.[11] Moreover, the version may be misbranded because it may lack certain information that is required under 21 U.S.C. §§ 352 or 353(b)(2) but is not required in the foreign country, or it may be labeled in a language other than English.[12]

Under FDA's regulations, the shipment and storage of prescription drugs must be properly documented and, when necessary, inspected.[13] One concern FDA has expressed is that, when a foreign manufacturer makes an FDA-approved drug in a foreign plant and then distributes it into foreign commerce, FDA has no assurance that the drug was properly stored or handled while abroad.

It is also important to note that the Controlled Substances Act (CSA), Title 21 U.S.C., Chapter 13, Subchapter II, specifically prohibits controlled substances to be imported except by DEA registrants. Any individual who imports controlled substances without being registered with DEA and without DEA authorization, is in violation of the CSA and is subject to prosecution.

### 2. Personal Importation Policy

Importing unapproved prescription drugs is illegal. However, FDA's long-standing policy on importing prescription drugs for personal use recognizes that there are circumstances in which FDA may exercise its enforcement discretion and not take action against illegal importation. The personal importation policy was first adopted in 1954; it was last modified in 1988 in response to concerns that certain AIDS treatments were not available in the U.S. Under the policy, FDA exercises its enforcement discretion to not stop individuals with serious conditions, such as a rare form of cancer, from bringing into the U.S. treatments that are legally available in foreign countries but are not approved in the U.S.

The current policy is not a law or a regulation, but serves as guidance for FDA field personnel. The importation of certain unapproved prescription medication for personal use may be allowed in some circumstances if all of the following factors apply:[14]

- If the intended use is for a serious condition for which effective treatment may not be available domestically;
- If the product is not considered to represent an unreasonable risk;
- If the individual seeking to import the drug affirms in writing that it is for the patient's own use and provides the name and address of the U.S.-licensed doctor responsible for his or her treatment with the drug or provides evidence that the drug is for continuation of a treatment begun in a foreign country;
- If the product is for personal use and is a three-month supply or less and not for resale. (Larger amounts would lend themselves to commercialization); and
- If there is no known commercialization or promotion to U.S. residents by those involved in distribution of the product.[15]

The majority of drugs coming into this country via personal importation today do not technically meet all of these factors. Nonetheless, given the high demand and limits on available resources it is difficult to effectively police this practice.

### 3. The Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA)

MMA provides authority for pharmacists and wholesalers to import drugs from Canada, subject to certain conditions. These specific conditions include:

- Requirements that importers and foreign sellers keep certain information and records;
- Qualified laboratory drug testing;
- Registration of Canadian sellers; and
- Use of approved labeling.

Once effective, MMA directs the Secretary to promulgate regulations to grant individuals a waiver to per-

mit importation of a 90-day supply of any FDA-approved prescription drug imported from Canada from a licensed pharmacy for personal use, if the drug is accompanied by a valid prescription, in a final finished dosage that was manufactured in a registered establishment, and imported under such other conditions as the Secretary determines necessary to ensure public safety.

Section 1121 of MMA provides that the drug importation program described above shall become effective only if the Secretary of HHS first certifies that implementing the program will pose no additional risk to public health and safety and will result in a significant reduction in the cost of drugs to the American consumer.

In 2000, Congress enacted legislation similar to the MMA as part of the Fiscal Year 2001 Appropriations Bill for the Department of Agriculture and Related Agencies, also known as the MEDS Act.[16] The MEDS Act, if implemented, would have allowed pharmacists or wholesalers in the U.S. to import FDA-approved prescription drugs that were manufactured in the U.S. in FDA-inspected facilities and exported to 26 specific foreign countries listed in the FD&C Act. On December 26, 2000, then-HHS Secretary Donna Shalala stated in a letter to President Clinton that she was unable to certify the safety and cost savings required by the MEDS Act.[17] Similarly, in a letter to Senator Jim Jeffords dated July 21, 2001, Secretary Thompson also declined to make the certification necessary to implement the MEDS Act due to safety concerns.[18]

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1 Pub. L. 108-173.
2 Pub. L. 106-387.
3 U.S. House of Representatives, Conference Report on H.R. 1, Medicare Prescription Drug And Modernization Act of 2003, H. Rept. 108-391, November 20, 2003. Accessed at http://thomas.loc.gov/cgi-bin/query/R?r108:FLD001:H11878 on 11/4/04.
4 U.S. Department of Health and Human Services, "HHS Announces Task Force on Drug Importation," February 26, 2004. Accessed at http://www.hhs.gov/news/press/2004pres/20040226.html on 11/4/04; U.S. Department of Health and Human Services, "HHS Names Members to Task Force on Drug Importation," March 16, 2004. Accessed at www.hhs.gov/news/press/2004pres/20040316.html on 11/4/04.
5 U.S. Food and Drug Administration Docket 2004N-0115. Accessed at www.fda.gov/ohrms/dockets/dockets/04n0115/04n0115.htm on 11/4/04.
6 69 Fed.Reg. 12810 (Mar. 18, 2004).
7 21 C.F.R. Part 211.
8 21 U.S.C. § 381(d)(1).
9 Pub. L. 100-293.
10 21 C.F.R. § 314.50.
11 21 U.S.C. § 355.
12 21 C.F.R. § 201.15(c).
13 21 C.F.R. § 205.50.
14 FDA, Regulatory Procedures Manual, Subchapter, "Import Operations/Actions: Coverage of Personal Importations," March 2004.
15 Pub. L. 108-173.
16 Pub. L. 106-387.
17 U.S. Department of Health and Human Services, Letter from Secretary Donna E. Shalala to President William J. Clinton, December 26, 2000.
18 U.S. Department of Health and Human Services, Letter from Secretary Tommy G. Thompson to Senator James Jeffords, July 9, 2001. Accessed at www.fda.gov/oc/po/thompson/medsact.html on 11/4/04.

# CHAPTER ONE

## Scope, Volume, and Safety of Unapproved Drugs

### Chapter Highlights:

The number of unapproved prescription drug products entering the U.S. is now very large. Nearly five million shipments, comprising about 12 million prescription drug products with a value of approximately $700 million, entered the U.S. from Canada alone in 2003, via internet sales and travel to Canada by American consumers. This report estimates that an equivalent amount of prescription drugs are currently coming in from the rest of the world, mostly through the mail and courier services.

Imported drugs are arriving from all corners of the world, including developed and emerging countries. Their scope is broad and includes tablets, capsules, inhalants, injectables, biologics, generics, brand name drugs, and controlled substances. Some of the arriving products appear to have been made in the U.S.; however, many are not. The majority of these currently imported drugs are unapproved by FDA and do not appear to conform in many aspects to the properly approved and manufactured products available in American pharmacies.

Numerous comments submitted to the Task Force described the current practice of internet purchases by American consumers who seek lower-priced drugs. Many state-licensed internet pharmacies provide a legitimate means for consumers to access safe and effective medicines, but others raise significant safety concerns. Most of these drugs are purchased by individual consumers via internet, phone, or fax, from entities that focus on providing drugs to Americans and other long-distance purchasers. These entities generally are cross-border foreign pharmacies that may not primarily serve the citizens of the country in which they are located, and their methods for providing drug products may not be subject to the same oversight that foreign governments provide for drugs and pharmacies serving their own citizens. When consumers order prescription drugs over the internet from international sources, they generally receive drugs that do not have regulatory assurances of equivalence to U.S. products or of safety and security in the distribution process.

Some sellers of imported drugs are "rogue" internet pharmacies that pretend to be legitimate and operate behind facades. Many of the drugs sold over the internet claim to be interchangeable with the approved U.S. drug, but are not. Imported drugs include those that pose special concerns, such as drugs that require special handling, drugs with high abuse potential, drugs that should be sterile, counterfeit drugs, improperly packaged drugs shipped loose in sandwich bags and envelopes, and drugs from countries that have differing and sometimes more limited regulatory authority to assure the safety of pharmaceuticals manufactured and exported from those countries. In sum, this report finds that American consumers currently purchasing drugs from overseas are generally doing so at significant risk.

# Key Points:

- Safety and protection of the public health are paramount; safety should not be sacrificed for affordability.
- The significantly increasing volume of imported drugs makes it difficult to quantify, monitor, control, and ensure safety.
- There are particular products of concern, including controlled substances, intravenous products, biologics, drugs that must be refrigerated or frozen, drugs that have specific post-marketing risk management programs, drugs that are highly susceptible to counterfeiting on the global market, and those that have less expensive alternatives (i.e., generics) in the U.S., that pose special concerns in the importation context.
- Imported drugs are not always therapeutically equivalent to FDA-approved drugs available in the U.S.
- Product testing at the border alone does not necessarily ensure that imported drugs were manufactured, handled, or stored in such a way as to maintain their quality, safety, and efficacy.
- Drugs from countries with less developed regulatory systems may pose greater risks.
- Purchasing prescription drugs over the internet without a prescription has been found to be relatively easy to accomplish. In those cases, the lack of an adequate health professional/patient relationship is of particular concern.

## I. WHAT WE SOUGHT COMMENT ON

As part of its study, Congress asked HHS to assess the scope, volume, and safety of unapproved drugs, including controlled substances, entering the U.S. via mail shipment. Congress requested that the assessment also include the percentage of drugs commercially available in other countries that conform in all respects to FDA requirements, and the limitations of visual inspection, sampling, and other testing methods to determine the quality of imported drug products.

### To further explore this issue, we asked for comment on the following:

- Information regarding the scope, volume, and safety of imported drugs (brand and generic) and biologics and any distinctions.
- Are there product characteristics that might be associated with lower risk when imported without going through the usual FDA approval and regulatory process?
- Information on ways in which products with different risk levels could be reliably distinguished or otherwise differentiated at the border or elsewhere.
- Information on whether or not any imported products can meet U.S. approval standards or the equivalent.
- What is the scope and volume of drugs commercially available in other countries that are FDA-approved?
- Discuss any approaches that can be used to determine whether they are equivalent to U.S. approved drugs.
- How would FDA and other Federal agencies identify, track, and limit or prohibit importation of products that are not eligible for importation?
- What proportion of different types of imported drugs meet typical standards of U.S. pharmacy practice (e.g., no faxed prescriptions from individuals, proper oversight by a practicing pharmacist, proper repackaging and labeling)?
- If the same level of safety that consumers expect from drugs purchased at U.S. licensed pharmacies cannot be assured, would a different level of risk be acceptable to consumers and how could that risk be conveyed?
- Should certain products be excluded from importation because of risk concerns?
- Can risk-based criteria for limitations be established?

## II. WHAT THE COMMENTS SAID

Many comments stated that drug and biological products are increasingly available from global sources. Most of these comments did not provide data to quantify the scope and volume of these imports. Rather, the comments that discussed volume and scope referred to the blitz operations in which FDA and CBP conducted short-term intensive evaluation of drug products that were entering the U.S. through specific international mail facilities. The comments also described the volume of drugs entering the U.S. from Mexico by citing information that found that a high percentage of people crossing the border carried prescription drugs into the U.S.

Several comments suggested that if importation of foreign drugs were legalized, certain products should be included or excluded from the importation scheme. For example, a few suggested that best-selling drugs be permitted or drugs that are used for specific chronic conditions, such as when the patient has been stabilized on the drug for a while. Others stated that a list would be useful, but only for commercial importation, since it would be more manageable to follow a list. The same comments stated that it would be impossible to limit personal importation to a list of specific drugs because patients and websites may not adhere to the list. Moreover, it would be difficult to distinguish the listed and non-listed drugs as they enter the U.S. at the international mail facilities or other entry points because of the sheer number of packages that would arrive daily. Several comments noted that injectables, biological products, controlled substances, drugs of narrow therapeutic range, drugs requiring refrigeration, and non-FDA approved drugs should be excluded from importation under any plan.

Of those comments that suggested that importation be limited to certain countries, several said that the program should start with importation from Canada and then expand to other countries, including those

in Europe. Some comments advocated for drugs to be permitted from any country, while others said that only drugs from countries that have a regulatory system equivalent to the U.S. should be permitted.

Comments contained different opinions about whether drugs sold in other countries are the same as or equivalent to drugs sold in the U.S. Many comments said that the drugs sold elsewhere were the same, but the comments did not provide any supporting documentation. Other comments said that visual inspection of the different dosage forms currently being imported clearly demonstrates that many of these products cannot possibly be the same as products sold in the U.S.

Most comments agreed that it is essential that any drug that is imported into the U.S. adhere to the "gold standard" of safety and efficacy that is expected from FDA-approved drugs. Concern was raised that if a two-tier system were established, lower quality drugs would disproportionately appear in markets serving economically disadvantaged communities. We heard during a listening session that a two-tier system is unacceptable and that imported drugs must be of the same high quality as FDA-approved products. A few comments noted that several countries, such as Canada, do require similar standards for safety and efficacy, but acknowledged that the drugs that U.S. consumers are currently importing are not necessarily Canadian-approved drugs.

Of those comments that discussed testing of imported drug products, many stated that it would be costly and difficult to develop a system of testing products at the border to ensure authenticity. Some comments said that only the manufacturer has the resources and analytical information to ensure that the product is authentic; however, other comments said that tools are available for rapid authentication for presence of active ingredient. Comments also stated that in order to adequately screen for authenticity, every lot in each shipment would have to be tested. Some comments noted that not only would the product have to be tested for the presence of active and inactive ingredients, but also for adulteration, impurities, strength, and whether proper storage conditions were maintained. Several comments maintained that quality cannot be tested into a product after it is manufactured and that the FDA gold standard is based on building quality into a product by ensuring that good manufacturing practices are used in the manufacturing, processing, and handling of the product. Comments also expressed concern that it would be costly, time consuming, and perhaps unrealistic to test the millions of packages that enter the U.S. yearly. On the other hand, many comments stated that it should not be left to the individual consumer to determine if a product is mislabeled, adulterated, contaminated, counterfeit, or substandard.

We have only anecdotal information on the proportion of personally imported drugs that are currently dispensed from foreign pharmacies that meet typical standards of U.S. pharmacy practice. Many comments stated that pharmacies in Canada are regulated and meet the same standards as pharmacies in the U.S. Other comments noted that many internet pharmacies accept orders for drugs without a prescription and are hard to locate to determine whether they adhere to pharmacy practice standards or from where they obtain their drug products. They noted several instances where the product received from an internet pharmacy was visibly different from the U.S.-approved drug and came with no labeling information or only with information that was written in a foreign language.

There were no comments that suggested a different level of risk that would be acceptable for imported drugs. Rather, the majority of comments stated that safety is paramount and that safety should not be sacrificed for affordability. Concern was expressed that many consumers are deciding not to buy their medicines, but no specific data was presented on how widespread this problem is. Other comments stated that that the U.S. approval and marketing system is not set up as a risk-based system. Rather, they said it is a system where safety must be affirmatively established before a product may be sold in the U.S. No comments discussed how to establish risk-based criteria for limitations on imported drugs.

## III. DISCUSSION

### A. The Scope and Volume of Currently Imported Unapproved Drugs

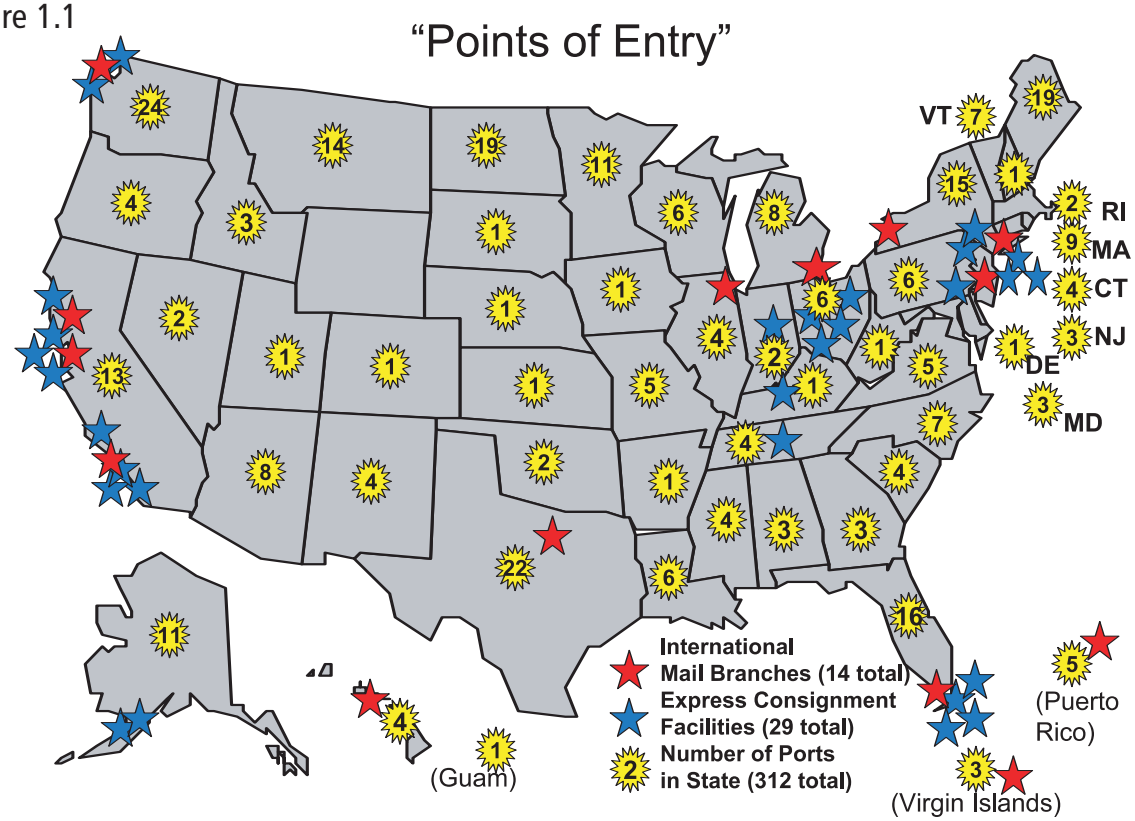
#### 1. Estimates of Volume of Imported Drugs

It is difficult to quantify the exact number of unapproved drugs entering the U.S. We note that the term "unapproved drugs" refers to those drugs that have not been approved by FDA, pursuant to the FD&C Act.[1] Although some unapproved drugs may be harmful or pose risks, others may not. However, if the drug has not been approved by FDA and maintained in the U.S. closed distribution system, the safety and efficacy of the unapproved product cannot be assured. Due to the sheer volume of packages arriving daily through the international mail, into ports, via couriers, or with persons traveling across a border, CBP and FDA told us that currently they have no mechanism for keeping an accurate account. According to CBP, there are 355 "points of entry" for access into the U.S. (See Figure 1.1) This includes 14 international mail branches, 29 express consignment facilities, and 312 ports.[2] At this time, there are too many packages to monitor and control the influx of drugs sent into the U.S., much less perform comprehensive examinations of all packages.

It is apparent that the volume of prescription drugs for personal use imported through the mail has increased significantly in recent years. FDA estimated that in 2001 approximately two million parcels containing FDA-regulated products for personal use entered the U.S. through international mail facilities.[3] This estimate is based on an extrapolation of data obtained during a pilot project conducted at the international mail facility in Carson, California. It is estimated that this number has increased significantly and that approximately ten million packages containing prescription drugs enter the U.S. annually from all over the world.

According to IMS Health data, in 2003 the U.S./Canada cross-border sales volume for prescription drugs was $695 million U.S. dollars. Of this vol-

Figure 1.1



ume, about $408 million was from internet pharmacy sales and $287 million was from foot traffic sales.[4] IMS Health data also reveal that there were 12 million prescriptions sold from Canadian pharmacies to the U.S. in 2003.[5] On average, we estimate that there are about 2.5 prescriptions per package, which would equate to 4.8 million packages of prescription drugs entering the U.S. in 2003 from Canada alone.

It is commonly known that a large number of Americans travel daily over the border to Mexico to purchase prescription medicines. For example, we heard during a listening session that on a typical Saturday, approximately 25,000 to 30,000 individuals walk across the bridge at the Nuevo Laredo, Mexico/Laredo, Texas border crossing. We heard an estimate that half of these individuals purchase prescription medicines in Mexico and bring them back into the U.S. Recently, there have been reports of counterfeit drugs dispensed to Americans at Mexican border-pharmacies.[6]

According to CBP, seizures of pharmaceuticals made by CBP at international mail and express consignment facilities were 43,659 during fiscal year 2004 and 31,725 during fiscal year 2003. The number of pharmaceutical seizures made solely at international mail facilities was 37,040 during FY 2004 and 24,891 during FY 2003. These figures cannot be distinguished by controlled versus non-controlled substances. It should be noted that these numbers represent the number of parcels and that each parcel may contain any number of individual containers of controlled substances.

Figure 1.2, Detained controlled substances at JFK international mail facility

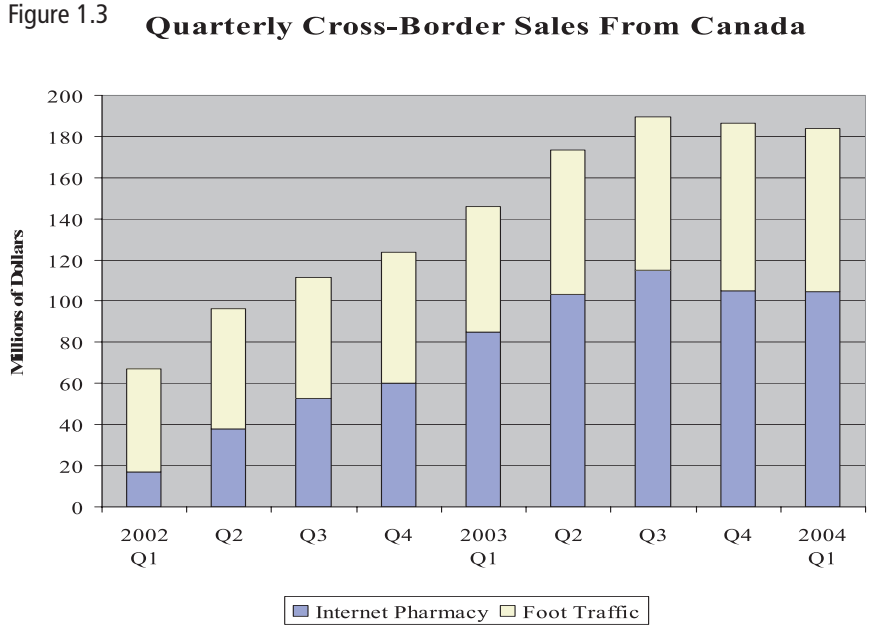
In June 2004, several Task Force members toured the JFK international mail facility to view first-hand the volume of packages arriving daily at a major port of entry. Because of the high volume of packages that travel through this facility daily, CBP and FDA have employed a risk-based approach towards their operations at international mail facilities and courier hubs (through which the majority of illegal drugs arrive from foreign sources for personal use) so that they can more effectively target, identify, and interdict those potentially unsafe and dangerous imported products that are offered for entry into the U.S. on a daily basis. CBP, however, seizes all controlled substances that it identifies and refers all non-controlled drugs to FDA for review. Using this risk-based approach, FDA considers the following to prioritize their work, so that they are able to provide the most protection given limited resources: whether the product has been counterfeited in the past; whether it is an injectable drug product; unlabeled drug product; compliance history and historical data of the exporter and/or importer and/or recipient; non-English labeling; and whether there is an import alert/bulletin.

Even with this risk-based approach, however, packages of unapproved drugs still enter the country. It is impossible for Federal officials to open and examine all packages and detain all those that violate Federal law. At the JFK facility, we observed unapproved drugs from every corner of the world, including traditional medicines, counterfeit drugs, unapproved generic versions of U.S.-approved innovator drugs, drugs requiring refrigeration that were sent with no provision to keep them cold, controlled substances, and drugs that were unknown because there were no identifying markings on the product or package.

### 2. What types of unapproved drugs are being imported into the U.S.?

There is little quantitative data on the types of drugs that are being purchased from foreign internet pharmacies. According to IMS data,[7] cross-border shipments are predominantly drugs for chronic conditions

Figure 1.3




Source: From approximate estimates based on an independent FDA Analysis of Information provided by IMS Health, IMS Management Consulting, Canadian Cross-Border PharmaceuticalSale, Q1/2002-Q1/2004

that are typically prescribed to older patients. Analysis of the IMS data shows that while there has been an upward trend from 2002-2003, sales are leveling off. This leveling off may indicate that (as IMS noted) import restrictions are having an effect, the Canadian system may be exporting all the drugs it can, U.S. consumers are beginning to go elsewhere for their prescription drugs, or some combination of these factors.

Additional insight into the types of drugs that are being imported can be gleaned from CBP and FDA activities. The agencies told us that they periodically conduct targeted examinations of international mail and courier shipments over three-day periods known as "import blitz examinations." The import blitz examinations of mail shipments of foreign drugs to U.S. consumers revealed that these shipments often contain dangerous, unapproved or illegal drugs that pose potentially serious safety problems. During the summer (July – August) and again in November of 2003, FDA and CBP conducted two series of "blitz" examinations at various international mail facilities and courier hubs. In all cases, CBP and FDA inspectors found that the overwhelming majority of the packages examined contained violative drugs.

During the import blitz examinations conducted by FDA and CBP during the summer of 2003 at the Miami, New York (JFK), San Francisco, and Carson (CA) international mail facilities, these agencies examined 1,153 imported products, the overwhelming majority of which were drugs. Inspection revealed that 1,019 (88%) of the 1,153 products were violative; and 861 of the 1,019 violative products (85%) were non-compliant because they appeared to be unapproved drugs. During the import blitz examinations conducted in November 2003 at the four international mail facilities in Buffalo, Dallas, Chicago and Seattle, and the two courier hubs in Cincinnati and Memphis, FDA and CBP examined 3,375 imported products, the overwhelming majority of which contained drugs. Of the 1,927 imported products examined during the blitz examinations at the mail facilities, 1,641 (85%) were deemed violative. The overwhelming majority of the violative products (69%) were non-compliant because they contained unapproved drugs.

The following examples are typical of unapproved drug products found during the blitzes and illustrate the potential scope of the products found and the risks they pose to their buyers:

- **Improperly Labeled Drugs:** Many of the drugs did not bear adequate labeling or instructions for proper, safe use.
- **Improperly packaged drugs:** Some drugs were shipped loose in sandwich bags, tissue paper or envelopes.
- **Controlled substances:** Over 25 different controlled substances were found. These have a significant abuse potential and can be dangerous when consumers take them inappropriately and without a doctor's supervision.
- **Drugs withdrawn from the U.S. market**

**for safety** reasons such as Buscapina, which appears to be the drug Dipyrone, removed from the market in 1977 due to reports of agranulocytosis — a sometimes fatal blood disease.

- **"Foreign versions" of FDA-approved drugs:** Foreign versions may vary in potency and purity from the U.S.-approved versions and may raise concerns regarding safety and efficacy.
- **Drugs requiring risk management and/or restricted distribution programs:** Drugs were shipped into the U.S. without any assurance that their use would be monitored by a doctor.
- **Drugs that require initial screening or periodic monitoring of patients:** Initial screening and periodic patient monitoring by a medical practitioner are recommended in FDA's approved labeling for some of the drugs found during the blitz operations.
- **Drugs requiring careful dosing:** For example, Synthroid (levothyroxine), Glucophage (metformin), Dilantin (phenytoin), digoxin, theophylline, and Coumadin (warfarin).
- **Drugs with clinically significant drug-drug interactions:** Zocor (simvastatin), imipramine, Viagra (sildenafil citrate) and tramadol have been associated with clinically significant interactions with other drugs the consumer may be taking.
- **Unlicensed biologic drugs, which should be administered by a healthcare provider.**
- **Investigational Products:** These products should only be shipped pursuant to FDA's Investigational New Drug (IND) regulations, which require that patients who use investigational products are fully informed of the drugs' investigational status and are not exposed to unreasonable risks. When these products are shipped through the mail, and used outside of the protections established to safeguard patients involved in clinical trials of experimental drugs, there is a significant risk that a patient may be harmed.
- **Animal drugs not approved for human use** such as Clenbuterol, a drug approved for the treatment of horses but also known as a substance of abuse in the "body building" community and banned by the International Olympic Committee.

### 3. What percentage of drugs from other countries are the same as the FDA-approved version?

Many FDA-approved drugs are made in foreign plants. To be FDA-approved, the drugs must be produced in FDA-inspected facilities, meet FDA safety and effectiveness standards, and be made in compliance with good manufacturing practices (quality controls) prescribed by FDA. Particular manufacturing lines for FDA-approved drugs in foreign plants must meet these FDA manufacturing standards. Although such plants may house additional lines of similar drug products, FDA has no de facto assurance that they meet FDA standards. Medicines produced on these other lines cannot be presumed to be equivalent to FDA-approved drugs. Although a foreign version of a drug may look identical to an FDA-approved version, there are many important differences that can exist between these different versions that can affect the way the drug works in the body, as described below.

For a medication to be approved for marketing in the U.S., FDA reviews scientific data to determine whether that specific formulation is safe and effective. Changes in the active ingredient or in an inactive ingredient can impact how well the drug works. For example, changes to an inactive ingredient can alter the amount of and speed with which the active ingredient is absorbed by the body. Ingredients purchased from suppliers that do not meet FDA's standards may contain impurities that can put patients at risk for adverse effects on their health. FDA also inspects the foreign plant to determine whether it meets the agency's exacting standards for quality production and control, so called good manufacturing practices, such as using state-of-the-art sterilization equipment. Failure to meet these standards can lead to drug products that are subpotent or superpotent, contain impurities, including infectious agents, or degrade quickly.

Different countries have different regulatory systems. Therefore, foreign versions of FDA-approved drugs may not be the same as their U.S. counterparts due to differences in formulation, source of ingredients or manufacturing processes. These differences may occur even when the FDA-approved

medicine and a foreign version are made in the same facility. In these cases, each drug is made on a different line and subject to different standards and controls to meet the requirements of the respective country.

When the foreign version is made in a separate facility there may be a greater likelihood of using different quality controls. For example, FDA recently alerted U.S. residents about a recall of GlaxoSmithKline "Diskus" medicines sold in Canada to treat asthma and chronic obstructive pulmonary disease. The products were recalled in Canada because their drug delivery system may not function properly. The FDA-approved versions were made in a different plant and did not experience the same problems as those medicines produced for the Canadian market.

Another significant difference is that the labeling of medicines produced overseas for foreign markets may not be in English and, therefore, important information regarding dosage, side effects, and safe use may not be available to the U.S. consumer.

Even when a drug produced for a foreign market contains the same or similar ingredients and uses the same or similar formulation as the FDA-approved medication, the foreign drug may not have been packaged and stored under appropriate conditions to prevent contamination, degradation, or substitution with another product once it leaves the manufacturer's facility. In the U.S., Federal or state government authorities tightly regulate all participants in the drug distribution system, such as wholesalers and pharmacies. However, FDA, its sister agencies, and the states lack the authority to oversee foreign distributors and pharmacies, and, therefore, cannot ensure that drugs from other countries are in fact the same – the same formulation composed of the same ingredients from the same sources, made in the same facility under the same manufacturing standards, with the same labeling, and packaged, stored, and handled by entities that meet Federal and state standards – as the medicines American consumers receive from the U.S. drug supply chain.

We could not determine the percentage of drugs commercially available in other countries that conform in all respects to FDA requirements. Companies do not share this information with FDA or publicize it by other means. Foreign countries do not share this information, and there are no applicable Memoranda of Understanding (MOU) that would permit the U.S. and other countries to do so. Furthermore, although the International Conference on Harmonization (ICH) has made significant strides in harmonizing processes and requirements for approving and reviewing prescription drugs, there are still significant differences that prevent mutual recognition of drug approvals, making it difficult to know whether the foreign-approved version is identical to the FDA-approved version.

### 4. Where are imported unapproved drugs coming from?

Unapproved drug products are pouring into the U.S. from all over the world. Several initiatives have been undertaken to quantify and characterize the source of these drugs.

#### a. Via Mail

FDA told us that during the blitz examinations they attempted to document the country of export for those parcels containing drug products that entered through the mail facilities. They determined that Canadian parcels appeared most frequently, but drugs came from a variety of other countries, including Japan, India, the Netherlands, Taiwan, Thailand, Belize, Malaysia, Philippines, Nicaragua, Romania, Cambodia, Uganda, and the U.K.

#### b. Travel Across the Border

During 2000-2001, FDA conducted surveys at U.S. borders to gather data on drug products carried by individuals entering the U.S. In 2000, FDA's Southwest Import District (SWID), with the assistance of other agencies, conducted a survey of prescription drugs being brought by pedestrians into the U.S. at eight ports-of-entry along the 2,000-mile border with Mexico. The survey looked at activity during four hours on a Saturday at border ports in California, Arizona, and Texas. The data collected from over 600

interviews indicated that the most common type of drug that these persons imported into the U.S. were antibiotics or pain relievers. Sixty-three percent of the persons interviewed had prescriptions; of these prescriptions, 59 percent were U.S. prescriptions while 41 percent were Mexican. While many of these products were foreign versions of FDA-approved drugs, some drugs bore no resemblance whatsoever to any FDA-approved product in the U.S.

In 2001, FDA, CBP, and other agencies conducted a survey of prescription drugs being brought into the U.S. at seven ports-of-entry along the U.S./Mexican border. During the four-hour survey, a total of 586 persons brought in a total of 1,120 drug products. Approximately 56 percent had a prescription for the medicines (61 percent of these were U.S. prescriptions, 39 percent were Mexican). As in the earlier survey, many of these products had currently marketed FDA versions in the U.S., while some were not approved for sale in this country.

#### c. Internet

According to FDA, based on a review conducted in early 2000 by their Office of Criminal Investigations (OCI) and a subsequent study by the General Accounting Office, there appeared to be approximately 300 to 400 Internet sites selling prescription drugs to consumers, approximately half of which are located in the U.S. and half located outside the U.S.[8] More recent data is not available; however, it is believed that this number has increased significantly in the four years since this survey was completed. It is important to note that, despite this trend, we believe that there are many licensed internet pharmacies that provide a legitimate means for consumers to access safe and effective medicines.

In addition to the internet pharmacies selling prescription drugs directly to consumers, several state and local governments have set up links from their websites to websites that purport to dispense drugs from Canada and other countries. We were told about several government-sponsored websites that facilitate the sale of unapproved drugs to U.S. consumers.

#### d. Organized Trips to Canada

Since 2000, organized bus and train trips to Canada have apparently increased steadily, the most common scenario being a group of senior citizens organized to travel by bus to a Canadian city with one or more pharmacies offering drugs at the government-established Canadian price. Some of these trips have been organized by public officials, such as governors or members of Congress, with the intention of highlighting the price disparity between the U.S. and Canada. However, to date, no studies have been conducted to ascertain the volume of drugs imported through those trips or the precise types of drugs being purchased (although it can be presumed that the predominance of drugs are those for chronic conditions in the elderly, such as hypertension, high cholesterol, arthritis, and diabetes).

#### e. Storefront Pharmacies

Beginning in early 2004, a new form of access for foreign drugs emerged with the advent of so-called "storefront pharmacies." These walk-in businesses appeared suddenly around the country, offering intermediary services between consumers and foreign (mostly Canadian) drugstores. They would receive the patient's prescription and fax it to a Canadian pharmacy, which would mail a Canadian drug directly to the patient; the storefront pharmacy would charge the patient's credit card and split the charge with the Canadian pharmacy. Many states took successful legal action against these businesses under their laws prohibiting the sale of drugs without a pharmacy license. A significant case was decided in Federal court against a large storefront pharmacy, Rx Depot, that was operating in numerous states. The judge ruled that drugs sold in this manner were both illegal and potentially unsafe. Despite these illegalities, such businesses continue to appear.

### B. The Safety of Unapproved Imported Drugs

An overwhelming number of comments told us that safety is paramount when it comes to imported drugs. For over 65 years, a comprehensive system of laws and regulations has protected the American

**Canadian Drugs**

We recognize that American consumers who travel to Canada and purchase prescription drugs from Canadian-regulated "brick and mortar" pharmacies that service Canadian citizens may very well get drugs that are fully regulated by Canadian drug safety authorities. However, practical experience and evidence shows that Americans are not always getting the same drugs as Canadian citizens when purchasing drugs from Canadian internet sites or sites purporting to be Canadian. We heard during the listening sessions that the Canadian drug supply cannot supply the needs of all Americans. The potential for shortages in the Canadian drug supply has prompted Canadian suppliers to search overseas for drugs to fill orders for American consumers.[9] As described in Chapter 6 of this report, most countries, including Canada, place lower priority on regulating drugs that are transshipped or exported. Even more troubling is the evidence we have seen that Canadian pharmacy internet sites are often not located in Canada or even regulated by the Canadian government.[10]

public from unapproved, adulterated, counterfeit, misbranded, and otherwise substandard drug products entering the U.S. drug distribution system. There are potential public health consequences associated with using imported unapproved drugs that bypass or do not meet the U.S. legal standards for safety and efficacy.

We were told that importation of unapproved drugs creates a "buyer beware" situation, where the consumer is left to accept the health risks and consequences of their purchase. The comprehensive regulatory system in place in the U.S. is intended to protect consumers who use drugs purchased within the legal, relatively closed distribution system in this country. Although some comments argued that drug importation is safe, a vast number of comments stated that there are several real potential safety concerns with imported drugs: quality assurance concerns, counterfeit potential, presence of untested substances, risks of unsupervised use, labeling and language issues, and a general lack of information.

In addition, there have been limited reports of harm from imported drugs, despite the significant number of current illegal imports, in part because there is no system in place to determine whether an imported drug caused an adverse event. FDA currently learns about adverse drug events through a combination of mandatory and voluntary reports submitted by manufacturers, health professionals, and consumers about FDA-approved medical products. FDA's adverse event reporting system is called MedWatch. Currently, the MedWatch system is not set up to distinguish whether an adverse event related to a drug product occurred from an FDA-approved product that was purchased within the closed U.S. distribution system, from an imported unapproved product purchased over the internet, or from a product personally brought over from another country. FDA told us that it constantly evaluates the MedWatch database to determine if there are any unusual trends that should be investigated further. They note, however, that it is difficult to determine if an increased incident of adverse events for a particular drug product is related to the approved product or an unapproved imported product because the health professional or consumer making the report typically does not report this information.

Another reason that there may be limited reports of adverse events associated with imported drugs is because the adverse event may be a "treatment failure." Treatment failures can occur with substandard imported drugs, however, it is difficult to tell if the failure is due to the imported drug or the patient's underlying disease itself. These reports are often not made to the MedWatch system because the patient's doctor often assumes that the drug is not working (not knowing that it may have come from a foreign source) and, instead, chooses a different treatment option.

### 1. Interchangeability Can Affect Safety

Although foreign versions of FDA-approved drugs may contain the same active ingredient, they are not

necessarily interchangeable. To be interchangeable under Federal law, drugs must be pharmaceutically equivalent, bioequivalent, and appropriately stored and handled. Pharmaceutically equivalent drugs have the same active ingredient, strength, dosage form, and route of administration. Bioequivalent drugs must have the same route and extent of absorption into the body, whereby the two drugs deliver the same amount of active ingredient into the bloodstream in the same amount of time. Foreign versions of FDA-approved drugs are not necessarily pharmaceutically equivalent or bioequivalent.

Unapproved drugs cannot be treated as generic versions of FDA-approved drugs, even if the products contain the same active ingredient and dosage. Unless two drugs have been shown to be bioequivalent, it is potentially dangerous to treat them as identical.

Drugs that are pharmaceutically equivalent are not necessarily bioequivalent because even small changes in the manufacturing process can affect a drug's absorption into the body. For example, a foreign version may have different amounts of active ingredients or inactive ingredients, such as fillers, binders, lubricants, disintegrants, glidants, starch, colors, or flavorings. Even these slight changes in formulation can affect whether the drugs are interchangeable, in addition to influencing the efficacy and side effects of the drug. If a foreign version of a drug is made on a different production line than the U.S.-approved version, the possible differences in equipment operation, settings, mixer efficiency, humidity, and drying materials could affect the quality or effectiveness of the products, resulting in non-interchangeable products. This could be the case even if the facility is FDA-registered and inspected. Additionally, for drugs that have a time-release mechanism, different mechanisms can affect interchangeability, such as delayed release, sustained release, or extended release.

For persons taking narrow-therapeutic range drugs, such as phenytoin and warfarin, where the patient's blood level of the drug must be carefully titrated within a certain range, even slight changes in the dose and/or the amount of drug in the blood could potentially have dangerous effects. Foreign versions of U.S. approved drugs that are not pharmaceutically equivalent or bioequivalent may result in different blood levels. Consequently, if a patient has been maintained on a particular formulation of the drug, switching formulations can cause their clinical condition to recur (due to a blood concentration of the drug below the narrow therapeutic range) or lead to toxicity (due to blood concentrations of the drug above the narrow therapeutic range.)

### 2. Risks of buying drugs from some internet pharmacies

There are an increasing number of foreign internet pharmacies capitalizing on the vulnerability of patients in search of less expensive prescription drugs. It is important to note that the internet is a valuable resource for consumers to find information and is a convenient way to purchase prescription drugs from legitimate, state-licensed pharmacies. There are efforts to help patients identify if an online pharmacy site is appropriately licensed, such as the Verified Internet Pharmacy Practice Site (VIPPS) certification program, run by the National Association of Boards of Pharmacy. Online pharmacies with the VIPPS logo also have successfully completed a rigorous inspection and review. The internet is also useful for telemedicine, which increases communications between and among patients and health professionals. However, the internet has created a marketplace for the sale of unapproved drugs, prescription drugs dispensed without a valid prescription, drugs from unknown origins, counterfeit drugs, and otherwise substandard drugs. Although there are a number of legitimate and reputable internet pharmacies in the U.S. that serve American consumers, there are a considerable number of internet pharmacies that are not legitimate and that unlawfully sell prescription drugs to American consumers.

Unfortunately, it is very easy to set up a webpage that misrepresents the pharmacy's location, the source and country of origin of its drugs, the regulatory status of the drugs (e.g., whether or not FDA-approved), and its compliance with applicable laws and regula-

tions. Moreover, many of these internet pharmacies require the patient to sign a disclaimer waiving their right to sue if harmed by the products they bought.

Legalizing personal importation in the U.S. could lead to the proliferation of these types of internet pharmacies. Because of the ease with which such websites can be established and obscure their physical location, it would be nearly impossible to monitor, find, or inspect all of these pharmacies. Furthermore, the volume of packages entering the U.S. today has been increasing at a steady rate. Under a personal importation program, it would be very difficult to distinguish which of these millions of packages are from 'permitted' internet pharmacies and which are from rogue websites, increasing the potential safety risks associated with imported drugs.

### a. Unapproved Versions of FDA-Approved Drugs

Some of these rogue internet pharmacies offer for sale what they claim to be FDA-approved prescription drugs or in some cases, generic versions, which in fact are unapproved, illegal, and unsafe copies of the drugs. For example, FDA identified a website from a spam email that was sent to consumers for www.canadiangenerics.com.[11] Every page of this site suggested that the internet pharmacy was located in, and operated out of, Canada. FDA made a purchase and determined, however, that neither the dispensers of the drugs nor the drugs themselves were Canadian. The registrants, technical contacts, and billing contacts for the website are listed with addresses in China. The reordering website for the purchase, as well as its registrant, technical contact, and billing contact have addresses in Belize. The drugs were shipped from Texas, with a customer service and return address in Florida.

The drugs that FDA purchased were described on the website as generic Viagra, generic Lipitor, and generic Ambien, all prescription drugs that have no generic version approved in the U.S. or Canada. No prescription was needed. Even more troubling is that when an FDA laboratory analyzed the drugs, they failed most of the purity, potency, and dissolution tests. All contained some amount of active ingredient, but two were found to be subpotent and one was found to be superpotent. (generic "Ambien" had 140% of declared potency; generic "Lipitor" had 81% of declared potency; generic "Viagra" had 65% of declared potency) Figure 1.4 summarizes the test results:

Figure 1.4 "Canadian Pseudo-Generics"

| Drug | Ambien[1] | Lipitor[2] | Viagra[3] |
|---|---|---|---|
| Drug Present | PASS | PASS | PASS |
| Potency | FAIL | FAIL | FAIL |
| Dissolution | PASS | FAIL | FAIL |
| Purity Test | PASS | FAIL | FAIL |

Source: FDA News July 13, 2004 FDA Test Results of Prescription Drugs from Bogus Canadian Website Show All Products Are Fake and Substandard (http://www.fda.gov/bbs/topics/news/2004//NEW01087.html)

### b. Misleading or Unknown Location of Pharmacy

As described in the example above, some internet pharmacies purport to be located in one country, such as Canada, but in fact the drugs are mailed from a location in another country. In addition, we recently learned that www.CanadaRx.net, an internet pharmacy claiming to be located in Canada, set up an operation in the Bahamas to serve consumers who thought that they were buying drugs from Canada. According to FDA, the orders were placed on the internet site claiming to be in Canada and filled in the Bahamas. From there, the drugs were shipped to the consumer in the U.S. The consumer received an invoice claiming that the pharmacy is located in Hamilton, Ontario and there was no acknowledge-

ment that the order was filled and sent from the Bahamas. In fact, it is reported that the drugs originated from the world market, from countries, including but not limited to, New Zealand, United Kingdom, and Singapore. It would be logical to question the integrity and safety of a product when the business that sold the product makes fraudulent claims and/or fails to disclose important information about the source of its drugs.

#### c. Pharmacy Noncompliance with Practice Standards

U.S. state-licensed pharmacies are required to abide by state laws and regulations that ensure the safe and effective use of FDA-approved drugs. Foreign internet pharmacies may or may not comply with the laws and regulations applicable in their country. An inspection by the state of Minnesota of several Canadian pharmacies showed the substandard practices followed at some pharmacies, which can lead to significant safety problems.[12] These practices included:

- Several pharmacies used unsupervised technicians, not trained pharmacists, to enter medication orders and to clarify prescription questions;
- One pharmacy had its pharmacists review 100 new prescriptions or 300 refill prescriptions per hour, a volume so high that it would have been impossible to assure safety;
- One pharmacy failed to label its products; instead, it shipped the labels unattached in the same shipping container, even to patients who received multiple medications in one shipment;
- Drugs requiring refrigeration were being shipped un-refrigerated with no evidence that the products would remain stable;
- At least one of the Canadian pharmacies visited by Minnesota health officials dispensed many drugs that apparently were not even of Canadian origin; and
- Many of the drugs were obtained from prescriptions that had been written and rewritten across multiple Canadian provinces.

These types of systematic problems would generally constitute regulatory violations under the comprehensive system of Federal and state regulation of drug safety in the U.S.

#### d. Prescription Drugs Obtained Without a Prescription

It is easy to purchase prescription drugs over the internet without a prescription. During our public meeting, we heard from a group that surveyed 250 websites and found that 167 did not require a prior prescription.[13] A recent General Accounting Office (GAO) report entitled, "Internet Pharmacies: Some Pose Safety Risks for Consumers,"[14] describes significant problems with internet pharmacies. Of 68 drug samples purchased from 68 different websites, GAO obtained 45 of 68 prescription drug samples either by a prescription issued after completing only an online medical questionnaire or without any prescription at all. GAO easily purchased without a prescription, drugs with special safety restrictions, such as Accutane (which can cause birth defects if taken when pregnant) and Clozaril (which requires close monitoring of blood levels to avoid serious side effects) as well as the highly addictive and abused narcotic, OxyContin. The lack of a health professional/patient relationship is of particular concern if a patient is using a drug for the first time or is taking other medications that the patient does not mention when filling out the online questionnaire. In essence, without a physician-patient relationship, the patient may be self-diagnosing a problem, which can magnify the safety risks associated with the use of prescription drugs.

### 4. Particular Products of Concern

Certain drugs can pose significant risks to patients if they require careful administration and monitoring, require special handling or storage, pose sterility concerns, are addictive or have a high abuse potential, or are highly susceptible to counterfeiting on the global market. The comments and the MMA acknowledge that drugs that have potential elevated safety concerns should be excluded from any legalized importation program. Particular products of concern include:

- Injectable drugs;
- Biological products;
- Drugs inhaled during surgery;
- Drugs that have specific post-marketing risk-

monitoring programs;
- Drugs that must be refrigerated or kept frozen;
- Controlled substances; and
- Drugs that are highly susceptible to counterfeiting on the global market.

### 5. Countries of Concern

Although there are countries that do meet high regulatory standards, there are other countries that have regulatory systems that are emerging or that fall short of the U.S. system. The available evidence reflects that importation from these countries of concern can become an avenue for drugs that may be adulterated, misbranded, counterfeit, or otherwise substandard, to enter the U.S. drug distribution system.

As the number of countries from which drugs can be imported increases, the potential for risk increases and safety concerns can arise. As the number of countries involved in the shipping and handling of drugs increases (creating a longer chain of custody) there is greater opportunity for substitution of problematic drugs. These risks may be alleviated with a shorter chain of custody and oversight by competent regulatory authorities, e.g., Canada.

For example, one comment stated that under Japanese law, it is legal to import or domestically purchase expired medical products, re-package them as new, and export them to other countries. Under U.S. law, these types of products would be illegal. The comment also noted that countries that do have oversight over transshipped products may not actively enforce their laws on those products.

### 6. Safety Cannot Be Tested Into a Product

A quality manufacturing process builds the foundation for the safety and efficacy of a drug product. A fundamental principle of drug regulation is that quality cannot be tested into a product. Rather, quality must be built into the product through the manufacturing process. Verification of product integrity and quality cannot be left to the consumer. From the evidence presented to us, visual inspection alone is not sufficiently reliable and consumers cannot tell if a drug contains the appropriate active or inactive ingredients, is adulterated, misbranded, contains impurities or was stored properly.

Some comments suggested that a testing requirement be instituted at the border or port of entry to validate or authenticate that an imported product is genuine. Although simple chemical analysis can verify if the active ingredient is present, such testing would be inadequate to identify the purity and potency of the product or to determine whether it was made according to cGMPs, is expired, has been stored under adverse or inappropriate conditions, or is counterfeit. Furthermore, we are not aware of any single technology or machine that could do these types of tests for all products as they enter the country. Even if such a technology or machine existed, it would be prohibitively expensive and resource-intensive, and it still would be logistically impossible to test all imported products. Such a process would delay access to, and availability of, the drugs while the test results were pending, and would substantially increase the cost of the drugs beyond any available discount that might have been realized.

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1 21 U.S.C. § 355.
2 A "port" is a location where an individual can transit into the U.S., such as an airport, seaport, or land border.
3 FDA, Statement of William K. Hubbard, Associate Commissioner for Policy and Planning, before the U.S. Senate Committee on Commerce, Science, and Transportation, Subcommittee on Consumer Affairs, Foreign Commerce, and Tourism, September 5, 2001.
4 IMS Health, IMS Management Consulting, Canadian Cross-Border Pharmaceutical Sales, Q1/2002-Q1/2004.
5 IMS Health, IMS National Sales Perspectives ™: Retail, Q1/2003-Q4/2003; IMS Health, NPA Plus ™: Monthly Rx Audit, Q1/2003-Q4/2003; IMS Health, IMS Management Consulting Canadian Cross-Border Pharmaceutical Sales, Q1/2003-Q4/2003.
6 FDA, "FDA Talk Paper: FDA warns consumers about counterfeit drugs purchased in Mexico," July 30, 2004. Accessed at http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01303.html on 11/4/04.
7 IMS Health, IMS Management Consulting Canadian Cross-Border Pharmaceutical Sales Q1/2002-Q1/2004
8 FDA, Statement of John M. Taylor, Associate

Commissioner for Regulatory Affairs before the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, March 10, 2003.

9 Los Angeles Times, "Canadian sites look overseas for drug supply: To combat shortages, online pharmacies used by U.S. consumers are seeking new sources. Safety could be an issue," August 30, 2004.

10 *See* FDA, U.S./Canadian Price Comparisons. Accessed at http://www.fda.gov/oc/opacom/hottopics/importdrugs/canadarx.html on 11/9/04.

11 FDA, "FDA News: FDA Test Results of Prescription Drugs from Bogus Canadian Website Show All Products Are Fake and Substandard," July 13, 2004. Accessed at http://www.fda.gov/bbs/topics/news/2004/NEW01087.html on 11/9/04.

12 FDA, Letter from William K. Hubbard, Associate Commissioner for Policy and Planning to the Honorable Tim Pawlenty, Governor of Minnesota, February 23, 2004. Accessed at http://www.fda.gov/oc/opacom/hottopics/importdrugs/pawlenty022304.html on 11/9/04.

13 HHS Task Force on Drug Importation Public Meeting, Testimony of Peter Neupert, Drugstore.com, April 14, 2004.

14 GAO report June 2004, "INTERNET PHARMACIES Some Pose Safety Risks for Consumers" Report to the Chairman, Permanent Subcommittee on Investigations, Committee on Governmental Affairs, U.S. Senate.

# CHAPTER TWO

## Limits on Resources and Authorities

### Chapter Highlights:

The Federal law governing drug safety in the U.S. establishes the standards by which FDA determines whether a prescription drug is "safe and effective" for sale in the U.S. These standards govern the way in which prescription drugs are manufactured, packaged, labeled, held, and shipped. Many of the prescription drugs that are imported into the U.S. now by individual citizens, via mail and courier services, fail to comply with some or all of these Federal standards. To ensure that imported prescription drugs are as safe as those that are legally sold in the U.S., an importation program for U.S.-approved drugs would have to ensure that the imported drugs meet the current (or equivalent) Federal standards. This report determines that it would be extraordinarily difficult to ensure that drugs personally imported by individual consumers could meet the necessary standards for a certification of safety to be made. Meanwhile, a commercial importation program could be feasible but would require new legal authorities, substantial additional resources, and significant restrictions on the type of drugs that could be imported, which could increase the costs of imported drugs.

### Key Points:

- The FD&C Act establishes the standards by which FDA determines whether a prescription drug is "safe and effective" for sale in the U.S. These standards govern the way in which prescription drugs are manufactured, packaged, labeled, held, and shipped.
- In order to assure that imported prescription drugs are as safe as those that are legally sold in the U.S., an importation program would need to assure that the imported drugs meet the same level of safety as current Federal standards. If imported drugs fail to meet these or equivalent standards, the Task Force believes that the Secretary would have difficulty in assuring U.S. consumers that imported drugs pose no additional risk to their health and safety.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to identify the limitations, including limitations in resources and, if applicable, in current legal authorities, that may inhibit the Secretary's ability to certify the safety of imported drugs.

### To further explore this issue, we asked for comment on:

- Changes in law, regulations, and guidances needed to assure a level of safety comparable to that provided in U.S.
- Resources needed to assure a level of safety comparable to that provided in the U.S.
- Whether and to what extent does the government need specific authorities and controls to assure the safety of imported drugs?
- What impact would restricting importation to products manufactured in or shipped from certain countries have on adequately regulating these products?
- Whether any current authorities for promoting the safety and security of food imports provide useful information for developing a system for safety assurances for drug imports.

## II. WHAT THE COMMENTS SAID

Several comments stated that numerous provisions of the FD&C Act prohibit the Secretary from certifying the safety of imported drugs. They argued that opening up the current closed distribution system would harm the public health by allowing larger amounts of potentially unsafe drugs into the U.S.

Many comments stressed that imported drugs should adhere to the standard of safety and efficacy that currently exists in the U.S. Most comments offered broad suggestions on ways to change laws, regulations, and guidances to assure that the level of safety would remain comparable to that provided in the U.S.

*Accreditation of internet pharmacies* - It was noted that while many internet pharmacies provide legitimate services, some pose significant risks to consumers. For example, one comment described an incident where a consumer received expired insulin, which led to a serious adverse event. Some comments said that since many imported drugs are ordered via the internet, FDA should consider adequate regulation of internet pharmacy sites. Several comments suggested establishment of a list of legitimate websites. One comment suggested that the list be linked to FDA's website so that consumers would have a reputable source to consult when making healthcare decisions.

*FDA authority to conduct foreign inspections* – Many comments recommended that FDA have the authority to inspect foreign manufacturing facilities in order to ensure adherence to good manufacturing practices.

*Pedigree requirements* – Several comments discussed the need for a pedigree, to trace a drug product back to the manufacturer, to help guard against counterfeit or adulterated drugs. Of the comments that discussed the pedigree requirement, there was overwhelming support for its implementation. Some comments stated that FDA has sufficient authorities for requiring pedigrees under the PDMA, however, FDA continues to stay the implementation of these requirements.

*Electronic track and trace technology* - Many comments agreed that electronic track and trace technology, although expensive, holds great promise and would help maintain the integrity of the drug supply. One comment suggested that FDA encourage manufacturers to include this technology in their product packaging.

*FDA authority to oversee international recalls* – One comment suggested that FDA have the same level of authority for international recalls as it currently has for domestic recalls. In addition, a system for assessing post-marketing complaints and adverse events for foreign drugs would need to be established.

*Higher penalties for drug counterfeiters* – A few comments stated that the current penalty for a felony drug counterfeiting violation is inadequate and should be increased.

*Product testing* - Some comments suggested requiring product testing at the border to authenticate products. There was conflicting information about the accuracy and feasibility of product testing. Some comments said that testing would be very expensive, resulting in higher prices. Other comments said that testing is necessary, accurate, and could be product-specific.

*Special packaging and prior notice* - One comment suggested that the value of special packaging for imported drugs would be limited, but that requiring importers to serve prior notice of the drugs they are bringing in, with reasonable time frames for FDA to inspect these products, would be useful.

## III. DISCUSSION

### A. Safety Certification

As previously discussed, the FD&C Act strictly limits the types of drugs that may be imported into the U.S.[1,2] Congress enacted these provisions to create a relatively closed drug distribution system, which helps ensure the safety, effectiveness, and high quality of prescription drugs for U.S. consumers. MMA establishes Federal authority in 21 U.S.C. § 384 to create an importation program, however, this section does not become effective unless the Secretary of HHS first certifies that implementing the importation program would pose no additional risk to public health and safety and would result in a significant reduction in the cost of drugs to the American consumer.

Under the MMA, FDA would have to promulgate substantial regulations to ensure that the drugs being imported are U.S.-approved drugs and that they comply with all of the requirements of the FD&C Act and its implementing regulations concerning FDA approval and how the prescription drugs are manufactured, packaged, labeled, held, and shipped.

Limitations in current legal authorities may inhibit the Secretary's ability to certify the safety of a drug importation program. The authorities and prohibitions in Title 19 of the U.S. Code and state pharmacy laws discussed below are examples of such legal limitations that impact the Secretary's ability to certify that importation would pose no additional risk to public health and safety.[3] Any importation program would need to address these standards.

Second, if Congress were to authorize the importation of non-U.S.-approved drugs, there are additional legal authorities that would be necessary to ensure that an importation program would pose no additional risk to public health and safety.[4]

The chart at the end of this chapter identifies additional issues and regulatory actions to consider with respect to commercial importation.

#### 1. Title 21, Food and Drugs

The FD&C Act establishes the standards by which FDA determines whether a prescription drug is "safe and effective" for sale in the U.S. These standards govern the way in which prescription drugs are manufactured, packaged, labeled, held, and shipped. As discussed in Chapter 1 of this report, most of the prescription drugs that are imported into the U.S. now by individual citizens, via mail and courier service, fail to comply with some or all of these Federal standards. In order to assure that imported prescription drugs are as safe as those that are legally sold in the U.S., an importation program would need to assure that the imported drugs meet the current Federal standards. Taken together, these standards represent the baseline level of safety that the Secretary would need to consider in weighing his ability to certify that an importation program poses no additional risk to the public's health and safety. If imported drugs fail to meet these (or equivalent) standards, we believe the Secretary would have difficulty certifying to U.S. consumers that imported drugs pose no additional risk. The discussion below outlines current legal requirements and assesses whether and how imported drugs could comply with these safety standards.

#### 2. 21 U.S.C. 355, Drug Approvals

Section 355 states that a "new drug"[5] may not be introduced into interstate commerce (which includes importation into the U.S.) unless it has been pre-approved by FDA. There are two basic ways a manufacturer of a new drug may obtain FDA approval.

First, a manufacturer may submit a New Drug Application (NDA) to FDA to demonstrate that its drug is safe and effective for its intended uses.[6] Second, a manufacturer may seek approval in an Abbreviated New Drug Application (ANDA) of a drug product that would be therapeutically equivalent (pharmaceutically equivalent and bioequivalent) to the approved innovator drug and, thus, substitutable. A drug that is approved under an ANDA is commonly referred to as a "generic" drug.[7] In either case, FDA drug approvals are product-specific and manufacturer-specific and, therefore, do not authorize the sale of any other drug.

### a. Safety and Effectiveness

The MMA's importation scheme requires safeguards to ensure that drugs imported from Canada comply with section 355. Most drugs imported into the U.S. from Canada now are not approved under section 355. Thus, their sale into the U.S. would remain illegal, even if the importation program under the MMA were to become effective. In this respect, whether this was intended or not, section 355 strictly limits the universe of drugs that are eligible to be imported from Canada. In other words, under MMA, very few drugs would be eligible for importation, specifically, a small subset of drugs that have approved NDAs and ANDAs.

If Congress were to further amend section 384 to allow importation of Canadian "versions" of U.S.-approved drugs, the volume of drugs available to U.S. consumers from Canada would increase.[8] Such legislation would necessarily provide an exemption from section 355's requirements for imported drugs. However, for the Secretary to make a safety certification, sufficient alternative safeguards would have to be imposed to ensure that imported drugs meet the same level of safety as drugs approved under section 355. Such alternative safeguards would not only have to be developed and implemented in the importation context, they would also have to be determined to be equivalent to the existing standards under section 355. As a result, the Secretary's ability to certify that an importation program would pose no additional risk to public health and safety would turn on whether and to what extent statutory and regulatory safeguards equivalent to section 355's requirements could be developed and implemented and whether adequate resources are available to enforce these safeguards.

### b. Bioequivalence and Substitutability

Under the MMA, the issue of substitutability is largely moot, at least from a legal standpoint. Since the drugs that are eligible to be imported under the MMA are limited to FDA-approved drugs, there should be no concern that the program legally sanctions labeling an unapproved Canadian drug with the label of an approved drug.

If, however, Congress amended section 384 to allow importation of unapproved drugs, section 355 could also impact the Secretary's ability to certify that importation would pose no additional risk to public health and safety. This is especially true if such program would allow or require the imported foreign "versions" of FDA-approved drugs to be labeled and sold as interchangeable, generic substitutes for their FDA-approved counterparts.

Section 355(j) sets out the approval standard for generic drugs. To obtain approval of a drug under section 355(j), an ANDA applicant generally must demonstrate that the proposed drug product has the same active ingredient, dosage form, route of administration, strength, and labeling as the innovator product. Only bioequivalent drug products that have the same active ingredient, dosage form, strength, and route of administration are considered therapeutically equivalent by FDA and, thus, substitutable.

Bioequivalence has been the basis for approving generic copies in the U.S. for more than 20 years. In addition, manufacturers of brand name drugs perform the same bioequivalence tests as generics when they reformulate to ensure substitutability. A showing that a drug product is safe and effective for its intended uses is independent of a showing of bioequivalence; two products used to treat the same condition may both be safe and effective for their intended uses, but they may not be bioequivalent. As a result, the two drugs cannot be substituted for each other.

If a drug imported from Canada is not actually an FDA-approved product, FDA cannot assure that an imported drug product is readily substitutable for the FDA-approved version without a showing of bioequivalence. Substitution or commingling of non-bioequivalent drugs may result in one version of a drug being super-potent or sub-potent compared to the other. In the case of some drugs, these differences in potency can have toxic effects (e.g., warfarin), or they may result in the delivery of insufficient active ingredient to treat a particular condition.

#### c. Repackaging

Section 355's requirements with respect to who may repackage drugs also affect the Secretary's ability to make the safety certification the MMA requires. As discussed above, every step in the manufacture, packing, and repacking of a new drug must be the subject of an NDA.[9] This means that when drugs are repackaged (other than in the practice of pharmacy), the repackaging generally must be covered by an FDA-approved drug application. In addition, NDA holders must obtain pre-market approval through a supplement for any change in packaging that might have an adverse effect on the identity, strength, quality, purity, or potency of a drug product.[10] This includes any change to a drug product container closure system that controls the drug product delivered to a consumer, or changes in the type or composition of a packaging component that may affect the impurity profile of the drug product.[11]

There is an important exception to the preceding NDA requirement for repackagers that is particularly applicable with respect to the importation of FDA-approved drugs under MMA. In section 446.100 of FDA's Compliance Policy Guide, FDA permits persons who repackage approved, solid oral dosage form drug products to do so without an NDA, so long as the labeling used for the repackaged product is equivalent to that of the approved drug, except for labeling changes necessary to comply with section 352(b). That provision requires the product label to bear an accurate statement of the quantity of the contents of the package. Since the drugs that are eligible to be imported under the MMA are, in general, the type of products described in the Compliance Policy Guide, it seems likely that, for the most part, prescription drugs imported under the MMA will fall into the exception to the requirement under section 355 for repackaging to be covered by an FDA-approved drug application.

If, however, Congress amended the MMA to allow importation of other dosage forms, persons wishing to repackage those drugs would need an NDA to do so, unless Congress modified these statutory requirements with respect to imported drugs.

### 3. 21 U.S.C. 352, Misbranding

Section 352 and its implementing regulations set forth the labeling requirements for drugs. These labeling requirements are both general and product-specific, and are intended to assure that drugs are safely handled, shipped, and used. Foreign drugs that are misbranded may not be legally imported into the U.S. pursuant to section 331(a). There are several provisions in the FD&C Act describing or defining misbranding that are potentially implicated by the importation of prescription drugs. First, under section 352(a), a drug is misbranded if its labeling is false or misleading in any particular. Second, under section 352(c), a drug is misbranded if any information (for example, expiration dates, specific product warnings, and lot numbers) required to appear on its label is not prominently displayed on the label. Third, under section 352(o), a drug is misbranded if it was not prepared, propagated, compounded, and/or processed in an establishment that was duly registered with FDA as required by section 360. Finally, under section 352(f), a drug is misbranded if its labeling does not bear adequate instructions for use.

The MMA provides that drugs imported from Canada must comply with the misbranding provisions of section 352.[12] The MMA's importation provisions do not appear to limit the authority in section 381(a), which requires FDA to refuse to admit into the U.S. any drug that appears to be misbranded.[13] Finally, the MMA requires the manufacturer of a prescription drug (as defined at section 384(a)(3)) to "provide an importer written authorization for the importer to use, at no cost, the approved labeling for the prescription drug."[14]

As we previously noted, drugs that do not comply with section 352 cannot be imported. Moreover, FDA is required to refuse admission to any drug that appears to be misbranded. The drugs that are permitted to be imported under the MMA, however, are FDA-approved drugs – or drugs that, if labeled with the FDA-approved labeling, would be FDA-approved drugs. Since misbranded products cannot be introduced into interstate commerce and drugs that appear misbranded can be refused admission, the re-labeling of the drugs that importers are permitted to import under the MMA with the FDA-approved labeling appears to be a practical problem that importers – to whom the manufacturers of such drugs are required by the MMA to provide a written authorization to use the approved labeling at no cost – would have to deal with.

The requirement in the MMA that manufacturers allow importers to use their FDA-approved labeling raises an additional practical problem that will need to be addressed: Are importers allowed to reproduce the FDA-approved labeling? Sanctioning the use of reproduced labeling may make the job of law enforcement more difficult. Certain drugs packaged with labeling that appears to have been reproduced on a color copier could be legally shipped in domestic commerce under the MMA, thus making it more difficult to differentiate counterfeit drug labeling from those reproduced drug labeling authorized by law. This concern applies even if, as in the case of the MMA, the drugs being re-labeled are FDA-approved drugs (or drugs that, if labeled with the FDA-approved labeling, would be FDA-approved drugs).

The labeling requirements in section 352 would raise even more difficult questions if Congress were to amend section 384 to authorize the importation of drugs that had not been approved by FDA. Under section 352(a), a drug is misbranded if its labeling is false or misleading in any particular. If Congress were to amend section 384 to permit or require labeling or re-labeling of an unapproved Canadian "version" of an FDA-approved drug with the labeling of its FDA-approved counterpart, it would do violence to the reasons for which the misbranding provisions of the FD&C Act exist. As noted above, drugs are not considered substitutable in the U.S. unless they have been shown to be bioequivalent under the standard in section 355. Thus, not only could such re-labeling mislead parties in the distribution chain regarding the identity of the drug they are receiving, the labeling would be literally false if the imported product contains different inactive ingredients, has a different manufacturer, or otherwise differs in some material respect from the FDA-approved version. Such differences could affect safety to the extent that individuals may be allergic to particular ingredients or certain active ingredients interact differently with different inactive ingredients.

Under section 352(c), a drug is misbranded if any information that is required by or under authority of the FD&C Act to appear on its label or labeling is not prominently placed thereon. Such information includes expiration dates, specific product warnings, and lot numbers. Foreign labels may not contain all of the required information, so a foreign drug may be misbranded when it is offered for import into the U.S. This is true, even if the drug inside the foreign label meets the requirements of the FD&C Act.

Under section 352(o), a drug is misbranded if it was not prepared, propagated, compounded, and/or processed in an establishment that was duly registered with FDA, as required by section 360. If Congress amends section 384 to authorize importation of unapproved drugs, section 360 must be addressed. Many foreign drugs are not manufactured in establishments that are properly registered with FDA, and so are misbranded under section 352(o) when sold into the U.S.

Under section 352(f), a drug product's labeling must also bear adequate directions for use. 21 CFR 201.5 defines adequate directions for use as "directions under which the layman can use a drug safely and for the purposes for which it is intended." In the case of prescription drugs, this is a highly technical requirement. A series of Federal cases holds that all unapproved prescription drugs lack adequate directions for use as a matter of law. [15]

There are two significant exemptions from section 352(f). First, 21 CFR 201.100 exempts prescription drugs from section 352(f) under certain specified cir-

cumstances. Under MMA, this regulation is significant because the FDA-approved prescription drugs imported by pharmacies or wholesalers would have to comply with its requirements to avoid being misbranded under section 352. However, the exemption in 201.100 extends only to approved drugs (or their components). Thus, while the regulation offers a potential safe harbor for the drugs that are eligible for importation under MMA, it would need to be revised if Congress decided to amend section 384 to authorize importation of unapproved foreign drugs.[16]

Second, under section 353(b)(2), a prescription drug lawfully dispensed pursuant to a valid prescription is also exempted from 352(f) (and 352(c) and (o), as well) so long as its label still displays certain basic information.

This second exemption would need to be addressed if Congress were to amend section 384 to authorize importation of unapproved new drugs. The exemption in section 353(b)(2), however, applies only to drugs that are lawfully dispensed pursuant to a valid prescription to individual consumers; by definition, it does not extend to drugs sold in wholesale distribution. Thus, the exemption would not apply in the case of a foreign pharmacy that sold drugs to a U.S. pharmacy or U.S. wholesaler, regardless of whether those drugs were FDA-approved.

Although not all misbranded drugs necessarily pose a safety risk, the FD&C Act and its implementing regulations clearly contemplate that labeling is a component of the safe use of a drug product.[17] The importation of drugs whose labeling did not meet the legal standards set forth in section 352 would be less safe compared to the current standards.

### 4. 21 U.S.C. 351, Adulteration

Section 351 sets forth the adulteration provisions in the FD&C Act. Foreign drugs that are adulterated may not be legally imported into the U.S. pursuant to section 331(a).

The adulteration requirements in section 351 range from general to highly technical. One has particular relevance under MMA.

Section 351(a)(2)(B) states that a drug is adulterated for purposes of section 331(a) unless it is manufactured and held in conformance with current good manufacturing practice (cGMP).[18] The concept of cGMP is intended in part to assure that drugs are properly handled and stored at all times before they are dispensed to consumers. One of the fundamental concerns about the importation of foreign drugs is that there is no way to assure that they have been appropriately stored, processed, and packaged.

This uncertainty impacts the Secretary's ability to certify whether implementation of MMA would pose no additional risk to the public health. When Congress added section 381(d)(1), it made a finding that drugs held abroad "were a health and safety risk to American consumers because they may have become subpotent or adulterated during foreign shipping and handling." [19]

MMA modifies section 381(d)(1). To address the issue of potential mishandling of drugs, it requires that certain tests be performed on imported drugs, and that Canadian sellers involved in the importation of drugs into the U.S. be registered with the Secretary. To certify, the Secretary must conclude that these provisions are sufficient to address the concerns that Congress identified when it enacted section 381(d)(1) in the late 1980s. Unfortunately, however, tests may not always substantiate whether a drug has been held in conformance with cGMP. Moreover, without a consistent physical presence abroad, it will be difficult to assess how different registrants actually handle the drugs they ship into the U.S.

The preceding concerns that Congress expressed in the 1980s about drug potency also implicate sections 351(b) and (c). These provisions state that a drug is adulterated if its strength differs from, or its purity or quality falls below, that which it purports to possess. These provisions are intended to help assure that drugs meet manufacturing specifications and do not contain dangerous impurities. These concerns apply to many foreign drugs offered for sale into the U.S., especially many of the unapproved new drugs shipped to the U.S. in small packages from countries with less developed regulatory systems. One practical limitation, however, is that it is very difficult to determine

whether a drug violates section 351(b) or (c) from mere visual inspection alone. To ascertain the purity of a drug, FDA typically must test it, and such tests are costly and extremely resource-intensive.

This concern is addressed to some degree by the MMA, to the extent that drugs imported into the U.S. must be manufactured and held in compliance with cGMP and must first be tested. However, no testing scheme is foolproof. In addition, as a practical matter, the opportunities for adulteration increase as the distribution chain and number of entities handling the products increase. The practical limitations of such a scheme are addressed elsewhere in this report. To ensure compliance with cGMP, FDA may need to inspect the facilities of the Canadian sellers. Assuming that inspections were required, a memorandum of understanding (MOU) with Canada to permit such inspections, or for Canada to carry out such inspections on FDA's behalf, would be needed.[20]

If Congress were to amend section 384 to authorize importation of unapproved drugs, the legal concerns related to adulteration would increase significantly. In the case of the U.S.-approved drugs at issue in the MMA, the primary concern is not how the drugs were manufactured—they were presumably manufactured in compliance with cGMPS since they were made in an FDA-inspected facility pursuant to an approved NDA—but whether the products were appropriately held while in foreign commerce. In the case of unapproved drugs, the concerns extend to all phases of the drug's development, and FDA has no assurance whether unapproved drugs were manufactured in compliance with cGMP.

As with the misbranding provisions, exempting certain foreign drugs from the pre-approval requirements of section 355 would not address separate violations of section 351. Any importation program that authorized importation of unapproved new drugs would have to comply with the provisions of section 351, or exempt imported drugs from section 351's requirements and ensure that sufficient alternative safeguards are in place to assure an equivalent level of safety.

### 5. 21 U.S.C. 381(a), Imports

Section 381(a) governs how FDA and CBP evaluate and process drugs that are offered for import into the U.S. Under section 381(a), FDA must refuse to admit any drug that "appears" (based on examination of samples or otherwise) to be an unapproved new drug within the meaning of section 355, an adulterated drug within the meaning of section 351, or a misbranded drug within the meaning of section 352. When FDA samples such products, it must provide notice of that fact to the drug's owner or consignee, either of whom has the right to appear before the agency and present testimony.

The "appearance" standard is the key to section 381 because it compels government investigators to refuse to admit suspect drugs into the U.S. This refusal of admission does not have to meet the same evidentiary burden required to prevail in a civil action under sections 332 or 334. In this respect, section 381(a) is the single most significant legal obstacle to the importation of unapproved or misbranded foreign drugs into the U.S., including Canadian "versions" of FDA-approved drugs.

Even if importation is limited to U.S.-approved drugs, FDA still must contend with whether those drugs "appear" to be adulterated because they have been handled in a manner inconsistent with section 351 (with which they have to comply under MMA), outside the U.S. (and therefore outside of Federal and state oversight). Thus, even in the case of the MMA, the Secretary would need to consider whether the FDA-approved drugs being imported into the U.S. had not been adulterated while abroad. Since, as noted, visual inspection reveals little about how a drug was handled, government investigators are confronted with a difficult challenge.

It is important to note, however, that drugs that "appear" to be unapproved, adulterated, or misbranded are entering the U.S. now; this is primarily a function of the volume of personally imported drugs that is streaming into the U.S., which is so great that FDA and CBP do not have sufficient resources to inspect them all.[21] The number of personal drug parcels that are shipped into the U.S. in violation of

the FD&C Act already far exceeds the number that the government has the resources to inspect and interdict.

Under section 381(a), FDA must meet certain notice and due process requirements before it can return noncompliant drug products to the sender, or authorize their destruction. Under 381(a), FDA shall detain any drug that appears to be adulterated, misbranded, or an unapproved new drug. FDA is required to notify either the owner or the consignee of that drug of such detention and must provide them with an opportunity to be heard regarding how the drug complies with the FD&C Act. These notice and hearing requirements consume government resources and thus may impact FDA's ability to effectively and efficiently process the high volume of drugs (both legal and illegal) that would be offered into the U.S. under any importation program. Thus, to free resources to help FDA inspect the large volume of drugs that would be imported under MMA, legal changes would be needed to amend 21 U.S.C. 381(a) to permit FDA to interdict noncompliant drug products without providing notice and opportunity for hearing in all cases.

### 6. 21 U.S.C. 381(d)(1), American Goods Returned

Section 381(d)(1) is often referred to as the "American goods returned" provision. Under section 381(d)(1), if a prescription drug was originally manufactured in the U.S. and then sent abroad, the only person who may import that drug back into the U.S. is the original manufacturer. This is true even if the drug complies with the FD&C Act in all other respects.

Section 381(d)(1) was passed as part of the PDMA, in part because Congress found that American goods returned were "a health and safety risk to American consumers because they may have become subpotent or adulterated during foreign shipping and handling."[22] Congress viewed storage and handling of prescription drugs as an important component of cGMP, without which there was significant risk that drugs would be adulterated or otherwise substandard.

The MMA modifies section 381(d)(1) by allowing persons other than the manufacturer to re-import U.S.-manufactured, FDA-approved drugs that had been sent abroad. However, as noted above, the cGMP concerns at the heart of 381(d)(1) would still apply to imported drugs. In the absence of 381(d)(1), equivalent protections with respect to the tracking, storage and handling of imported drugs would likely need to be imposed and developed in order to assure that imported drugs meet the same safety and effectiveness standards as those that have been held in the U.S. at all times. The MMA offers some new safeguards, (in addition to the requirement of compliance with cGMP), such as product testing and registration, which the Secretary must assess against the concerns that prompted Congress to adopt section 381 (d)(1) in the first place—risks involving adulteration, mishandling, and counterfeiting.

### 7. Title 19 of the U.S. Code, Trademarks

19 U.S.C. 1526 prohibits the importation of merchandise of foreign manufacture if the label bears a trademark owned by a citizen or corporation in the U.S., unless written consent of the trademark owner is produced at the time of entry. This provision is relevant to drug importation because, as discussed above, the MMA appears to authorize importers to label Canadian drugs with FDA-approved labels. In most instances, both a drug's trade name and trade dress are protected intellectual property. However, the MMA requires the manufacturer of the FDA-approved drug to authorize the importer to use, at no cost, its approved drug labeling. To the extent such labeling could result in confusion along the distribution chain and inadvertent substitution of non-bioequivalent drugs, it raises both safety concerns and intellectual property issues. The intellectual property issues are discussed further in Chapter 9 of this report.

### 8. State Pharmacy Laws

The requirements of the FD&C Act notwithstanding, foreign pharmacies that dispense drugs into the U.S. also typically violate state pharmacy laws. Most states prohibit a pharmacy from dispensing drugs to its citizens unless the pharmacy is licensed in that state. Moreover, the autonomy of each state legislature makes it difficult to solve this problem by conditioning the legality of importation on compliance

with state law. To do so, FDA and CBP would have to reconcile such a Federal importation law with licensure requirements on a state-by-state basis.

For example, presume a Canadian online pharmacy that obtained state licenses to dispense drugs into Montana, Nevada, and Oregon, but still attempted to dispense drugs into other states as well. Assume that other Canadian pharmacies operated in a similar fashion, having just a handful of state licenses. How could FDA field investigators be expected to know which foreign pharmacies could legally dispense into which states? Would they have a master list to consult? If so, who would keep it updated? How? And, when processing the imported drugs, would FDA personnel be allowed to rely on a package's address to determine whether it appeared to be legal (i.e., whether it was intended for Nevada as opposed to a state in which the pharmacy at issue was unlicensed)? Such obligations likely would frustrate the efficiency of the import evaluation process and aggravate the resource concerns tied to the notice and hearing requirements in section 381(a). Finally, as noted above, concerns regarding intellectual property could affect whether Canadian labels are able to comply with state laws.

### B. Resource Limitations

While the volume of imported drugs has increased enormously, neither FDA nor CBP has received additional resources or authorities to process these shipments. Chapter 5 of this report provides a more detailed discussion of the types and amount of resources that would be needed for FDA to adequately inspect the current amount of imported pharmaceuticals. It is likely that legalizing importation would increase the volume of imported drugs even further. In addition, FDA would have to build a program capable of managing the types of activities specified in MMA and implement any additional measures necessary to ensure the health and safety of the American public.

Based on the importation program proposed by the MMA, additional issues to be addressed would include, but may not be limited to, the elements noted in the chart below. Numerous issues identified would require additional statutory and regulatory authority, as well as concomitant resources. It is difficult to predict the actual costs of an importation program without specific information on the type of program, however, it is clear that any program would need substantial resources for infrastructure, IT needs, personnel, and associated required measures.

| ISSUE | ASSOCIATED ACTIVITIES |
|---|---|
| **Eligible Products** | • Development and maintenance of list of eligible products.<br>• Public dissemination of information about which products are eligible.<br>• Additional manufacturing inspections. |
| **Excluded Products** | • Develop list of excluded products.<br>• Update list. |
| **Exporters** | • Guidance and rulemaking for registration policies and procedures, including submission, denial, suspension, revocation, and bond forfeiture.<br>• Partnerships with foreign health authorities to verify status of exporters.<br>• Development and maintenance of an electronic database.<br>• Enforcement.<br>• Adequacy of notice regarding eligible exporters. |
| **Importers** | • Guidance and regulation development for registration policies and procedures, including necessary information, submission, recordkeeping requirements, denial, suspension, revocation, and bond forfeiture.<br>• Partnerships with states to verify licensure including State enforcement of licensure, etc., and good standing.<br>• Development and maintenance of an electronic database.<br>• Enforcement against unregistered importers. |
| **Limits on Personal Importation** | • Examination of any necessary changes to the personal importation policy.<br>• Examination of packages. Inadequacy of resources.<br>• Return and/or destruction of illegally imported drugs.<br>• Enforcement against those facilitating personal imports. |
| **Pedigree** | • Guidance or rulemaking re: pedigree requirement.<br>• Enforcement.<br>• Partnerships with foreign health authorities to verify transactions. |
| **Labeling and Disclosure Requirements** | • Rulemaking re: any additional labeling requirements for imported drugs.<br>• Development and maintenance of electronic repository of labeling.<br>• Enforcement.<br>• Partnerships with states to ensure that pharmacists comply with labeling requirement. |
| **Packaging Requirements** | • Rulemaking re: any additional packaging requirement for imported drugs.<br>• Enforcement. |
| **Authority to Stop Imports** | • Monitoring packages at border and destruction and/or return to sender.<br>• Working agreements with Customs.<br>• Statutory due process. |
| **Adverse Event Reporting** | • Guidance or rulemaking re: reporting for imported drugs.<br>• Adequacy of adverse event reporting.<br>• Monitoring and following-up on adverse events. |
| **Reporting of Quality Problems by Importers** | • Guidance or rulemaking on when, where, and how to report.<br>• Receipt and follow-up on reports.<br>• Enforcement. |
| **Recall** | • Guidance or rulemaking on recall procedures.<br>• Management of recalls. |
| **Inspections** | • Develop inspectional program; Conduct inspections; Analyze results.<br>• Enforcement if adverse inspectional results. |
| **Means of Monitoring Impact on Public Health** | • Develop sampling and testing plan.<br>• Conduct sampling and testing.<br>• Analyze, disseminate, and act on results. |
| **Means of Terminating Some or All Imports on an Emergency Basis** | • Means of Terminating Some or All Imports on an Emergency Basis Monitoring for risks to health.<br>• Communication to field and public.<br>• Limiting Ports of Entry. |
| **Limiting Ports of Entry** | • Rulemaking.<br>• Enforcement. |

1 For the most part, where we discuss "importation" in this chapter, we are referring to commercial importation.
2 Because importation under MMA is limited to Canada, the discussion in this Chapter addresses importation from Canada, unless otherwise noted.
3 Intellectual property laws would impact an importation program as well. *See* Chapter 9 of this report for an analysis of the impact on intellectual property rights.
4 Drug importation may also impact other U.S. laws and regulations that are enforced by agencies, such as CBP and the U.S. Postal Service, however, a legal analysis for these agencies was not performed for this report.
5 Under 21 U.S.C. 321(p), a "new drug" is defined to include "any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." This definition is broad enough to include all prescription drugs offered for sale into the U.S. from abroad.
6 *See* 21 U.S.C. 355(a), (b), and (d).
7 ANDAs may also be approved for drugs that differ from the approved innovator drug in terms of an active ingredient, dosage form, strength, or route of administration. Drugs approved through this mechanism are not therapeutically equivalent to the innovator product and, thus, not substitutable.
8 If, as the MMA provides, the drugs allowed into the U.S. are restricted to FDA-approved drugs, there are other potential safety concerns discussed elsewhere in this chapter that are not tied directly to the pre-approval process in section 355. Limiting importation to FDA-approved drugs may limit the number of drugs eligible for importation for a number of reasons, including the product-specific scope of an NDA approval, as discussed above, and other reasons, including a manufacturer's ability to limit foreign sales of its FDA-approved drugs, which are elaborated in detail in Chapter 7.
9 *See* United States v. Baxter Healthcare Corp., 712 F. Supp. 1352 (N.D. Ill. 1989), aff'd, 901 F.2d 1401 (7th Cir. 1990).
10 *See* 21 CFR 314.70(b).
11 *See* 21 CFR 314.70(b)(2)(vi).
12 21 U.S.C. § 384(c)(1).
13 21 U.S.C. § 384(k) provides that "[n]othing in this section limits the authority of the Secretary relating to the importation of prescription drugs, other than with respect to section 801(d)(1) as provided in this section."
14 21 U.S.C. § 384(h). Trademark and other issues associated with this provision are discussed in Chapter 9.
15 *See* U.S. v. Articles of Drug, 625 F.2d 665, 673-75 (5th Cir. 1980); U.S. v. Baxter Healthcare Corp., 712 F. Supp. 1352, 1359 (N.D. Ill. 1989), aff'd, 901 F.2d 1401 (7th Cir. 1990); U.S. v. Premo Pharmaceutical Laboratories Inc., 511 F. Supp. 958, 977 n.23 (D.N.J. 1981).
16 *See* 21 CFR 201.100(c)(2).
17 *See* 21 CFR 201.5.
18 *See* 21 CFR Parts 210 and 211.
19 P.L. 100-293, Section 2(4).
20 *See* Chapter 6 of this report for a discussion of the issues associated with such agreements.
21 *See* Chapters 1 and 5 of this report for additional discussion of the current volume of imported drugs and the agency resources necessary to adequately inspect these packages.
22 P.L. 100-293, section 2(4).

# CHAPTER THREE

# Impact on the Pharmaceutical Distribution System

## Chapter Highlights:

The drug distribution network for legal prescription drugs in the U.S. is a "closed" system that involves several players (e.g., manufacturers, wholesalers, pharmacies) who move drug products from the point of manufacture to the end user, and provides the American public with multiple levels of protection against receiving unsafe, ineffective, or poor quality medications. This system evolved as a result of legislative requirements that drugs be treated as potentially dangerous consumer goods that require professional oversight to protect the public health. The result has been a level of safety for drug products that is widely recognized as the world's "gold standard." Legalized importation of drugs in such a way that creates an opening in the "closed" system will likely result in some increase in risk, as the evidence shows that weaknesses in the oversight of drug regulation and the distribution system have been exploited. For example, doing so would increase the opportunity for counterfeit and other substandard drugs to enter and be dispersed into the U.S. drug distribution system.

## Key Points:

- The U.S. distribution system is a relatively closed system. Legalizing importation will open this system likely resulting in some increase in risk.
- Importation increases the opportunities for counterfeit and other substandard drugs to enter and be dispersed into the U.S. drug distribution system.
- A commercial importation scheme could be feasible with adequate resources and authorities where specific measures could be implemented to maintain a closed distribution system with necessary checks and balances. However, it would be extraordinarily difficult to achieve this result if personal importation were legalized.
- Additional authorities and resources may be needed to create a U.S.-based registration and licensure scheme for importers and exporters.
- To maintain current levels of safety, standards of practice at the level that currently exist in the U.S. would need to apply to all foreign drug suppliers under a commercial importation program. In addition, Memoranda of Understanding (MOU) may be needed with the affected countries to ensure effective enforcement.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to assess the pharmaceutical distribution chain and the need for, and feasibility of, modifications in order to assure the safety of imported products.

### To further explore this issue, we asked for comment on:

- Is it appropriate or necessary to limit importation to specific persons (e.g., pharmacists, wholesalers, individuals under certain circumstances) and how would such limitations impact the availability of these products?
- Should a U.S. licensure or certification process be implemented for foreign entities?
- Is it appropriate for the U.S. to impose additional requirements for the import distribution system to assure safety?
- What processes and criteria would be necessary to ensure (i.e., certify) that a specific importer abides by the standards of pharmacy practice that are at least as rigorous as U.S. standards? Would limiting the number of countries from which importation be permitted make the certification less costly and more effective?
- Should legal importation be limited to wholesale shipments?
- Should legal importation by individuals be restricted to pharmacies that serve citizens of the exporting country or those that only export?
- Does FDA or other agencies need additional authorities to inspect facilities making products intended for export to the U.S.? What types of inspection authority?
- Would additional requirements for drug pedigree and track and trace records be useful in assisting in the assurance of the security of these imports? What other mechanisms would be required to enable tracking to ensure compliance with U.S. laws and regulations or requirements for importation?
- Would special import packaging and prior notification be useful?
- What reporting requirements would be needed for adverse events and how would they be enforced? What about foreign reporting requirements?

## II. WHAT THE COMMENTS SAID

Many comments discussed concerns about the safety of a drug importation program. Several comments suggested limiting importation to wholesalers and pharmacies. Some stated that they want the benefit of lower-cost imported drugs, but they want to go to their local pharmacy to get their prescriptions. Others noted that limiting importation to commercial entities, rather than individuals, would help to maintain the relatively closed distribution system in the U.S. Other comments noted that the closed distribution system in the U.S. has ensured a safe drug supply in this country, and that introduction of drugs that have not been maintained within the control of the U.S. distribution system could permit counterfeit, adulterated, misbranded, or other problem products to enter the U.S. distribution system. Several comments suggested that importation be limited to wholesale shipments because it would be impossible to monitor the influx of the enormous volume of small packages that would be entering the U.S. daily if personal importation were legalized. Still other comments suggested legalizing drug importation only from licensed Canadian pharmacies to licensed U.S. pharmacies.

Of the comments that supported drug importation, several stated that importation should be restricted to foreign pharmacies and wholesalers that are licensed in the foreign country by a reputable, governmental entity, are routinely inspected, and that comply with the usual and customary practice for dispensing and distributing drugs. A few comments suggested that either the states or FDA accredit exporting pharmacies and wholesalers and that they be subject to oversight by the accrediting entity.

Many comments supported the use of a pedigree to document the chain of custody of the drug. They believed that it is important to document the movement of the drug from the manufacturer through each subsequent sale or transaction until it ultimately reaches the consumer. Some comments, although supportive of the concept, were critical of paper pedigrees because they can be forged. However, these comments also noted that the widespread adoption of an electronic pedigree is many years away.

Comments did not suggest specific processes or criteria to ensure that a specific exporter would abide by standards of practice that are at least as rigorous as U.S. pharmacy standards. A few comments pointed to the verified internet pharmacy practice site (VIPPS) program that is managed by the National Association of Boards of Pharmacy as a means of certifying and credentialing internet pharmacies. They noted that this system maintains rigorous standards to ensure that internet pharmacies follow usual and customary pharmacy practice standards. We received no comments on whether limiting the countries from which importation is permitted would make a certification process less costly or more effective, or both.

We received no specific comments discussing whether personal importation should be restricted to Canadian pharmacies that serve a significant number of citizens; however, several comments noted that if the pharmacies are good enough for Canadian citizens, they should be good enough for U.S. citizens. These comments appear to presume that the pharmacies currently selling drugs into the U.S. are the same pharmacies serving Canadian citizens. Other comments expressed concern that pharmacies that are set up in foreign countries specifically for export may be used as portals for transshipment of unregulated drugs into the U.S., especially if the foreign government does not closely oversee these 'for export only' pharmacies.

A few comments suggested that FDA would need additional authority to conduct foreign inspections at foreign manufacturing facilities and to certify the production lines they make.

One comment suggested that the value of special packaging for imported drugs would be limited, but that prior notification, with reasonable time frames, would be useful.

Some comments recognized that a system must be established to address adverse events or quality problems with imported drugs. One comment stated that both the U.S. and Canada have sufficient reporting systems and should share the information. A few comments noted that physicians need to be educated to ask where the patient got the medication if they suspect that an adverse event is associated with the drug.

## III. DISCUSSION

### A. Overview of the Current U.S. Drug Distribution System

The current regulatory system provides the American public with multiple levels of protection against receiving unsafe, ineffective, or poor quality medications. First, as required under the FD&C Act, FDA maintains high standards for prescription drug approval.

Second, once the drug is approved, the manufacturer must continue to comply with cGMP regulations to ensure that the quality of the product is systematically evaluated throughout the manufacturing process. The specific registered facility where the product is manufactured remains subject to periodic inspection by FDA.

Third, pharmacies and wholesalers who sell or distribute prescription drugs in the U.S. must be licensed or authorized by the states in which they operate.

Fourth, there are limited channels of entry into the American drug supply, thereby reducing the opportunity to place counterfeit or poor quality medications into the U.S. commercial distribution system. Today, prescription drugs on U.S. pharmacy shelves generally arrive either directly from a manufacturing facility, domestic or foreign, that meets FDA requirements, or from a U.S. wholesaler who receives the approved drug from a manufacturing facility that meets FDA requirements. Together, FDA and the states can exercise oversight of every step within the commercial drug distribution chain from the manufacturing of the product to the point of sale to the consumer. One exception to this process is when the original U.S. manufacturer re-imports its own FDA-approved product into the U.S. However, even in this instance, the manufacturer must possess documentation that the product is authentic, has been properly handled, and is (as necessary) relabeled for the U.S. market. And, since the manufacturer is best equipped to evaluate the authenticity and quality of the re-imported drug,

the law allows only the original U.S. manufacturer to bring its own U.S.-made drugs back into the U.S. This helps assure that U.S.-made drugs that were mishandled abroad are not placed into U.S. commerce by other importers who do not have sufficient familiarity with the drugs to recognize if their quality or integrity has been compromised.

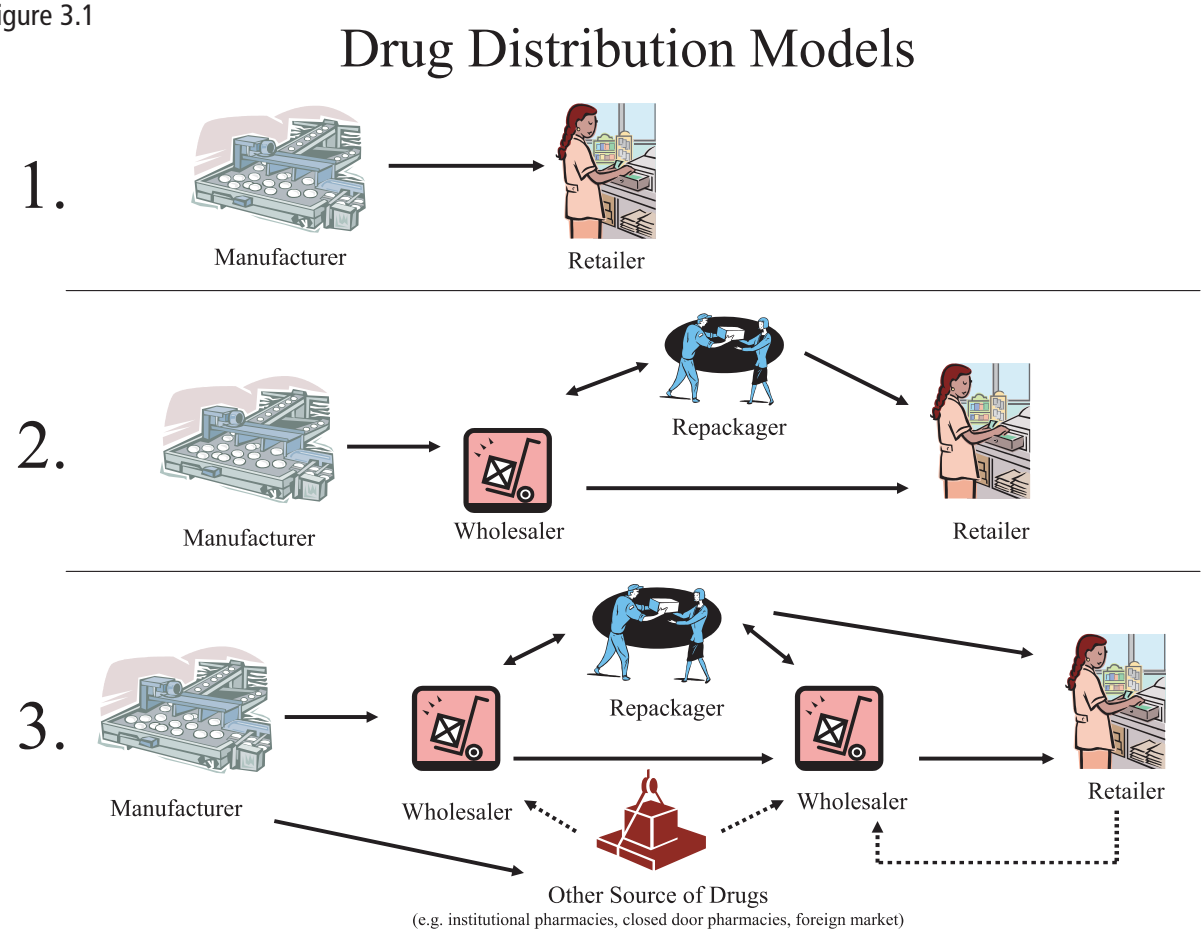
The U.S drug distribution system is a relatively closed system that involves several players (e.g., manufacturers, wholesalers, retailers) who move drug products from the point of manufacturing to the end user who dispenses the drug to the patient. As part of this system, each player is accountable to maintain the integrity of the product in its possession as it moves through the supply chain, which ensures that the product the consumer receives will be safe and effective and is of high quality. This system is intended to ensure that the American public does not consume drugs that do not meet FDA and state standards. Once a product leaves this closed system, FDA's ability to assure that it is an authentic FDA-approved product or being properly handled is significantly hampered.

Figure 3.1 shows several models that are used to move prescription drug products through the U.S. distribution system.

## B. Vulnerabilities in the U.S. Drug Distribution System

Even though the U.S. drug distribution system is among the safest in the world, vulnerabilities in the system create opportunities for unscrupulous activity. FDA's Counterfeit Drug Task Force Report[1] describes several of these vulnerabilities. Such activities include counterfeiting, diversion, incomplete pedigrees, inadequate or no authentication, repackaging, tamper-evident packaging, and illegal importation.

Figure 3.1



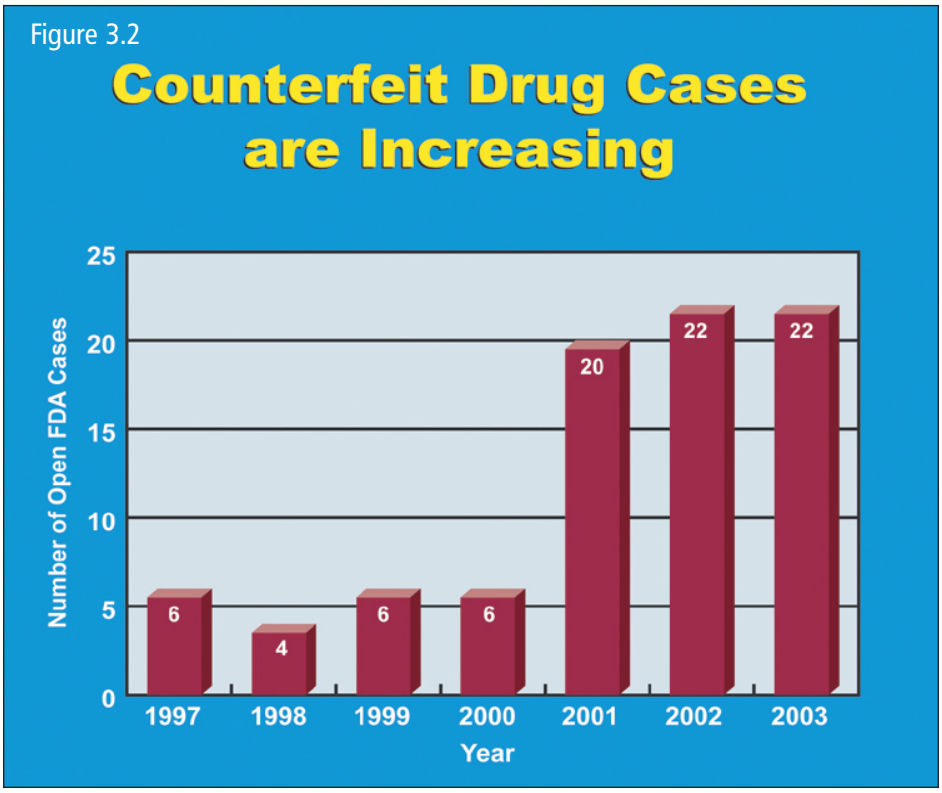
### 1. Counterfeit Drugs

Counterfeiting of medications is a particularly devious practice. Drug counterfeiters not only defraud consumers, they also deny ill patients the therapies that can alleviate suffering and save lives. Although we received different figures describing the global prevalence of counterfeit drugs, it is clear that in some countries counterfeiting is endemic—with some consumers having a better chance of getting a fake medicine than a real one. In many more countries, counterfeit drugs are common. In the U.S., a relatively comprehensive system of laws, regulations, and enforcement by Federal and state authorities has kept counterfeiting rare, so that Americans can have a high degree of confidence in the drugs they obtain through legal domestic channels. In recent years, however, there have been growing efforts by increasingly well-organized counterfeiters backed by increasingly sophisticated technologies and criminal operations to profit from drug counterfeiting at the expense of American consumers. Figure 3.2 illustrates that the number of counterfeit cases FDA has opened over the last seven years has been rising steadily.

### 2. Diversion

Diversion is the sale of drugs outside of the distribution channels for which they were originally intended. Diverted drugs can originate domestically, when there is illegal redirection of prescription drugs from otherwise legitimate sources. For example, free samples supplied to health care providers or lower-priced drugs intended for nonprofit clinics or Medicaid programs may be diverted and illegally sold into the U.S. distribution system. Additionally, diverted drugs can originate in a foreign market. For example, diversion occurs when donated or lower-priced product that is intended for use in one country is, instead, shipped to and sold in another country where the market price is higher. Counterfeit drugs also are associated with the practice of diversion. Diversion facilitates the entry of counterfeit drugs into the U.S. distribution system. Those individuals or entities who sell or purchase diverted drugs are less able to verify the integrity of these drugs because they are purchased outside the normal distribution chain and without the usual regulatory safeguards. This allows unscrupulous peddlers to commingle counterfeit, substandard, or otherwise adulterated or misbranded products with authentic drugs in the U.S. distribution system.

Figure 3.2




### 3. Incomplete Pedigrees

A pedigree is a statement of origin that traces the drug from the point of manufacture and contains information about all transactions that the product undergoes until it reaches the end user. It is also referred to as "chain of custody" documentation. Not all wholesalers are required to provide pedigrees under Federal law. However, when they are required, products with incomplete pedigrees, such as pedigrees that are missing one or more transac-

tions along the chain of distribution are more difficult to track and trace to establish authenticity than products that have complete pedigree information.

### 4. Inadequate or No Authentication

It is important for purchasers in the U.S. drug distribution chain to have confidence that the products they are purchasing are genuine articles (i.e., by authenticating the product). Counterfeiters are using tools and processes to copy drug products and their labeling and packaging to such an exact degree that even the manufacturer of the authentic product has difficulty determining whether a product is real or fake. On the other hand, there are new and emerging technologies that can be used to identify counterfeits. Unfortunately, at this time, these authenticating technologies often are not incorporated into the drug product, labeling, or packaging.

### 5. Repackaging

Repackaging may destroy the anti-counterfeiting measures used in the original packaging and labeling of the drug. It may also provide a point of entry for expired, adulterated, or counterfeit drugs into the distribution system because they may be repackaged in a way that makes them appear to be legitimate products. Finally, counterfeit and diverted product may be commingled with authentic product during the repackaging process, thereby finding its way to an end user.

### 6. Tamper-Evident Packaging

Currently, many prescription drug products do not utilize tamper-evident features. Without tamper-evident features, the original packaging may be reused for counterfeit or diverted product so that it is more easily passed off as legitimate product. The reuse of old prescription drug containers found in trash facilities or taken from hospitals and clinics is also a significant problem; because no tamper-evident feature has to be replicated, this packaging can be reused easily to distribute counterfeit, adulterated, or unapproved drugs. While tamper-evident packaging can be an important part of a company's anti-counterfeiting approach, it has limits because counterfeit products can be repackaged into legitimate-appearing packaging (including features intended to mimic legitimate tamper-evident features).

### 7. Importation

When consumers purchase medications from outside the U.S. (e.g., internet purchases, cross-border purchases), whether safe or unsafe, a portal of entry is created for counterfeit drugs into the U.S. distribution system. Counterfeiters can take advantage of this entryway by combining many small purchases from foreign countries into one and selling them to U.S. wholesalers or other unsuspecting entities. Due to the extensive resources involved in preventing small quantities of drugs from entering the U.S., as the volume of unapproved drug imports increases, it is more difficult for FDA to use its existing resources to identify and stop unsafe importations.

## C. Recent Efforts to Strengthen the U.S. Drug Distribution System

FDA's Counterfeit Drug Task Force report, which was released in February 2004, includes a comprehensive framework for securing the pharmaceutical supply chain against modern counterfeit threats. The FDA Counterfeit Drug Task Force reached the following conclusions about securing the Nation's drug supply:

- Implementation of new technologies is needed to better protect our drug supply;
- The adoption and common use of reliable track and trace technology is feasible by 2007 and would help secure the integrity of the drug supply chain by providing an accurate drug "pedigree;"
- Authentication technologies for pharmaceuticals have been sufficiently improved so that they can now serve as a critical component of any strategy to protect products against counterfeiting;
- Adoption of electronic track and trace technologies is necessary to accomplish and surpass the goals of the PDMA;
- States must adopt and enforce strong, proven anti-counterfeiting laws and regulations;
- Increased criminal penalties could help to deter counterfeiting and more adequately punish those

convicted;
- All participants in the drug supply chain should adopt secure business practices;
- FDA must develop a system that helps ensure effective reporting of counterfeit drugs and strengthens FDA's rapid response to such reports;
- FDA must educate consumers and health professionals about the risks of counterfeit drugs and how to protect against these risks; and
- FDA must collaborate with foreign stakeholders to develop strategies to deter and detect counterfeit drugs globally.

We find that the efforts of the National Association of Boards of Pharmacy in updating the Model Rules for Licensure of Wholesale Distributors, if and when adopted by all of the states, would make a significant impact in ensuring that wholesalers who distribute drugs in the U.S. are legitimate and take the necessary steps to maintain the integrity of the U.S. drug supply. Although some states are beginning to consider adoption of these Model Rules, we are aware of only three states that have adopted these or similar laws to date. Without stronger state laws for the licensure of wholesale distributors, legalized drug importation would create avenues for unscrupulous wholesalers to capitalize on access to global markets to obtain counterfeit, adulterated, substandard, and otherwise questionable drugs, and introduce them into the U.S. drug supply chain.

## D. Need and Feasibility of Modifications to Ensure Safety of Foreign Imports

In assessing whether modifications to the U.S. drug distribution system are needed or feasible to ensure the safety of foreign imports, it is important to consider commercial importation separate and distinct from personal importation. Under a commercial importation scheme, although there potentially could be tens of thousands of participants involved in importation transactions, with adequate resources and authorities, specific measures could be implemented to maintain a closed distribution system with necessary checks and balances. However, under a personal importation scheme, each individual consumer becomes an importer who has limited knowledge and resources to ensure the legitimacy of entities that offer drugs for sale, particularly over the internet. As discussed earlier in this report, the sheer volume of packages that would come in under a personal importation scheme would make it extraordinarily difficult for FDA and CBP to adequately inspect drugs for compliance, regardless of the specific requirements under the importation program. It would be nearly impossible to maintain a closed distribution system in this "buyer beware" environment.

### 1. Commercial Importation

#### a. Licensure scheme

Although an exporting wholesaler or pharmacy may be licensed or registered in the exporting country, the usual and customary standards of practice in that country may be different than those in the U.S. As discussed later in this report, many laws and regulations in foreign countries do not extend to exporters or to the products they export, which would create openings in the distribution system.

A number of comments noted that an essential component of maintaining a safe system is knowing who is involved in the distribution chain and ensuring that they abide by the required rules and regulations. Only then could FDA guarantee the safe and proper handling of the drugs and assure that only legal drugs are imported. Consequently, under a legalized commercial importation program, foreign wholesalers and pharmacies would need to abide by a level of standards of practice that are at least as rigorous as U.S. wholesale and pharmacy standards. This may include registration and licensure in the U.S. by a state or Federal entity, and consist of, among other things, background checks, periodic inspections, minimal standards for storage and handling, due diligence, and recordkeeping requirements.

Additional statutory authority and resources may be needed to create a U.S.-based registration and licensure scheme for importers and exporters. In addition, Memoranda of Understanding may be needed with the affected countries to ensure effective enforcement, such as agreement that the U.S. government can inspect entities in the foreign country.

### b. Chain of Custody

A reliable pedigree that documents the chain of custody of the drug product from the point of manufacturer to the point of dispensing is crucial to ensure that the integrity of the product is maintained while it is abroad. Paper pedigrees, which are in use today, have significant limitations. They are subject to failures to keep adequate records and can be forged, thus making them an unreliable means for documenting the chain of custody.

Mass serialization, which involves assigning a unique number to each case, pallet, and package of drugs, is considered the most effective way to secure and monitor the movement of drugs through the distribution chain. Both private and public efforts to implement radio-frequency identification (RFID) as a means of mass serialization to create a de facto electronic pedigree are currently underway. FDA's Counterfeit Drug Task Force Report urged the adoption and common use of RFID as the standard track and trace technology in the U.S. by 2007.

Migration to RFID as a primary means of creating an electronic pedigree is voluntary for the private sector. FDA did not issue any regulations or requirements for implementation. Rather, FDA is relying on the momentum and enthusiasm demonstrated by the private sector towards implementation. At the same time, some wholesalers and retailers may find it economically infeasible to purchase the necessary technology as early adopters, leaving part of the distribution chain to rely on other means to document the chain of custody. However, even in these instances (which are expected to be rare), these U.S. wholesalers and retailers will be doing business within the U.S. closed distribution system, which provides for other checks and balances in the system.

The current RFID efforts are focused on securing the domestic drug supply. Although there are discussions to create a comprehensive, global RFID system, adoption would be many years away. Even when RFID is fully implemented in the U.S., it cannot be relied upon to secure products that leave the U.S. The widespread implementation foreseen in the U.S. will allow the RFID-tag on products to be read seamlessly as they travel in and out of warehouses, distribution centers, and retailer establishments, creating an electronic pedigree. This would not be the case for an imported product, even if it originated in the U.S. When an RFID-tagged product leaves the U.S., it could be handled by many entities that are outside the U.S. closed system and may not be RFID-equipped. Even if an RFID-tagged drug product comes into the U.S. from an RFID-equipped exporter, there is no way to know who else handled the product, whether it was handled or stored appropriately, what other countries the product passed through, or even whether it was opened and the contents replaced with counterfeit, adulterated, or substandard product.

### c. Prior notice

One mechanism raised by the comments that is used by FDA and CBP to aid in prioritizing their efforts to evaluate food imports is the prior notice requirements. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act)[2] requires that FDA receive prior notice of food imported into the U.S. Under the Bioterrorism Act, information is provided electronically to CBP and FDA in advance of an imported food's arrival to the U.S. Such information includes, among other things, identification of the submitter, including name, telephone and fax numbers, email address, firm name and address; mode of entry (e.g., boat, plane, truck); identification of the manufacturer; country of production; shipper information; and anticipated arrival information. FDA uses this information in advance of the arrival to review, evaluate, and assess the information, and determine whether to further inspect or hold the imported food.

Although FDA only recently implemented the prior notice system for foods in December 2003, the experience and lessons learned from developing, implementing, and running this system could be evaluated to determine if it would be feasible to implement a similar system for a drug importation program and what, if any, modifications should be considered. New statutory authority and sufficient resources may be needed to develop, implement, and carry out a prior notification system for imported drugs.

### d. Markings/Country of Origin

Consumers want to know if the drug product they are taking was distributed first in foreign commerce or if it is an FDA-approved product that was manufactured at an FDA-inspected facility and was subject to the requirements of the current domestic drug distribution system at all times. Furthermore, without any markings on the package indicating that the product was imported under an importation program or listing the country of origin, domestic and foreign product can become commingled as they travel through the U.S. drug distribution system. This foreign versus domestic distinction could be maintained if a reliable chain of custody pedigree followed the product through the supply chain, however, as discussed above, it may be several years before a reliable pedigree system is available. The addition of country of origin information to the labeling of non-FDA approved drug products would also provide more accurate and useful information when reporting an adverse event to FDA.

### e. Inventory Control

We heard from the comments that if importation were legalized, U.S. warehouses and distribution centers that import drugs would need to have processes and procedures in place to distinguish and segregate imported drug products from domestic drug products in their inventory. Some pharmacies may not want to purchase the imported product or some consumers may not want to get the imported product if it is not FDA-approved. As a result, unless a wholesaler or retailer deals solely in U.S. inventory, control and recordkeeping systems would have to be modified to meet this new demand.

### f. Labeling

Sections 352 and 352(b)(2) of the FD&C Act and their implementing regulations set forth labeling requirements for prescription drugs. These requirements are important to ensure the safe and effective use of the drug. The labeling for prescription drugs is approved by FDA and is specific for each drug. Even if an imported foreign drug is chemically identical to an FDA-approved product, it may not have the FDA-approved labeling for the product. Under a legalized importation program, accommodation would need to be made in the U.S. drug distribution system for the re-labeling of imported drugs unless the U.S.-approved labeling is accompanying the product.

Re-labeling of imported drugs raises several concerns. First, re-labeling raises a drug safety issue because it leaves the product vulnerable for product mix-ups in the process. Second, as mentioned above, the labeling is specific for each drug. Merely attaching the labeling for one drug product to another drug product may not be appropriate if there are differences in the imported and domestic product, such as inactive ingredients or dyes.

### g. Testing/Authentication

It is critical to guarantee that the imported drug is authentic product. As discussed in Chapter 6, foreign health agencies do not guarantee the safety and efficacy of exported products from their countries. Furthermore, opportunities exist for drugs to be illegally transshipped through a foreign country and imported into the U.S. In this situation, imported drugs may appear to be coming from one country, but actually originate in another country and just pass through the exporting country. A safe distribution system cannot exist when transshipment occurs because the source of the drugs and the integrity of the drugs are called into question.

Testing or authentication of the imported drug can verify if the active ingredient is present. However, these tests cannot identify the purity and potency of the product. Furthermore, there is no single technology or machine that could do this test for all products as they enter the country and, even if there was, it would be prohibitively resource intensive and logistically impossible to test all imported products. Even if this could be done, it would slow down the access and availability of drugs while the results were pending. Nonetheless, a significant testing regime of imported products would be needed to ensure the safety of imported drug products.[3]

### h. Oversight of International Recalls

Recalls are actions taken by a manufacturer to remove a drug from the market. Recalls may be conducted voluntarily by a manufacturer or by FDA request. We heard from a number of comments that if importation were legalized, a system to monitor recalls of foreign drugs would need to be established so that American consumers would know when a foreign drug is recalled. This system would have to distinguish between the foreign version and the FDA-approved version because recalls do not always cover all versions of a drug.

## 2. Personal Importation

We find that it would be extraordinarily difficult to modify the U.S. pharmaceutical distribution system in any way to ensure the safety of imported drugs by individuals under a personal importation program without increasing the risks to patients of receiving substandard medicines. Personal importation creates numerous vulnerabilities in the drug distribution system, making it extraordinarily difficult to ensure that imported drugs are safe and effective, and putting patients at risk.

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1 Combating Counterfeit Drugs, Safe and Secure: A Report of the Food and Drug Administration, February 2004; U. S. Department of Health and Human Services, Food and Drug Administration, Rockville, Maryland 20857.

2 Pub. L. 107-481.

3 Furthermore, a requirement to test all products would raise liability concerns for the U.S. government because it would preclude the application of the discretionary function exception to the Federal Tort Claims Act. This is discussed in more detail in Chapter 10.

# CHAPTER FOUR

## Role of New Technologies

### Chapter Highlights:

There are a number of anti-counterfeiting technologies that show potential for effectively assuring the authenticity of drugs and, thus, for combating the counterfeiting of drugs. Some examples include holograms, color shifting inks, and watermarks currently employed for U.S. currency. So-called "track and trace" technologies, such as radio-frequency identification (RFID) and sophisticated bar coding, can provide effective monitoring of a drug's movement from the point of manufacture through the U.S. distribution chain. Although these new and emerging technologies are promising, until they are fully adopted internationally they cannot be adequately relied upon to secure the safety, efficacy, and integrity of the global market to safely import prescription drugs into the U.S.

### Key Points:

- There are promising new and emerging anti-counterfeiting technologies; however, until they are universally adopted, they cannot be adequately relied upon to secure the safety, efficacy, and integrity of the global market to safely import prescription drugs into the U.S.

- Widespread adoption of authentication technologies, while theoretically able to secure the U.S. drug supply, is a daunting task that could raise the cost of imported drugs, thereby reducing any expected savings from importation.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to assess the role of new technologies in drug importation. This includes estimating the costs borne by entities within the distribution chain to utilize anti-counterfeiting technologies that may be required to provide import security and analyzing whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as those products that may be imported.

### To further explore this issue, we asked for comment on:

- Is it feasible to impose anti-counterfeiting technologies on drugs not subject to U.S. regulatory requirements and what is their ability to prevent counterfeit or otherwise unsafe drugs?
- Comment on implementation of technologies discussed in FDA's recent counterfeit drug initiative to assure security of imported drugs.
- What are the costs associated with implementing these new technologies?
- Identify the magnitude of the counterfeit drug problem currently in the U.S.
- To what extent are internet pharmacies contributing to the problem?

## II. WHAT THE COMMENTS SAID

Many comments favored the use of anti-counterfeiting technologies as a means of ensuring product authenticity; however, several noted that because these technologies can ultimately be defeated, they must be changed every 12-24 months. It was also noted that repackaging, either domestically or internationally, inactivates any anti-counterfeiting features that had been applied to the product by the manufacturer. Some comments cautioned against tracking anti-counterfeiting technologies as a solution for drug importation because they are only effective when they are used with other methods to ensure product integrity.

Several manufacturers noted that they have already started to incorporate authentication technologies into their products and packaging. Some noted that they are using a risk-based analysis to determine which products are in need of these measures first. Some comments noted that it can take between 6-12 months to incorporate and validate the use of authentication anti-counterfeiting technologies, in many cases, FDA approval is needed before the product can be marketed with the feature. Some comments noted that authentication technologies are costly, while other comments said that the overall cost of using these technologies is minimal considering the profits generated from drug products.

Many comments stated that RFID is very promising for tracking and tracing drug products and as a means of minimizing the risk of counterfeit drugs being introduced into the drug distribution system. They noted that this technology would be extremely difficult (if not impossible) to forge and would allow identification of the product and where it has been since it left the manufacturer. Although RFID is promising, many comments acknowledged that implementation of RFID throughout the domestic drug distribution system is many years away. Currently, members of the U.S. drug supply chain are conducting small-scale feasibility tests using RFID. Several firms have announced they will tag one or more of their products in the near future.

Some comments suggested that tamper-evident and unit-of-use packaging would be useful as a means to minimize the risk of counterfeiting.

Limited information was provided on the costs associated with authentication and track and trace anti-counterfeiting technologies. One comment noted that it would cost about a penny per unit to incorporate anti-counterfeiting technologies into and to validate the product.

In identifying the magnitude of drug counterfeiting in the U.S., the comments relied on the figures reported in FDA's Counterfeit Drug Task Force Final Report. No new data or numbers were presented. Some comments discussed drug counterfeiting as a global problem, but they did not provide data to quantify it on a global scale.

Of the comments that discussed internet pharmacies, most noted that it was difficult to distinguish legitimate foreign websites from rogue websites. Several

comments expressed concern that foreign internet pharmacies provide an easy way for counterfeiters to get their fake drugs into the U.S. A few comments discussed actual incidents where consumers received counterfeit drugs from internet websites. Some comments stated that they were satisfied with the drugs they received from foreign internet pharmacies and were confident that the drugs were identical to the drugs they received from U.S. pharmacies. Many comments were concerned that internet pharmacies compromise patient safety, and because their location is often disguised or unknown, the source of drugs may also be unknown or questionable. Several comments recommended that internet pharmacies be licensed or certified and be subject to the same regulations and oversight as traditional pharmacies.

## III. DISCUSSION

### A. Overview of Current Anti-Counterfeiting Technologies

It is clear that counterfeiters are sophisticated, well-funded, and have significant technological capabilities to copy prescription drugs. FDA's Counterfeit Drug Task Force found that there is no single "magic bullet" that provides long-term assurance to secure the Nation's drug supply. Rather, the Counterfeit Drug Task Force stated that a multi-layer approach, utilizing rapidly improving and advancing anti-counterfeiting technologies, can provide a great level of security. Currently, there are two general classifications of anti-counterfeiting technologies: "authentication technology" and "track and trace technology." Figure 4.1 lists some types of anti-counterfeiting technologies.

#### 1. Authentication Technologies

Authentication technologies are used to verify that a product is genuine and not a fake. Manufacturers are currently using a variety of authentication technologies on a product-by-product basis. Authentication technologies may be overt (easily visible to the eye, such as color shifting inks and holograms), covert (not visible to the eye, requiring special equipment to visualize, such as chemical markers, fluorescent inks, and invisible bar codes), or forensic (not visible to the eye, requiring sophisticated analytic equipment to identify, such as taggants and chemical markers). CBP and FDA agents, pharmacists, and consumers could easily identify overt technologies. However, special equipment (e.g., readers) or forensic analysis would be needed in order to authenticate a product, packaging, or labeling on which covert technologies are used. A few covert technologies allow rapid authentication, which could be useful at points of entry into the U.S.

Authentication technologies are useful and needed. However, we acknowledge the limitations as well—that any single technology can be defeated and the technologies used to protect drugs must be changed at frequent intervals. Moreover, incorporating authentication technologies into the product, packaging, or labeling may increase the cost of drugs. New manufacturing processes, feasibility testing, new quality control procedures, re-labeling, FDA approval of the new technology for the product, and the cost of the feature itself lead to additional costs. The costs are aggravated if such technologies are changed or modified at frequent intervals for any particular drug product.

#### 2. Track and Trace Technologies

Track and trace technologies assign a unique number to packages, cases, or pallets of drugs. This number is used to identify the product as it moves through the distribution chain. The unique number can be incorporated into an electronic tag (RFID) or into a barcode. The unique number is then "read" and associated with other product-specific information that is in a database, which can be used to verify that the product is authentic and list all of the transactions associated with the product, creating an electronic pedigree.

RFID involves the attachment of electromagnetic chips/tags that contain specific product information and a unique serial number. The system includes the tags, antennae affixed to the tags, readers to receive data from the tags, and an information database that is used to manage the data. RFID may be the most promising way to accomplish track and trace because it does not require line of sight "reading" and has numerous associated benefits, including inventory management, theft control, recall management, and reduced labor costs due to automation.

Figure 4.1

**Types of Anti-Counterfeiting Technologies**

| Authentication Technologies | Tracking Technologies |
| --- | --- |
| • Taggants<br>• Substrate<br>• Watermark<br>• Planchettes<br>• Optical Pigments & Dyes<br>• Inks<br>• Holograms | • Radio Frequency Identification Devices (RFID)<br>• Barcodes |

ures frequently to stay ahead of counterfeiters. There is a significant amount of development, implementation, and education that must be done in the domestic market to fully integrate authentication into the U.S. distribution system.

In order to assure the safety of the U.S. drug supply using these technologies, multiple, frequently changing authentication technologies would likely be needed for drugs eligible for importation. Additionally, one or more of these technologies would need to allow for rapid, accurate authentication at a point of entry into the U.S.

## B. Use of Anti-Counterfeiting Technologies to Control Domestic and Imported Drugs

### 1. Authentication

FDA's Counterfeit Drug Task Force report suggested the use of one or more authentication technologies on drug products, particularly those likely to be counterfeited. The Counterfeit Drug Task Force did not recommend that FDA require the use of authentication technologies. Rather, they noted that the decision to deploy authentication technologies is best made by the manufacturer, based on a product specific risk-benefit analysis. Manufacturers are just starting to incorporate overt and covert technologies in drugs likely to be counterfeited. However, an infrastructure for authenticating products with authentication technologies is not available yet in the U.S. To be useful for participants in the U.S. drug distribution system, all participants would have to have the ability to authenticate the product. This means that they would need appropriate devices to authenticate covert measures, know what the legitimate overt measures are on the genuine product and how to authenticate those measures, and develop an up-to-date system for communicating changes, since manufacturers will be changing authentication measures frequently to stay ahead of counterfeiters. There is a significant amount of development, implementation, and education that must be done in the domestic market to fully integrate authentication into the U.S. distribution system.

A manufacturer of a FDA-approved drug product may have to file an application supplement with FDA if authentication technologies are added to the product, packaging, or labeling. Authentication measures cannot simply be added to imported products without regard for the impact they may have on products they are intended to authenticate. These measures could affect the stability of the product, obscure important labeling information, leach into the product packaging, or otherwise affect the safety, efficacy, or integrity of the product. For these reasons, FDA would have to ensure that any newly applied authentication technology did not affect the quality of the drug product or its labeling.

We found that individual consumers are not in the best position to know what is fake and what is genuine. Also, the devices used to authenticate products are too expensive for home use.

In summary, widespread adoption of authentication technologies, while theoretically able to secure the U.S. drug supply, is a daunting task that could raise the cost of imported drugs, thereby reducing any expected savings from importation. Moreover, given the complexity of the technologies used, the time and expense to educate CBP and FDA agents, pharmacists, and wholesalers, and the sheer volume of products coming in, it is possible that consumers will still be exposed to

counterfeit, adulterated, or otherwise substandard drug products that are shipped into the U.S.

### 2. RFID

FDA did not issue any regulations nor did the agency require that the private sector implement RFID. Rather, FDA is relying on the momentum and enthusiasm demonstrated by the private sector to voluntarily implement this technology. Recently, FDA released a compliance policy guide[1] that will facilitate private sector RFID feasibility studies and pilot programs to evaluate the use of this technology.

At the moment, some wholesalers and retailers may find it economically infeasible to purchase the necessary electronic readers and software, leaving part of the distribution chain to rely on other means to document the chain of custody. However, even in these rare instances, these U.S. wholesalers and retailers will be doing business within the U.S. closed distribution system, which provides other checks and balances.

As discussed in Chapter 3 of this report, the current RFID efforts are focused on securing the domestic drug supply and a global RFID system is many years away. For RFID technology to ensure the security of imported drugs, all custodians of the product would have to be RFID-enabled, and RFID-enabled purchasers would need to report inaccurate or suspicious pedigrees upon receipt (e.g., if the last custodian listed on the pedigree was not the seller or there was a suspiciously long period spent at a particular custodian's facility). In addition, private sector feasibility studies are still underway to assess development, implementation, and use of RFID in the domestic market. Furthermore, it is virtually impossible for any single entity, government or otherwise, to mandate the use of RFID globally. Until RFID is universally adopted and used in both the domestic and international drug supply chain, it cannot be relied upon to secure the safety, efficacy, and integrity of the global market for imported drugs.

## C. Costs of Anti-Counterfeiting Technologies

We received inadequate information to assess the potential costs borne by entities in the distribution chain to utilize anti-counterfeiting technologies. Most of the technologies are still in the nascent stages of development and use, so any estimates at this point would be unreliable. It is clear, however, that use of these technologies may increase the cost of drugs, whether domestic or imported. The extent of this increase is unknown.

Some of the costs associated with using anti-counterfeiting technologies include:

- Purchase of the technology;
- Purchase of associated equipment (e.g., barcode scanners, RFID readers, access to electronic databases) and services;
- Integrating the technology into the manufacturing process;
- FDA review, if required, for the technology;
- Adopting new anti-counterfeiting measures as old ones are defeated;
- Creation of infrastructure throughout the distribution system; and
- Educating users, including CBP and FDA.

It is important to note that the costs of incorporating anti-counterfeiting measures are likely to be offset by the benefits that anti-counterfeiting measures will provide, for both authentication and track and trace technologies. These include:

- Improved inventory management and control (with resulting reductions in inventory expenses for distributors and pharmacies);
- Reduced labor cost due to automation;
- Reduced theft and product loss due to other causes;
- Reduced diverted product;
- Improved ability to recall product;
- Protection of drugs from intentional tampering; and
- Protection of drugs from being used in an act of terrorism.

1 FDA, "FDA Announces New Initiative to Protect the U.S. Drug Supply Through the Use Of Radio-frequency Identification Technology," November 15, 2004. Accessed on 12/1/04 at www.fda/gov/bbs/topics/news/2004/NEW01133.html.

# CHAPTER FIVE

# Agency Resources Associated with Drug Importation Activities

## Chapter Highlights:

FDA currently has about 3,800 employees assigned to field activities (e.g., inspections) involved in protecting the many thousands of products that make up the Nation's food, drug, biologic, medical device, and veterinary drug supply. Of the 3,800 field staff, 450 are involved in investigative import activities. Only a limited number of FDA inspectors are available to staff the 14 international mail facilities in the U.S., where they historically have had to inspect a small number of large commercial pharmaceutical imports. FDA managers have repeatedly noted that the large number of personal drug shipments coming into the international mail and courier facilities is overwhelming the available staff.

This report finds that despite significant efforts, including joint efforts with CBP and import alerts/bulletins, FDA currently does not have sufficient resources to ensure adequate inspection of current levels and categories of personal shipments of prescription drugs entering the U.S. With respect to commercial shipments, based on the information presented to the Task Force, FDA would need a meaningful investment, among other things, in new information technology and personnel, as well as appropriate standards to ensure adequate inspection of commercial quantities of drug products if importation were legalized.

## Key Points:

- There are not sufficient resources currently available to ensure adequate inspection of current levels of prescription drugs entering the U.S.
- To maintain adequate inspection of current levels of commercially imported pharmaceutical products requires significant investment in information technology and personnel, among other things.
- There is no realistic level of resources that could ensure that personally imported drugs are adequately inspected to assure their safety since visual inspection, testing and oversight of all personally imported prescription drugs are not feasible or practical at this time.

## I. WHAT WE SOUGHT COMMENT ON

As part of its study, Congress asked HHS to estimate agency resources, including additional field personnel, needed to adequately inspect the current amount of pharmaceutical products entering into the country. This estimate shall detail the number of field personnel needed in order to appropriately secure all ports of entry.

**To further explore this issue, we asked for comment on the following:**

- Information on prioritizing components of an importation program.
- Should federal appropriations, user fees, or other means cover the costs of a program?
- What programmatic changes would be needed to generate and collect data about imported products?
- Other than FDA, are there other federal agencies that would need funding? Any non-federal entities?

## II. WHAT THE COMMENTS SAID

There were no comments that provided information on prioritizing components of an importation program. Many comments stated that FDA would need significantly greater resources to examine imported products for quality, purity, safety, and effectiveness. One comment noted that FDA currently has inadequate resources to handle drug importation issues nationwide, and its investigative authority is limited relative to its ever-increasing law enforcement responsibilities. One comment stated that an importation program would demand incalculable resources. Another comment stated that the costs required to ensure the safety of imported drugs could be in the range of billions of dollars.

One comment suggested that importers should pay user fees to finance the cost of an importation program. Others disagreed, stating that those fees would be passed on to consumers, resulting in diminished cost savings. Some comments suggested that significant and continuing additional appropriations to FDA should finance the cost of an importation program.

Many comments stated that various government agencies other than FDA, including CBP, would also need adequate resources.

## III. DISCUSSION

### A. General

Because little information was submitted to adequately address this issue, we sought input and information from FDA. The analysis that follows is based on experience FDA has had with imported drugs.[1] To date, physical inspections have been conducted on a very small percentage of imports. In order to ensure these are done in a risk-based or "directed"[2] manner, information technology (IT) systems are critical. One of the reasons why regulating personal importation is extraordinarily difficult relates to the cost of screening imported drugs to evaluate whether they meet U.S. standards for safety and efficacy. Much of this cost relates to the legal requirements the agency must follow in screening these products and the time required to perform these functions. This chapter estimates this burden and also describes the IT systems currently in place. A more integrated and improved IT system is needed to cope with the volume of imported drugs entering the U.S. This would be critical under any scheme to legalize drug importation.

There are also additional resources expended by other agencies that are not reflected in this report. These include the resources associated with the import responsibilities of CBP, many of which precede the import responsibilities of FDA. CBP told us it has the primary responsibility for the 312 ports of entry into the U.S., and provides the initial IT system support that feeds information into FDA's Operational and Administrative System for Import Support (OASIS). Currently, CBP is involved in upgrading the IT systems relied upon by FDA. The U.S. Postal Service (USPS), the Department of

Justice (DOJ), and other Federal and state agencies also provide support and expend resources. For example, FDA has been involved in legal actions to address the illegal importation of unapproved drugs into the U.S., which require the assistance of DOJ and often other Federal and state agencies.

According to FDA, the vast majority of commercial pharmaceutical imports are reviewed electronically through OASIS. This database system includes information fed to it by CBP, derived from custom brokerage forms, as well as agency generated data. Although OASIS automatically screens FDA regulated products, a number of entries require additional manual review of information in FDA's Center for Drug Evaluation and Research (CDER), for Biologics Evaluation and Research (CBER), and Center for Veterinary Medicine (CVM) Center-specific registration databases. Currently, there is no IT integration of Center databases with OASIS. FDA told us that the current process to access these databases, review the information they contain, and make a decision based on that information is inefficient and difficult for the import reviewers in the field. Improvements could include enhanced processes for data retrieval from those databases. Improved IT capability would also help FDA personnel address import-related concerns that extend beyond the inspection of pharmaceutical products. To effectively share information, more information will need to be available to a wider audience.

Without adequate funding, such improvements will not be possible; however, it is difficult to predict the level of funding that would be needed. Improvements in IT for individual drug databases are also necessary to ensure adequate import screening. For example, improvements such as FDA's eDRLS (electronic drug registration and listing) initiative, impacting registration databases, would require significant investment of resources.

## B. Personnel

The responsibility within FDA to inspect imported drugs entering the U.S. falls primarily on the Office of Regulatory Affairs (ORA). We are aware that there are a number of activities beyond the border inspections carried out by FDA Centers/Offices that are critical to the success of the inspectional activities. Many of these non-border functions involve post-market compliance and import support activities carried out by the Centers. The Centers also provide financial support for the ORA border functions.

Inspection of imported pharmaceutical products is a labor intensive activity which requires a significant number of staff. This could possibly be reduced through the use of improved IT systems.

## C. Current Inspections

### 1. Commercial Inspections

There are 312 customs ports at which products and persons cross into the U.S. Of the 312 ports, approximately 95 are non-courier ports through which shipments of pharmaceutical product entered in FY 2003. There are multiple border crossings that are not fully staffed by FDA. There are some ports that are not covered at all, covered only for certain hours, for certain days, or on call from a distance. The total number of ORA personnel with responsibility for all FDA import activities is currently 450 investigators and 276 laboratory analysts.

Pharmaceutical products entering the U.S. includes bulk and finished dosage forms. All commercial shipments should be reviewed as "line entries" through OASIS. A line represents a broker's entry of an imported product. Each line can represent a varying amount of drug product. For example one line could be ten boxes or 200 boxes of the same drug product. The total number of lines for commercial pharmaceutical products was approximately 197,420 in FY 2003 out of over nine million total lines of imported products under FDA's jurisdiction. For FY 2004, FDA estimates that there will be 234,930 lines of pharmaceutical products.

After review of the commercial lines through OASIS, a certain portion of the entries may be

required to submit additional information or to undergo physical inspection. Of the approximately 197,420 lines of commercial pharmaceutical product, approximately 5,124 detentions occurred (excluding courier detentions discussed below). Each detention represents one line. Each detention required an individual determination that the detention met the legal standard required under section 381. Each detention also required FDA personnel to comply with the notice and due process requirements set forth in section 381. Detentions, investigations, and testing are all follow-up activities to the initial line entry review, are labor-intensive, and are heavily dependent on an adequate number of personnel.

We find that there are not sufficient resources available to ensure adequate inspection of current levels of prescription drugs entering the U.S for personal importation. The U.S. drug supply has experienced an increase in the incidence of counterfeit drugs and theft from both domestic and international sources. In addition, illicit diversion and theft of prescription drugs in domestic and international markets has increased dramatically in recent years causing an increased vulnerability to the introduction of counterfeit drugs and further compromising legitimate distribution channels. The public health implications stemming from this problem have never been greater, and the likelihood of a crisis increases exponentially as relatively fewer resources are available to address the problem. In order to address these anticipated increases, as well as expected increases in the volume of legally and illegally imported drugs, additional field personnel for FDA would be essential. Additional field personnel could be used to conduct examinations above the current level to address anticipated increases in volume. They also could do more "directed" inspections, where needed, to keep potentially harmful drugs from entering the U.S. distribution system or reaching the U.S. consumer.

According to FDA, new technology and replacement of obsolete equipment at FDA's Forensic Chemistry Center Laboratory is needed. Up-to-date laboratory instrumentation would allow more rapid screening of counterfeit pharmaceuticals for harmful chemicals or conditions that might cause a life-sustaining drug to be ineffective. Additional analytical chemists would provide forensic support for the increasing number of counterfeit and diverted pharmaceutical investigations conducted by FDA. Laboratory analysis is critical for providing the data needed by FDA to evaluate authenticity, assess risk, develop an appropriate response to protect the public from harm, and support criminal prosecutions.

### 2. Personal Importation

Personal shipments of imported drugs may not contain the U.S.-approved formulations or include the U.S.-approved label and required patient information. FDA exercises enforcement discretion through its personal importation guidance policy (described in the background section of this report) to allow certain products into the U.S. These personal shipments enter through courier/express consignment ports, international mail facilities, and various ports as personal baggage with travelers, including "foot" traffic at border crossings. Most drugs coming in through personal shipment, however, do not comply with FDA's personal importation policy. Even with any reasonable amount of additional resources, FDA would not be able to adequately screen these shipments as explained below.

There are 14 international mail facilities and a large number of ports through which mail and travelers enter with personal pharmaceutical products. The greatest number of personal drug importations are shipments sent through international mail facilities, with lesser but significant amounts coming through land borders. There is no data systematically collected by FDA or CBP on the amount of mail that comes into the international mail facilities that contains drugs and thus it is difficult to provide accurate counts of non-commercial pharmaceutical imports. Nonetheless, FDA and CBP were able to provide various estimates of the mail by extrapolating data collected from several mail blitzes conducted at the various international mail

facilities. These blitzes are described in more detail in Chapter 1 of this report. In addition, IMS data provides some insight into the volume of personal prescription drug importations from Canada. These data, discussed further in Chapter 1 of this report, provide a perspective on the resources required to inspect the current level of personal importations and what might be necessary if some type of personal importation were made legal. By any measure, there has been a steady increase in the volume of personal importations and in the number of detentions issued by FDA.

FDA told us that there are no data systematically collected on the number of mail packages set aside daily by CBP for examination by FDA. FDA does collect some data in OASIS on mail and baggage inspections conducted by the agency. The data reflect the number of lines examined and the number of lines detained, but not the number of individual packages reviewed. The data, however, provide some general information on the number of illegal, unapproved drugs that continue to flow into the U.S. as personal importations that are detained by FDA. These data are contained in Figure 5.1 provided by FDA. The number of lines inspected is based only on estimates provided by FDA field personnel after the inspections of the packages. The number of detentions is based on the actual number of notices sent to individuals detailing the number of lines of product detained.

FDA's blitz data also provides some insight into the volume of illegal personal importations that continue to flow through the international mail facilities and also provides a perspective on the time and costs associated with the review and processing of packages. FDA estimated that it took ten minutes to open and process a single envelope with one non-labeled suspect drug and an estimated three hours to open and process a large package with multiple suspect drugs not labeled in English. This processing did not include the procedures involved with detaining suspect packages.

Figure 5.1

| Mail and Baggage | Detentions of Unapproved Drugs (Based on Lines) | Number of Lines Inspected by FDA Containing Drugs Including Antibiotics (Estimated by Field Personnel) |
|---|---|---|
| ***FY 2003*** | 12,911 | 14,280 |
| ***FY 2002*** | 7,915 | 8,526 |
| ***FY 2001*** | 2,447 | 3,405 |

Figure 5.2 provided by FDA, details two examples of the FDA staff time required to process the 300 packages set aside by CBP for FDA during the November 2003 blitz activity. The figure provides the average time and cost per package to process the packages. Typical activities conducted at the mail facility include opening the mail packages, examining the products enclosed, searching references to determine the nature of the product, recordkeeping, photographing the product, and securing the product in locked wall lockers at the facility. In some instances, samples also were taken for testing. The support and follow-up activities noted in the chart include processing detentions, refusals, releases, and notices.

Figure 5.2

These figures provide the basis for estimating the

| | Seattle District Office | Southwest Import District Office |
|---|---|---|
| Days of Blitz | 11/4-7/2003 | 11/4-6/2003 |
| FDA staff (full or part-time at mail facility) | 6 | 3 |
| Hours (working at facility on blitz) | 88.75 | 44 |
| FDA staff (full or part time outside of mail facility) | 9 | 3 |
| Hours (spent in support/follow-up including processing detentions) | 757.5 | 790 |
| Total Hours (mail facility and support/follow-up) | 846.25 | 834 |
| Average hours spent per package (including support activity) (300 packages examined) | 2.82 | 2.78 |
| Average cost of examining and processing each package | $267.90 | $264.10 |

resources necessary to ensure the adequate inspection of current levels of personally imported drugs. Current estimates of personal mail importations from Canada alone are approximately five million packages per year (as described in more detail in Chapter 1). There is no systematically collected data, however, that is available to estimate the number of personal importations from countries other than Canada. Using the blitz data and the figure of five million packages from Canada, we estimated that approximately 50 percent of the mail packages enter from countries other than Canada. This equates to ten million packages entering the U.S. with imported prescription drug products based on the estimates from FDA's prior experience with personal shipments, to examine ten million packages would be estimated at nearly $3 billion ($3 billion = $264.10 per package x 10 million packages). Even assuming that a different and lower level of inspection could be considered adequate, and assuming additional resources are available to upgrade IT systems, the costs would be significant.

The number of FDA employees assigned to the international mail facilities has increased over the last few years. The total number of ORA staff who work at international mail facilities is currently 16.91 for most of FY 2004. At one facility, coverage in 2001 was once a week with one investigator; in 2004, this facility has full-time coverage with three investigators. The total number of FDA staff hours at international mail facilities is noted in Figure 5.3.

FDA also shared with us data for inspections and detentions conducted at courier facilities. There are both commercial and personal shipments shipped through courier facilities, so it is difficult to determine the exact number that are strictly personal importations. FDA field offices estimate that a large portion of the detentions are for personal, not commercial, importations. There are 29 courier/express consignment ports through which such drugs entered. Personal shipments through the 29 courier/express consignment ports are reviewed as line entries similar to commercial line entries. The Figure 5.4 data captures both commercial and personal importations and detentions.

Figure 5.3

FY 2004* - FDA Staffing of International Mail Facilities

| District Office | Mail Facility Covered | Actual Resources (Full Time Equivalent) |
|---|---|---|
| **NYK-DO** | JFK | 7 |
| | Buffalo | |
| | Newark | |
| **CHI-DO** | Chicago | 2 |
| **DET-DO** | Detroit | 0.6 |
| **FLA-DO** | Miami | 2 |
| **LOS-DO** | Carson (Los Angeles) | 3 |
| **SJN-DO** | Virgin Islands | .05 |
| **SAN-DO** | Oakland | 2 |
| | San Francisco | |
| | Honolulu, HI | |
| **SWID** | Dallas-Fort Worth | 0.6 |
| **SEA-DO** | Tacoma | 0.2 |
| **TOTAL** | | **16.91** |

Source: FDA
*The information was collected during FY 2004 but may not reflect FDA staff activity that occurred during the entire FY 2004.

Figure 5.4

| Courier | Detentions of Unapproved Drugs (Based on Lines) | Lines Containing Drugs |
|---|---|---|
| ***FY 2003*** | 6,588 | 91,766 |
| ***FY 2002*** | 11,787 | 64,967 |
| ***FY 2001*** | 5,710 | 42,326 |

## D. Activity Cost Estimates

FDA has provided us with the current average costs for individual agency work tasks associated with ORA inspection of imported drugs (Figure 5.5). This is a cost based on current levels of total activity and the total number of ORA staff assigned to the duties noted. These figures reflect staff and associated costs for FY 2003.

While these costs may be used to estimate the costs of performing these specific activities as the volume of the pharmaceutical imports changes, they would not be accurate predictors of total costs if volume were to increase dramatically. This is true because costs will rise due to inflation and other pressures in the future years. Personnel costs, facilities, transportation, communications, IT and security related costs are likely to change the costs in future years. The costs reflected in the chart below are based on the current compliance tools available and the current level of enforcement. As FDA changes its operations to address the risks of increasing volume, the costs will change. Compliance activities may consume more import resources than they do now as the volume and types of compliance activities change. For example, the cost of performing an import field exam to determine if a proposed drug entry appears to violate the FD&C Act is one way to estimate the cost of preventing that shipment from entering domestic commerce. However, it does not estimate FDA's costs to further investigate that product, should it become necessary.

Figure 5.5

Calculation of Costs for Individual Inspection Activities FY 2004

| **Inspections of Imported Pharmaceutical Products** | |
|---|---|
| Type of Activity | Estimated Cost Per Task for FY 2004 |
| Line Entry Review | $11 |
| Detentions | $76 |
| Import Field Exams | $76 |
| Import Sample Collection and Analyses | $2,062 |
| Counterfeit Analyses | $3,729 |

1 Drug importation may also impact other U.S. laws and regulations that are enforced by agencies, such as CBP and the U.S. Postal Service, however, an impact analysis for these agencies was not performed for this report.

2 A "directed" inspection is an in-depth inspection in which an investigator has been charged with obtaining specific information about an FDA-regulated commodity. Such an inspection may include obtaining detailed information concerning the origin of a product, its manufacturing, shipping and storage conditions, documentation of the chain of custody of the product, etc. It may also include the collection of a physical sample for subsequent analysis by the Agency.

# CHAPTER SIX

# Role of Foreign Health Agencies

## Chapter Highlights:

Just as the U.S. is responsible for the safety and effectiveness of drugs made available to its citizens, foreign governments give priority to ensuring the safety of drugs used by their citizens. Foreign governments have little incentive and limited resources to ensure the safety of drugs exported from their countries, particularly when those drugs are transshipped or are not intended for import. No country expressed any interest or willingness to ensure the safety and effectiveness of drugs exported from their country in any expansion of legal U.S. importation. Although we specifically solicited them, few comments were submitted by foreign governments, and none outlined a specific strategy for new steps to collaborate with the U.S. government on the effective oversight of importation, suggesting that they are not willing or do not have the means to ensure the safety of exported products and that the primary safety responsibilities would have to remain with the U.S.

## Key Points:

- The U.S. is responsible for the safety and effectiveness of drugs made available to its citizens.
- Foreign governments give priority to ensuring the safety of drugs used by their citizens. Foreign governments have little incentive to ensure the safety of exported drugs.
- The lack of meaningful comments or response to direct inquiries from foreign governments suggests that foreign governments are not willing or do not have the means to ensure the safety of exported products.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to determine the extent to which foreign health agencies are willing and able to ensure the safety of drugs being exported from their countries to the U.S. To further explore this issue, we asked for comment on the extent to which foreign health agencies are willing or able to implement new or additional protections to ensure the safety of exported or transshipped drugs.

## II. WHAT THE COMMENTS SAID

One foreign health agency commented that the regulation of drug safety worldwide is based on the premise that each country is responsible for the safety of products made available to its citizens. This foreign health agency, as well as several provincial regulatory agencies, noted that the law in their country would not allow for the export or transshipment of products that did not comply with its own laws. We received conflicting information as to whether it is legal for Canadian pharmacies to refer American consumers to other countries.

Multiple comments stated that fewer protections exist for exported or transshipped products. One comment examined the laws in 25 countries worldwide and found that, while most impose regulatory requirements related to the domestic distribution and sale of pharmaceutical products, almost all countries, including the U.S., impose a lesser level of regulation on products intended for export to other countries and most countries do not regulate products that are merely transshipped through their territory. This comment concluded that, based on its examination, the laws in many of the countries surveyed cannot guarantee the safety, quality, or efficacy of products exported to the U. S.

No comments directly addressed the extent to which foreign health agencies are willing or able to implement new or additional protections to ensure the safety of exported or transshipped drugs. One comment suggested the development of international standards and agreements that confirm and enforce patient care as the primary goal, such as the development of a mutual international recognition for the licensing of wholesalers, pharmacists and pharmacies located in Canada and the U.S., and development of memoranda of understanding regarding which laws are enforced and enforceable for the safety and benefit of the patient, as many cross-border businesses require disclaimers, agreements and powers of attorney that remove patient autonomy as a condition of sale. This comment also suggested that the cross-border pharmacy sale of drugs under the authority of a prescription should be limited or temporarily suspended until U.S. and Canadian authorities establish an information exchange process to openly and reliably share information.

## III. DISCUSSION

The top priority of each foreign health agency is to ensure the safety and effectiveness of drugs for its own citizens, as it is in the U.S. Even if foreign health agencies were able, they have little incentive to guarantee the safety and effectiveness of exported drugs, given their limited resources and the possibility of drug shortages for their citizens. Even if foreign health agencies were willing to help ensure the safety and effectiveness of drugs exported from their countries to the U.S., FDA would still need to verify in some way that the drugs are safe and effective under U.S. standards for U.S. consumers.

As the comments highlighted, the ability of foreign regulatory authorities to ensure the safety and effectiveness of exported drugs is complicated by two distinct, practical problems. First, most countries impose a lesser level of regulation on products intended for export to other countries, such as the U.S. Second, many countries do not regulate products that are merely transshipped through their country. In both cases, the result is that most foreign governments currently do not have the legal or regulatory tools available to guarantee the safety, quality, or efficacy of products exported to the U.S.

Many Americans import prescription drugs from Canada or Mexico, due to their proximity to the U.S. Canadian Federal and provincial law is based on the premise that each country is responsible for the safety of drug products made available to its own citizens. Health Canada does not assure that products being

sold to U.S. citizens are safe, effective, and of high quality, and does not intend to do so in the future.[1] We have no indication that Mexico would be willing to do anything different.

In addition to Health Canada, we also heard from three Canadian provincial regulatory authorities: the Manitoba Pharmaceutical Association, the Quebec Order of Pharmacists, and the Ontario College of Pharmacists. Overall, the provincial regulatory authorities told us that pharmacists within their jurisdiction are of the same competence as American pharmacists and that products that are Canadian-approved would be safe for American consumers. Even with safety protections in place, the provincial regulatory authorities pointed to issues raised by importation such as transshipment and illegitimate websites.

The Manitoba Pharmaceutical Association identified patient safety and product quality and safety as a major concern and provided us with a list of points that would need to be addressed if the importation of drugs from Canada is legalized. Additionally, this

**If parallel importation works for the European Union, why can't it work for the U.S.?**

The European Union (EU) is comprised of 25 countries or "Member States." One of the goals of the EU is to promote the free flow of goods among Member States, much as the U.S. Constitution does for trade between the states in the U.S.

The EU Charter permits a wholesaler in Member State "A" to buy prescription drugs from a wholesaler in another Member State "B" and sell those products in Member State "A." This practice is called "parallel importation" or "parallel trade." Parallel traders buy pharmaceuticals in Member States with lower prices (usually imposed by the government) and sell them in other Member States with higher prices or government reimbursement rates.

Importantly, the EU has established a regulatory scheme for pharmaceutical products, which governs market authorization, distribution, and handling among the Member States. The EU's European Medicines Agency (EMEA) is responsible for protecting and promoting the public health and brings together the scientific resources of the EU Member States to ensure a high level of evaluation and supervision of medicines in Europe under one marketing authorization, including one authorized physician label and patient leaflet, which is valid throughout the EU. This centralized regulatory oversight is critical to ensuring that pharmaceuticals flowing between EU countries are safe, effective, properly labeled, and manufactured in a uniform manner.

A drug importation model in which consumers import drugs into the U.S. from Canada or other countries is very different from the practice of parallel trade between the Member States of the EU. The correct analogy for the sale of drug products from one Member State (such as Spain) to another Member State (such as Germany) is not the sale of drug products between Canada and the U.S., but rather the sale of drug products from one U.S. state to another. This is because the laws and regulations governing the marketing authorization, including labeling and manufacturing of the products, is controlled at the Federal/European level and assures that the product is indeed the same whether it is sold in Maryland or Virginia (or in Spain or Germany). However, the laws and regulations between the U.S. and other countries are not the same, and there is no central regulatory body that has authority over the U.S. and the other country. Therefore, there is no assurance that drug safety, efficacy, purity, potency, handling, labeling, manufacturing, and storage would be the same between the U.S. and other countries, unlike the assurance that exists as there is under the parallel importation/trade system in the EU.

province recommended that importation be limited or temporarily suspended until these issues are resolved. The Quebec Order of Pharmacists stated that although they exercise oversight over the professional practice of pharmacy, they cannot control drugs that transit through their border that are not intended to reach their consumers. The Ontario College of Pharmacists told us about the increasing number of illegitimate pharmacy websites. In some cases, enforcement action is taken; however, we were told that such actions are extremely resource intensive.

The U.S. does work closely with Canada and Mexico to determine ways to work together to promote and protect the public health. In February 2004, Federal agencies in Canada, Mexico, and the U.S. signed a trilateral cooperation charter to increase communication, collaboration, and the exchange of information among the three countries in the areas of drugs, biologics, medical devices, food safety, and nutrition to protect and promote human health.[2]

We also solicited input from European health agencies for inclusion in this report. Switzerland's health agency, Swissmedic, stated that drugs imported into the U.S. from licensed Swiss pharmacies would meet Swiss requirements for safety, efficacy, and quality.[3] Swissmedic noted, however, that transshipment of drugs through Switzerland makes the distribution system vulnerable to counterfeiting and fraud. Swissmedic concluded that although they can do a lot to help guarantee the safety of drugs exported to the U.S., they cannot give complete assurance that drugs imported by U.S. consumers would be safe and effective, or otherwise meet U.S. standards.

We requested comment, but did not receive information, from the European Commission (EC). One comment provided detailed information on Europe's practice of parallel trade of pharmaceuticals across national borders within the European Union's (EU) internal market. Only two foreign health agencies, Health Canada and Swissmedic, provided information to us on their willingness or ability to assure the safety of drugs exported to U.S. consumers. If foreign health agencies were willing to ensure the safety and effectiveness of drugs exported from their countries to the U.S., one would expect a greater global response. On the other hand, if a foreign health agency were interested in ensuring the safety and effectiveness of exported drugs, international agreements such as mutual recognition agreements (MRA) and memoranda of understanding (MOU) would be useful tools to set standards for drug safety and effectiveness.

An MRA is an agreement between two countries that provides for official mutual reliance on portions of a foreign regulatory system. Development of MRAs is extremely time-consuming and would require significant resources to put in place. Currently, one MRA is in place for the purpose of assisting the U.S. with certain aspects of the drug review and approval process (e.g., GMP inspections); however, we have been told by FDA that it has not yet entered the operational phase because the U.S. is pursuing other approaches to drug agency cooperation at the moment. In addition, it would no doubt be problematic for the U.S. to rely completely on foreign regulatory systems to review and approve drugs for U.S. consumers.

MOUs are non-binding arrangements between governments to carry out programs of cooperation; in this case, cooperation with respect to a drug importation program. In the importation context, the governments of exporting countries could agree to ensure that products from their country destined for the U.S. meet certain safety standards. As mentioned above, for a variety of reasons, foreign health agencies have little incentive to ensure the safety and effectiveness of drugs bound for the U.S. market, making MOUs difficult to negotiate. Even if the U.S. were able to enter into an MOU with a foreign health agency to help ensure that drugs exported to the U.S. meet FDA standards, FDA would still need to obtain such verification. This might involve FDA inspections of certain foreign facilities, FDA review of certificates of analysis, FDA testing of certain products, etc. Such inspections by FDA of foreign facilities in another country would likewise require an agreement between FDA and the regulatory authorities of the other country to permit FDA to carry out inspections in that country.

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1 Health Canada, Letter from Diane C. Gorman, Assistant Deputy Minister, to Richard H. Carmona, Surgeon General of the U.S. Public Health Service, June 1, 2004.

2 Food and Drug Administration Talk Paper, "Canada, Mexico, and the United States Sign Charter," February 27, 2004. Accessed at www.fda.gov/bbs/topics/NEWS/2004/NEW01028.html on 11/4/04.

3 Swissmedic, Letter from Klaus-Joerg Dogwiler, Executive Director, to Murray M. Lumpkin, Senior Associate Commissioner for International Activities and Strategic Inititatives, U.S. Food and Drug Administration, August 27, 2004.

# CHAPTER SEVEN

## Effects of Importation on Prices and Consumer Savings

### Chapter Highlights:

Consumers seek to import prescription drugs from other countries in part because they believe they can save money if they purchase their drugs from outside the U.S. In many instances, U.S. consumers have been able to purchase from abroad foreign versions of U.S.-approved brand name drugs at lower prices. However, based on an analysis of actual data on drug prices and volumes, this report finds that total savings to consumers from legalized importation under a commercial system would be a small percentage relative to total drug spending in the U.S. (about one to two percent). These savings are much smaller than some specific international comparisons of retail prices for certain drugs might suggest. Under any safe, legalized commercial importation program, when the scope is limited, intermediaries would likely capture a large part of the price differences. (This is based on evidence from European countries where some form of importation is legal.)

This report also finds that generic drugs are often cheaper in the U.S. compared to international prices for similar drugs. Other independent studies have reached similar conclusions. The prices foreigners pay for generic drugs are on average 50 percent greater than Americans pay for generic drugs. Furthermore, there is evidence that greater use of U.S.-approved generic drugs by Americans could reduce drug spending by billions of dollars annually. In addition, to the extent that prescription drugs are eligible for importation from the same company at a lower price than in the U.S., potential quantity constraints imposed by manufacturers or foreign governments would limit the eligible supply and the benefits to U.S. consumers.

### Key Points:

- Total savings to drug buyers from legalized commercial importation would be one to two percent of total drug spending and much less than international price comparisons might suggest. The savings going directly to individuals would be less than one percent of total spending. Most of the savings would likely go to third party payers, such as insurance companies and HMOs.
- Under legalized commercial importation, intermediaries may capture a large part of the potential savings.
- Savings from legal commercial importation would likely to be limited because the total volume of imports may not be as large as expected.
- Estimates of direct savings for E.U. countries where importation is legal range from less than one percent to 2.5 percent of total drug spending in those countries.
- About 30 percent of total drug spending may be unchanged by legalizing commercial importation because about that much is now spent on products that are inappropriate for importation (e.g., drugs that are inhaled during surgery, injectables, biologics, and controlled substances) or generally unavailable abroad for less (e.g., generic products).
- The prices foreigners pay for generic drugs are on average 50 percent greater than the prices Americans pay for generic drugs. Furthermore, there is evidence that greater use of U.S.-approved generic drugs by Americans could reduce drug spending by billions of dollars annually.
- Americans have a greater choice of newly launched pharmaceutical products than foreigners. In recent years, more than 40 percent of new drugs were launched first in the U.S.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to assess the potential short- and long-term impacts on drug prices and prices for consumers associated with importing drugs from other countries.

### To further explore this issue, we asked for comment on:

- What is the evidence on savings for patients from existing parallel importation programs?
- In legalized systems of parallel importation, to what extent do international differences in drug prices translate into price differences "captured" by middlemen or arbitragers?

## II. WHAT THE COMMENTS SAID

A few comments stated that legalizing Canadian drug importation could save a significant amount of money. Some of these comments presented data that retail Canadian drug prices average 40 percent less than U.S. retail prices.

Many comments expressed concern for the short-term impact on the Canadian drug supply. Some evidence was presented that some Canadian provinces are experiencing shortages for some drugs and this trend is increasing. These comments noted the discrepancy in the size of the U.S. market and the Canadian market and suggested that if the drugs intended for Canadians were exported to the U.S. legally and on a commercial basis, then the Canadian drug supply will suffer and Canadian patients will be at risk. Health Canada[1] announced that potential shortages might arise from legalizing commercial importation. Some comments asserted that up to 40 percent of the Canadian drug supply is diverted to the U.S. A few comments noted that despite agreements between drug manufacturers and Canadian wholesalers and pharmacies that drugs will not be sold to U.S. citizens, drugs are being diverted to export pharmacies.

A number of comments stated that drug importation would not significantly reduce drug prices in the U.S. Some of the reasons mentioned include the belief that the drugs will pass through so many hands that each transaction will add cost to the drugs and ultimately drive the cost back up to U.S. prices.

Several comments cited research from the London School of Economics, which quantified the economic impact of parallel trade in six countries. These researchers found that there is little evidence of savings to consumers or inter- or intra-country competition effects or price convergences. One comment stated that the London School of Economics study is flawed because the authors did not look at all products that were imported under parallel trade and only examined a small portion of those drugs that are imported.

Other comments suggested that parallel trade could work in the U.S. and offered ways to construct a parallel import scheme. For example, a few of these comments stated that parallel importation should be limited to countries that have regulatory systems comparable to the U.S.

## III. DISCUSSION

### A. Overview

Based on these public comments, extensive review of both the published peer-reviewed literature and analysis of proprietary data from IMS Health, Inc.,[2] we have assessed the effects of legalizing commercial importation on U.S. prices and consumer savings. We obtained and analyzed proprietary data from IMS on prices, sales, quantities, and other information for ten countries including the U.S. We also considered price data reported to CMS under the Medicaid program. Throughout this chapter we will discuss the IMS data; Appendix A provides a detailed discussion of how our data were selected. We assess a change in policy that would allow drugs equivalent to FDA-approved products to be imported into the U.S. from a significant but unspecified set of countries belonging to the Organization of Cooperation and Economic Development.

Although many proponents of legalizing drug imports argue imports would greatly help U.S. consumers, the existence of lower prices abroad is not sufficient to ensure significant savings from legalizing commercial importation. The volume and type of foreign drugs that may be imported is also critical in determining total savings — a measure valuable to national policy-makers. In addition, the importers' share of total savings, their compensation for the costs of finding and shipping the drugs, bearing liability risk, and complying with applicable safety regulations, may be quite large. In this chapter, we analyze the impact of these factors on the likely savings to drug buyers. We find that savings from legalizing drug imports would likely be a small percentage of total drug spending, a finding similar to that of the Congressional Budget Office.[3]

Savings from legalized commercial importation will likely be small as a percent of total drug spending because of three factors.

- U.S. drug buyers—families, HMOs and insurance companies, etc. —may get a discount much less than the full difference between U.S. prices and foreign prices. U.S. drug buyers may get discounts of only 20 percent or less, with the rest of the difference between U.S. and foreign prices going to commercial importers that find less expensive drugs abroad and import them in compliance with applicable safety regulations.
- About 30 percent of total drug spending may be unchanged by legalizing commercial importation because about that much is now spent on products that are inappropriate for importation (e.g., drugs that are inhaled during surgery, injectables, biologics, and controlled substances) or generally unavailable abroad for less (e.g., generic products).
- The foreign supply of patented brand-name drugs may be limited relative to the total volume of such drugs consumed in the U.S. market. Imported drugs may be around 12 percent of total use of such drugs in the U.S., depending on the scope of any importation program, because drug companies have incentives to impede exports and some foreign governments may curtail exports to preserve access to low-priced drugs.

These figures, which are derived and discussed below, suggest that overall savings from legalizing commercial drug importation may be small—one to two percent of total drug spending.[4] This amount would be between roughly $2 billion and $4 billion per year, based on U.S. spending in 2003 on pharmaceutical products described below.

Individual consumers (as distinct from insurance companies and government programs that buy drugs) would enjoy only some of the total savings because only a small fraction of all spending on drugs comes directly out of their pockets. The MMA, when fully implemented, will offer drug coverage to the over-65 population. In 2001, 26 percent of all spending on retail prescriptions was paid for out-of-pocket by people under-65 years of age.[5] Thus, the total savings from legalized importation that go directly to consumers may be less than one percent of total spending.

The finding that overall savings will likely be a small percentage of overall drug spending is consistent with the observation that some individuals may enjoy significant savings. Uninsured people who buy chronic use patented name-brand drugs on a regular basis may enjoy meaningful savings if they are able to buy safe and effective foreign versions of U.S. drugs for significantly less than what they would pay for U.S. drugs. This analysis finds, however, that savings in aggregate may be small relative to overall spending on drugs.

To put in perspective the idea that consumer savings from commercial importation are small, we note that potential savings from commercialized importation may be less than the savings available to U.S. drug buyers by switching from more expensive brand-name products to exclusive use of FDA-approved generic products already on U.S. pharmacy shelves. We base this conclusion on an assessment of the magnitude of such savings using detailed information on products containing 29 unpatented molecules described later in this chapter. As described in Appendix E, we find evidence that savings from full use of FDA-approved generics could reach billions of dollars per year, or a few percentage points of total drug spending. An analysis of IMS data from 2003,

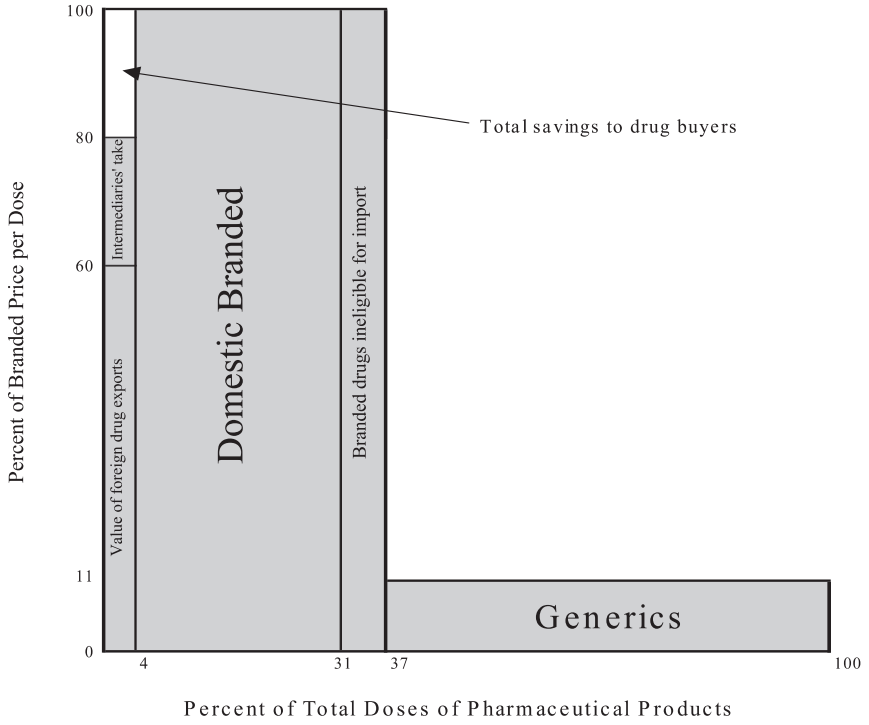
combined with estimates prepared by CBO regarding generic drug utilization, indicate that in 2003, U.S. consumers could have saved as much as an additional $17 billion on U.S.-approved drugs by purchasing available generic substitutes for brand name drugs.

We note that estimates presented in this chapter are quite uncertain because of data limitations. There is little relevant precedent for legalizing commercial importation of pharmaceutical products. Alternative assumptions about particular parameters, especially the amount of foreign drugs that might be imported into the U.S., could affect overall estimates of savings. Alternative assumptions consistent with the data presented here would do relatively little to change the bottom line that savings to drug buyers would be small as a percent of total drug spending.

The relationship between perceived large international price differences and our findings of small likely savings is illustrated in Figure 7.1, which reflects the relative prices and volumes of branded and generic drug products in the U.S. in 2002. Distances along the horizontal axis in Figure 7.1 measure the percent of doses prescribed per year, the vertical axis measures the price per dose expressed as a percent of the branded price per dose, and area reflects total spending on prescription drug products. Generic drugs account for approximately 63 percent of total doses prescribed, but slightly less than a sixth of all spending, according to IMS Health, IMS National Sales Perspective (TM), 2002, because they are less expensive. Spending on some branded drug products accounting for six percent of all doses will be unaffected by importation, either because they are drugs

Figure 7.1

**Savings to Drug Buyers From Legalized Commercial Importation May Be Small Relative to Total Drug Spending**




Source: Analysis completed by HHS based on data from IMS Health, IMS National Sales Perspective (TM), 2002, extracted September 30, 2003.

of special concern (e.g., biologics and injectables), or because foreign versions of a U.S. drug are produced and manufactured abroad by a foreign corporation that has only a licensing agreement with the FDA-approved manufacturer. Most spending would continue to be on domestic branded drugs and at prices unaffected by importation because foreign supply is small and limited relative to U.S. demand. Drug manufacturers commonly charge different prices to different buyers in the U.S. Spending on the four percent of total doses that would be imported would not be at the foreign price, which is approximately 60 percent of the U.S. price, but instead at an imported price significantly above the foreign price because of markups by intermediaries. Savings to U.S. drug buyers would be the unshaded rectangle at the top left of the figure. Given these assumptions, savings to all drug buyers would amount to less than two percent of total drug spending. Most of the savings would go to third party payers, such as insurance companies and HMOs. Savings that go directly to consumers, as opposed to insurance companies and other third-party payers, may be a fraction of one percent.

In the rest of this chapter, we gauge 1) potential discounts on foreign drugs, taking both foreign prices and intermediaries' markups into account, 2) spending on drugs likely to be unaffected by importation because the drugs are unsuitable for importation or unavailable abroad for less, and 3) the likely volume of imported drugs, given the incentives that manufacturers' and foreign governments will face to restrain exports.

## B. Potential Discounts to U.S. Drug Buyers

A first step in assessing the potential consumer savings from commercial importation is measuring existing price differences among countries. This is not a simple exercise, however, as there is no single definition of a drug nor is there a single measure of price. A second step, presented at the end of this section, is to estimate how much intermediaries may charge for importing foreign drugs. Together, these estimates suggest the potential discounts to U.S. drug buyers for imported drugs.

***Why do individual consumers find that they do save money when they buy brand name drugs from Canada, but this report says there will be little or no savings?***

Individual consumers who purchase brand name drugs from Canada may, in particular cases, save money. However, under a legalized commercial importation program, the system costs associated with the development, implementation, and additional safeguards needed to ensure safety and efficacy of the drug products, will affect the potential savings that an individual consumer would enjoy. Experience with other countries that do permit importation shows that intermediaries (exporters/importers) will take a large portion of the price differences. Additionally, because the importable supply will be limited, there may be an increased demand for products exported from Canada, thus, increasing their price. Finally, third party payers (e.g., HMOs, insurance companies) will also take a portion of the potential savings before the drug product reaches the consumer.

### 1. Existing Research

The academic literature includes several detailed, systematic, and methodologically sound comparisons of international drug prices. F.M. Scherer[6] provides a useful and recent discussion of pricing and research and development incentives. Perhaps the most comprehensive work, by Patricia M. Danzon and Michael F. Furukawa,[7] indicates that in 1999, Japanese prices were higher than U.S. prices, and other foreign prices ranged from six percent to 33 percent lower than U.S. prices. While they assess a variety of price measures, they focus on estimates that define drug products as a specific molecule and indication, or a specific molecule and indication and strength. They use dose as a measure of quantity, impute discounts of approximately eight percent to U.S. branded drug prices, and rely on manufacturer prices, rather than wholesale or

retail measures. These results are for a sample that includes both branded drugs available from a single innovator company and generic drugs marketed by companies that compete after patents have expired.

International price differences vary according to whether drug products are produced by innovator companies holding patents (brand-name drugs) or by companies that market products as generics after patents have expired. Danzon and Furukawa state that for brand-name drugs, France and Italy have the lowest prices (approximately 40 percent below U.S. levels), Canada is nearly as low, while the U.K. prices are about 25 percent below U.S. levels.

Danzon and Furukawa report U.S. generic prices are significantly lower than foreign prices. In Italy, generic prices are nearly double the level of U.S. generic prices. Earlier research by FDA also found that generic drugs were generally cheaper in the U.S. than in Canada.[8]

***Why are drugs cheaper in Canada?***

Unlike the U.S., many countries, including Canada, regulate prices for drug products. Prices are regulated directly or indirectly through controls on reimbursement, limits on overall spending, or limits on the rate of return on capital.[9] For example, Canada's Patent Medicine Prices Review Board regulates the prices manufacturers may charge in Canada. Manufacturers who launch a product in the U.S. often may not charge the same price in Canada as they do in the U.S. due to these Canadian government controls.[10]

## 2. Our Analysis of Price Differences

Our own assessment of the prices of different drugs reaches similar findings. Comparing the prices manufacturers charge, we find that foreign prices for top-selling[11] brand name products that represent nearly 45 percent of the U.S. market in 2002 were approximately 60 percent[12] of the U.S. price during 2003. For this estimate, prices are dollar per kilogram of the active ingredient, with an adjustment for the salt content. Appendix A provides discussion of how the top-selling drug products were selected for this study.

To summarize price differences, we calculate price indices using U.S. quantities (kg or IU) as weights.[13] U.S. quantities are used because we are interested in effects on U.S. buyers.

While the IMS data we use—from its MIDAS™ database—are widely acknowledged to be the best available for systematic international price comparisons, they do not include payments and accounting adjustments that do not appear on invoices. We adjust for discounts and rebates using data from CMS on average manufacturer's price, a measure that reflects prices for all non-Medicaid sales to retail pharmacies and some hospitals with independent pharmacies. We also adjust prices for Medicaid discounts by using the share of total retail drug spending by Medicaid, based on prescription sales data provided by IMS Health, IMS National Prescription Audit (TM), 2003, and the Medicaid price net of rebates, as reported by CMS. Our assessment of these prices for the top-selling products in our dataset indicates that market prices including Medicaid are slightly less than the IMS invoice prices for comparable transactions.

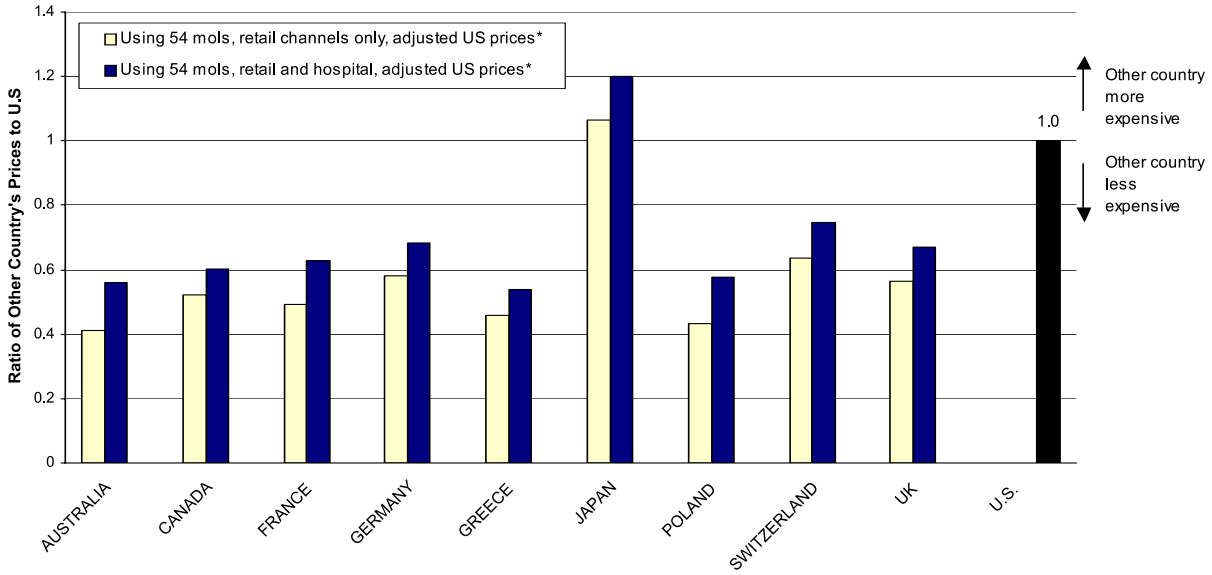
Applying these off-invoice adjustments to manufacturers' prices to both the retail sector and the hospital sector suggests that manufacturers' prices to hospitals and retail distributors together are somewhat lower than prices to retail establishments alone. Figure 7.2 shows that in several countries, foreign prices for the retail and hospital sectors combined tend to be approximately 60 percent of U.S. prices, when prices are measured in this way.

These international price comparisons may overstate future international price differences because they use 2003 data and, therefore, do not take into account the declines in U.S. prices anticipated as seniors gain health insurance coverage for drugs and health insurers negotiate price discounts with drug companies.

Figure 7.2

## Price Indices of Innovator and Licensed Products in Nine Countries Relative to the U.S. in 2003

**All Comparable 54 Top-selling 2002 US Products, Manufacturer Prices for Retail Outlets (US$/kilo or IU), Weighted by US Consumption (kilos or IU)**

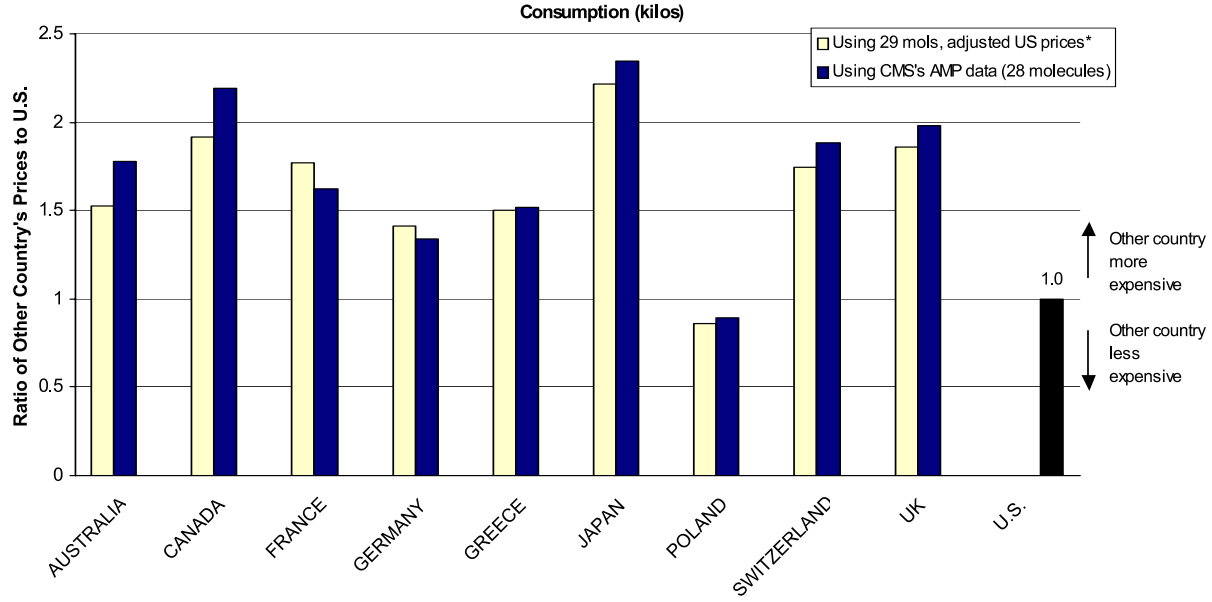



Sources: Analysis completed by HHS based on data from IMS Health, IMS MIDAS (TM), Q4/2003; IMS Health, IMS MIDAS (TM), Q1/2003 - Q4/2003; IMS Health, IMS National Sales Perspective (TM), 2003, extracted October 2004; IMS Health, IMS National Prescription Audit (TM), 2003.
*US prices increased by 1.45 percent for non-Medicaid sales to account for differences between MIDAS's manufacturer prices and CMS's manufacturer prices and reduced by 46.75% for Medicaid sales which represent 15.2 percent of total sales for innovator and licensed branded products.

Figure 7.3

## Price Indices of Generic (Non-Innovator/Non-Licensed) Products in Nine Countries Relative to the U.S. in 2003

**All Comparable of 29 Top-selling 2002 Generics, Manufacturer Prices for Retail Outlets (US$/kilo), Weighted by U.S. Consumption (kilos)**




Sources: Analysis completed by HHS based on data from IMS Health, IMS MIDAS (TM) Q4/2003; IMS Health, IMS MIDAS (TM), Q1/2003 - Q4/2003; IMS Health, IMS National Sales Perspective (TM), 2003, extracted October 2004; IMS Health, IMS National Prescription Audit (TM), 2003.
*US prices discounted 24 percent to account for differences between MIDAS's manufacturer prices and CMS's manufacturer prices for non-innovator / unlicensed products.

The international price differences presented here are also likely to significantly overstate current international price differences because the value of the dollar relative to other currencies, such as the Euro, has declined markedly since 2003. To the extent that the value of the dollar relative to other currencies remains lower than it was in 2003, estimates of savings from legalized commercial importation that we present here may be too high.

For a large set of widely available off-patent molecules, U.S. prices of generic products are lower than in foreign countries, a conclusion broadly consistent with earlier research.[14] We find, however, that non-Medicaid prices for generics are even lower than expected, because the off-invoice discounts and rebates that manufacturers report to CMS are large relative to the invoice prices reported by IMS. In particular, we find that these off-invoice adjustments on average are approximately 24 percent of the invoice price. We lack sufficient information on the best prices to adjust U.S. prices to take into account the Medicaid discounts—though such adjustments would serve to lower further the low prices of U.S. generics. As shown in Figure 7.3 the prices foreigners pay for generics are more than 50 percent greater than prices Americans pay, provided prices are averaged using U.S. quantities. (Poland is an exception.) The exact price difference is somewhat sensitive to the method of estimating prices. In particular, if we assume that the off-invoice adjustments apply to all of the IMS data we consider, and not just the products for which we have information for both CMS and IMS prices, international price differences may be lower or higher.

### 3. Internet Prices

The preceding analyses of manufacturer's prices offer little specific information about prices paid by U.S. residents who lack health insurance and are paying for prescription drugs directly out of their own pockets. We have therefore conducted a limited quantitative assessment of internet pharmacies describing themselves as American or Canadian.[15] For a set of top-selling drugs, we find that the lowest internet pharmacy prices available to U.S. consumers for branded drugs are approximately 37 percent less in Canada than in the U.S., while U.S. generic drugs are approximately 32 percent lower in price than Canadian generic prices. See Appendix B for a discussion of price differences among internet pharmacies. A more comprehensive and systematic comparison of international retail prices is very difficult. IMS does not maintain retail price information by payer type outside the U.S., in part because only a negligible share of total drug spending in some foreign markets is by consumers who are not covered by national health insurance.

***Case Study: Cost of Generic Drugs***

CBP recently detained more than 400 packages containing 808 prescription drug products at the Miami mail facility. FDA reviewed a list of the drugs contained in these packages and observed that about half of the drugs were foreign generic drugs or drugs for which there were generic versions available in the U.S. The detained packages appeared to be sent to U.S. addresses from a source in the Bahamas by a Canadian pharmacy, Kohler's Drugstore of Hamilton, Ontario, which recently set up an internet operation (www.canadarx.net) to do business with American consumers. FDA analyzed the prices charged to the customers that was listed on the invoices of the detained foreign drug products. Invoice prices were converted to U.S. dollars and the prices at four U.S. pharmacies were evaluated for comparison. In every instance, a U.S. pharmacy price for the FDA-approved generic drug was less than what consumers had paid for the foreign generic drug ordered from Kohler's Drugstore in Canada. Even some of the brand name products could be purchased from one of the U.S. pharmacies at a price within twenty dollars of the Kohler price. For further information on generics, see Appendix E.

### 4. Accounting for International Differences in Drugs

Comparisons of drug prices are greatly complicated because many pharmaceutical products are slightly different in different countries. Dosage form, strength, or package size tends to vary across countries, complicating a direct comparison. Moreover, a comprehensive comparison of products across countries would essentially have many "blanks" because few products would be sold the same way in every country. For example, esomeprazole is sold in the U.S. as 20 mg and 40 mg tablets in quantities of 30, 90, 100, and 1000, while in Canada it is sold as 20 mg and 40 mg capsules in quantities of 14, 28, 56, 70, and 100. Zolpidem is sold in both the U.S. and U.K. as five and ten mg film-coated tablets. In the U.S., package sizes range from four tablets to 500 tablets while the only package sizes sold in the U.K. are 28 and 30. The only identical matches are the 10 mg, 30-tablet packages. Comparing prices of products that are identical in terms of molecule, dosage form, strength, and package size would mean that 86 percent of the products in our IMS dataset would be excluded. In Appendix C, we analyze the loss of observations in our IMS dataset as we use more specific definitions of a drug.

One alternative approach that we adopt here is to define a drug at a more aggregated level, such as all products having the same active ingredients. With this approach, we have far fewer "blanks" and can make comparisons ignoring dosage forms and package sizes, although we may lose some precision by not comparing identical products. As explained in Appendix C, alternative definitions of drug product do not significantly affect our findings.

### 5. Drug Prices Vary Within Each Country

Of course, these comparisons of average prices in different countries may mask important variations in price within a country. In the U.S., uninsured consumers generally pay the highest prices, but they face a variety of prices for the exact same product, even in the same metropolitan area. A recent article focusing on the retail price of 17 prescription drugs shows that consumers can save on average more than 40 percent on prescription drug prices by shopping from the lower range stores compared to the higher range stores in the Washington D.C. area.[16] Moreover, one Washington D.C. area chain's drug prices "averaged about 34 percent lower than the average for the area's highest priced chain," and six percent below the average U.S. online/mail-order pharmacy.[17]

### 6. Intermediaries' Share

The final step in assessing possible discounts that drug buyers might experience with legalized commercial importation is an evaluation of the intermediaries' share of potential savings. Intermediaries that bring drugs from foreign markets to the U.S. will likely receive a large part of the gains from importation. They will bear the costs of searching for drugs in low-priced countries, and the sundry costs of keeping and managing inventory, as well as shipping products to willing wholesalers, or retail pharmacies and hospitals in the U.S. In addition they will bear the costs of complying with regulations intended to ensure safety equivalent to that associated with drugs distributed through the conventional channels.

While it is difficult to assess how much of the gains from trade will go to intermediaries, the E.U. experience with legal commercial drug importation may be instructive. Elements of market structure appear similar although there may be differences in the importance of economic incentives to buy cheaper drugs. The E.U. experience suggests that the intermediaries will consume a large part—one half or better—of potential savings. A recent study of drug importation within the E.U. published by the London School of Economics[18] suggests that such intermediaries may take so much of the gains that the price reduction observed by consumers is negligible. This study indicates that profits to importers were six times greater than savings to drug buyers, and that the benefits to patients were nearly nil. A separate paper by Mattias Ganslandt and Keith E. Maskus[19] show that gains to importers in Sweden "could be more than the gain to consumers from lower prices." See appendix D for more on importation in the E.U. Additionally, a recent analysis of importation in the E.U. suggests that the savings that reach consumers are small as a percent of total drug spending. In Denmark, Germany,

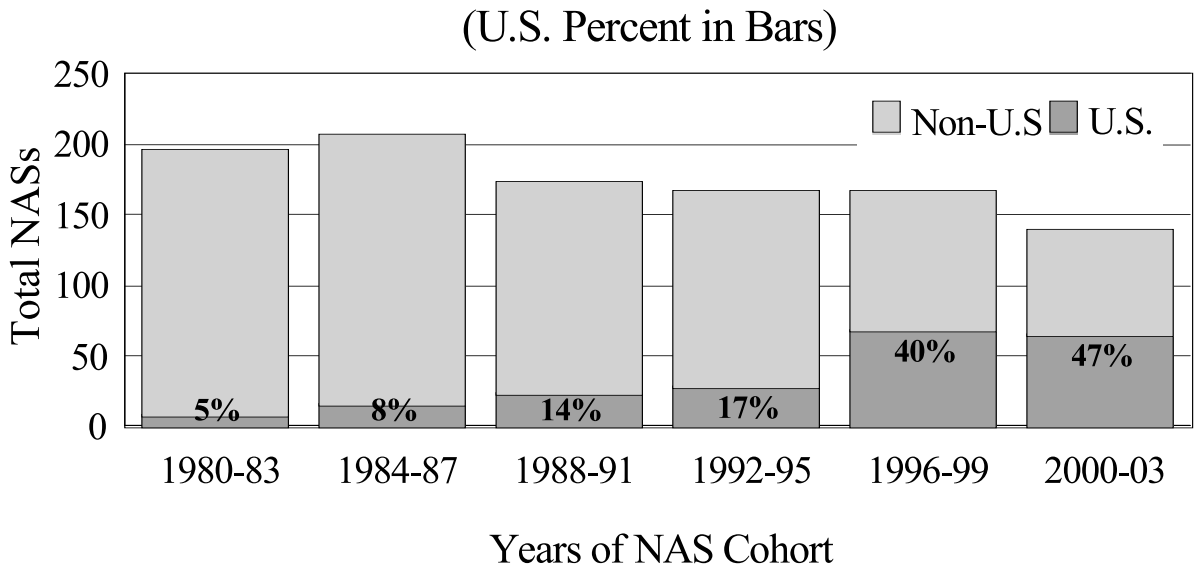
Netherlands, Sweden, and the U.K., estimated savings as a percent of total drug spending ranged from less than one percent to 2.5 percent.[20]

Discounts for imported drugs may also reflect consumer's perception of risk—a belief that imported drugs are inferior to conventional FDA-approved drugs. Consumers may believe that the foreign drugs are not as safe and effective as FDA-approved products because of inferior manufacturing abroad. In addition, there may be risk associated with the handling of the drugs in the distribution chain that begins overseas and lacks sufficient regulatory oversight at the border. These discounts, thus, raise questions about whether the associated savings justify the increased risk, a topic not addressed in this chapter.

Intermediaries would consume a large part of potential savings even if both personal and commercial importation were legalized. In this case, firms that import commercial volumes would bid for any sizable inventories of importable drugs in exporting countries. Such bids would generally exceed bids by internet pharmacies trying to export to individual U.S. consumers, because the costs of commercially importing and distributing drugs are much less than the costs of personal importation. The costs of driving or flying a single shipment of 10,000 bottles to the U.S. are vastly less than the costs of shipping 10,000 bottles separately to that many separate destinations. Moreover, a small truckload of high value drugs would earn its owner such high profits, if imported from Canada or France, that legalized commercial importation would make it difficult for internet pharmacies seeking to export drugs to keep drugs in stock. As a result, Americans seeking to buy drugs from foreign internet pharmacies may find that the drugs are unavailable because legalizing commercial importation would consume a substantial share of possible savings, in part because it would draw supplies of importable drugs away from internet pharmacies.

Combining the earlier estimates on price differences and these estimates of the intermediaries' markups

Figure 7.4




Sources: Scrip Magazine, Scrip Review Issue, Script Yearbook, Scrip 1987 NCE Review, Scrip NCE Review, Scrip World Pharmaceutical News.

Figure 7.5

**Summary of New Drug Availability in Selected Countries**

| COUNTRIES | NASs of 360 launched since 1994 | Available in the US and comparison country | Available in the US but not in the comparison country | Available in the comparison country but not in the US | Drug Availability Index (NASs launched/NASs launched worldwide) |
|---|---|---|---|---|---|
| USA | 227 | - | - | - | .63 |
| AUSTRALIA | 167 | 152 | 75 | 15 | .46 |
| CANADA | 174 | 163 | 64 | 11 | .48 |
| FRANCE | 190 | 168 | 59 | 22 | .53 |
| GERMANY | 203 | 175 | 52 | 28 | .56 |
| GREECE | 162 | 139 | 88 | 23 | .45 |
| ITALY | 185 | 157 | 70 | 28 | .51 |
| JAPAN | 151 | 77 | 150 | 74 | .42 |
| POLAND | 110 | 97 | 130 | 13 | .31 |
| SWITZERLAND | 189 | 164 | 63 | 25 | .53 |
| UK | 207 | 177 | 50 | 30 | .58 |

Source: Analysis completed by HHS based on data from IMS Health, IMS Chemindex (TM), 2003.

suggests discounts to U.S. drug purchasers will average 20 percent of the price of equivalent U.S. pharmaceutical products.

## C. Eligibility and Availability of Drugs for Importation

The existence of cheaper drugs abroad does not necessarily imply that these drugs would be available for U.S. consumers to purchase. For a variety of reasons, such drugs may be ineligible or unavailable for importation. Lower-priced foreign drugs generate savings only to the extent that they can be obtained at those prices.

The MMA would prohibit importation of biologics, injectables, controlled substances, intravenous (IV) products and certain parenterals, and drugs inhaled during surgery. In addition, many of the drugs available in other countries are not from the same firm or the same dosage form as the U.S.-approved drug and would probably not be eligible for importation. A review of our data indicates that drugs equivalent to 19 percent of spending in our data set potentially would be ineligible for importation.

Generics account for approximately nine percent of spending on drugs in our dataset. Taking into account the drugs that are both generic and ineligible for other reasons (see above), 25 percent of spending in our dataset is on drugs that are ineligible for import, or likely to be unavailable abroad at lower prices.

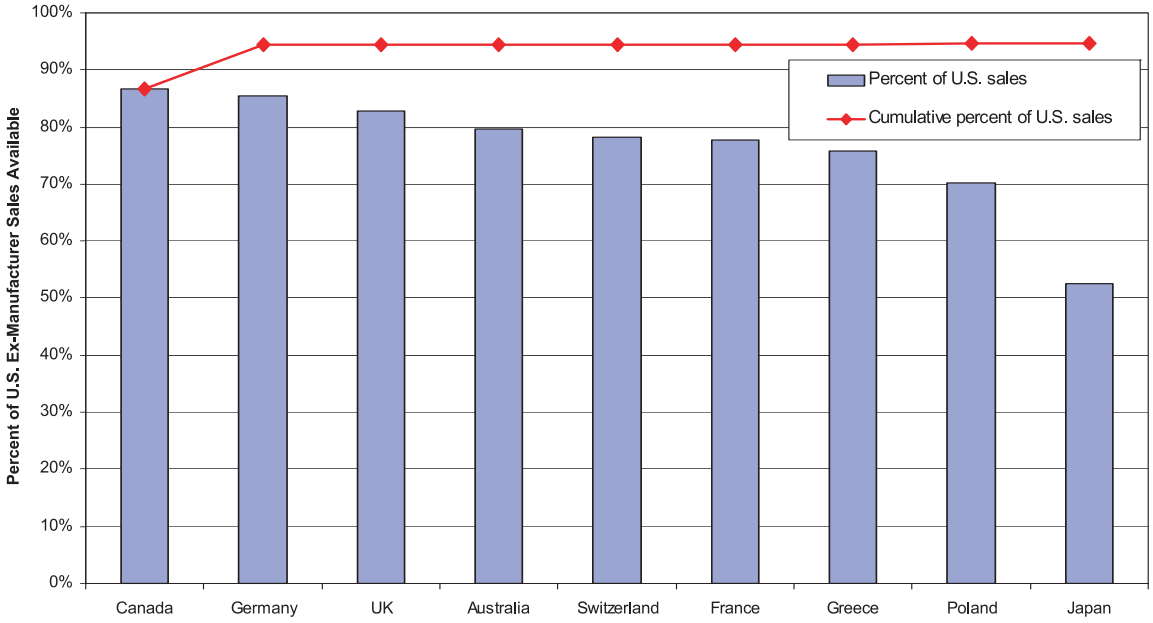
Savings from importation also may be limited because some new drugs are not available in other countries, although such limits to savings appear modest. This occurs largely because a number of new drugs are launched in the U.S. before they are sold in other countries. As a percent of total drug launches, this number has been growing. The data in Figure 7.4 suggests that, prior to 1995, less than 20 percent of new drugs were launched first in the U.S., whereas more recently more than 40 percent of new drugs were first launched in the U.S. This trend shows that Americans have a greater choice of newly launched pharmaceutical products than foreigners.

Ten percent of all recently approved new active substances (NASs)[21] are unavailable outside the U.S. This conclusion was reached using data on the number of NASs approved and marketed in each of 11 countries from IMS Health, IMS Chemindex (TM), 2003. Our analysis focuses on NASs launched between January 1, 1994 and December 31, 2003.[22] U.S. residents had access to 63 percent of all NASs launched anywhere in the world during this period. The UK was second with 58 percent, and Germany third with 56 percent. We present the results of this analysis in Figure 7.5. We also considered the availability of drugs in other countries cumulatively. Ten percent of the NASs approved in the U.S. over the last ten years would not be available for importation from these nine industrialized countries.

Figure 7.6

**Availability of 54 Top-selling 2002 U.S. Molecules Eligible for Importation* in Other Countries in 2003**

**Product defined as unique molecule and corporation (dosage form, strength, and pack size ignored)**




* Under the Pharmaceutical Market Access Act of 2003 (Referred to Senate Committee), S. 1781 RTS
Source: Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.

According to data from IMS Health, IMS National Sales Perspectives (TM), 2003, total sales of all single ingredient products using these molecules was about $1.09 billion in 2003, or approximately 0.5 percent of aggregate U.S. sales.[23]

Under the MMA and under recent legislative proposals, foreign drugs may also be unavailable for importation if the products are not sold by the same corporation. Of those drugs potentially eligible for importation and having the same molecule and dosage form as in the U.S., five percent are not available from the same corporation overseas as in the U.S. Figure 7.6 shows how the percent of sales from products available for importation among potentially eligible products is constant as the number of potential exporting countries grows.

We also note that our analysis of the top two hundred drugs sold by retail pharmacies in 2003, eliminating those drugs that would not meet the criteria set forth in the MMA for importation, shows that the fifty best-sellers account for about half of the $142 billion spent in the U.S. on prescriptions in 2003 in retail pharmacies.[24]

In summary, these data collectively suggest that pharmaceutical drugs representing about 30 percent of

total U.S. drug spending will not be imported. This estimate assumes 25 percent of spending is for ineligibles and generics, 0.5 percent of spending is for NASs not approved abroad, and five percent of spending is on drugs that are unavailable abroad in the same dosage form and from the same manufacturer. Conversely, for purposes of this analysis, 70 percent of spending is on drugs likely to be imported or eligible for importation under the MMA and recent legislative proposals.

## D. Low Volume Available for Importation

Savings from legalizing commercial importation is likely to be limited because the total volume of imports may not be as large as expected given the price differences. The volume may be limited because drug companies, and even foreign governments, may decide to restrict exports to the U.S. Furthermore, the size of the U.S. market and the availability of drugs abroad suggest that drug importation would be modest. Finally, although the EU has for several years adopted a policy of encouraging parallel trade among member states, imports in the importing countries do not dominate markets for pharmaceuticals. We elaborate on these points in this section, after discussing briefly why trade in pharmaceutical products is different from international trade generally.

Legalizing drug imports could have a fundamentally different effect than suggested by the writings of Adam Smith on the merits of free trade. Trade liberalization typically creates incentives for producers in exporting countries to increase production. Legalizing drug importation, however, would not increase production of legitimate drugs abroad because the products likely to be imported are generally all patented and controlled by a single seller. Such a seller's patents amount to a legal monopoly under which it is economically rational to charge different prices in different countries, according to differences in income and other economic and institutional factors. Legalization of importation in a high-price country such as the U.S. would generally reduce profits by shifting sales to the low-price country, thereby reducing, rather than increasing, overall incentives to produce.

To preserve their profitability, firms may decide to respond in a variety of ways.[25] They may restrict shipments to foreign wholesalers, to other entities involved in exports to the U.S., or to an exporting country as a whole. Drug companies may adopt packaging and labeling that are not the FDA-approved labeling, thereby increasing the costs to firms wishing to import drugs. They may shift production to facilities that are not inspected by FDA, thereby rendering products from such facilities ineligible for importation under most legislative proposals. Drug manufacturers may delay product launches in foreign countries prone to export to the U.S., thereby reducing the period of the product life when trade would undercut U.S. sales.

Foreign governments may not stand idly by if importation into the U.S. reduces the supplies of inexpensive drugs in their countries. Statements by Canadian groups suggest that there will be significant pressures on foreign governments, including the Canadian government, to take actions to protect the supply of inexpensive pharmaceutical products in their countries. Canadian pharmacists have already experienced some difficulties in finding drugs because much of the supply is going to internet pharmacies that export pharmaceutical products to the U.S. A survey of pharmacists in Manitoba found that over 80 percent reported that more drugs were in short supply compared to six months earlier.[26] They also reported having to increase the time and effort they spend to ensure they have adequate supplies of drugs for their customers. Two Canadian patient advocacy groups told us that importation has already caused problems for Canadian patients and that legalization of the practice in the U.S. "would exacerbate the problem."[27] These statements suggest that there will be significant pressures on foreign governments, including the Canadian government, to take actions to protect their supply of inexpensive pharmaceutical products.

Foreign drug supplies in many countries that might export to the U.S. are sufficiently small relative to U.S. drug consumption as to raise questions about the sustainability of high-volume exports from those countries. Figure 7.7 shows the total standard units (i.e., doses) distributed by each country for a set of

Figure 7.7

## Total Quantity of Drugs by Country in 2003
## 54 Top-Selling Molecules

| | Standard Units (billions of doses) | Percent of U.S. Quantity |
|---|---|---|
| AUSTRALIA | 2.02 | 4.6 |
| CANADA | 4.84 | 10.2 |
| FRANCE | 5.46 | 12.4 |
| GERMANY | 6.63 | 15.1 |
| GREECE | .91 | 2.1 |
| JAPAN | 9.13 | 20.8 |
| POLAND | 1.55 | 3.5 |
| SWITZERLAND | .55 | 1.2 |
| U.K. | 5.23 | 11.9 |
| USA | 43.85 | 100.0 |
| TOTAL | 79.81 | |

Source: IMS Health, IMS MIDAS (TM), Q4/2003.

top-selling U.S. drugs likely to be imported.

The total number of standard units sold in Canada, France, Germany, and the UK amounts to less than 50 percent of the number sold in the U.S. Adding Australia, Greece and Poland raises the total number of doses available to approximately 60 percent. If 20 percent of the standard units for this set of top-selling drugs came from this set of countries (with the exclusion of Japan, where prices tend to be higher than in the U.S.), supplies in those countries would have to fall by that amount, or production would have to increase by that much to make up the shortfall in supply.[28] But the supply of drugs imported to the U.S. in this case would amount to roughly 12 percent of the total U.S. market. (.12 = .6 x .2) This scenario presumes that drug companies and foreign governments acquiesce to the export of quantities equivalent to one in five prescriptions sold in local markets and that supplies are limited to quantities from approved countries, without inviting transshipment or counterfeit drugs. Greater volumes of imports into the U.S. would require even greater volumes of exports from those foreign countries, which we believe would be relatively less likely due to quantity constraints.

Our detailed IMS data identify imported products in Germany and the UK, two members of the EU in which imported drugs has become increasingly important. Using products from our dataset of 54 top-selling molecules that are common to both countries, we find that the total volume of imported drugs increased during the last ten years, reaching highs in

2002 of approximately five percent of total standard units in Germany and approximately 22 percent of total standard units in the UK. Imports as a percent of total standard units fell in both countries from 2002 to 2003. These data suggest limits to the growth of imports. In particular, in a regulatory environment that encouraged parallel imports and discouraged or prohibited actions by governments of exporting countries and by drug companies to deter parallel imports, trade may have reached a plateau. [29]

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1 Macafee, Michelle, "Health Canada has Plan for Drug Shortages Caused by Internet Trade: Documents," June 6, 2004, October 15, 2004. Accessed at http://www.globalaging.org/health/world/2004/short.htm on 11/4/04.

2 IMS Health is an independent collector of global pharmaceutical information and data, with offices in Plymouth Meeting, Pennsylvania.

3 Congressional Budget Office, "The Pharmaceutical Market Access Act of 2003," CBO Cost Estimate, November 19, 2003. Accessed at http://www.cbo.gov/ftpdocs/48xx/doc4852/hr2427.pdf (hereinafter cited as CBO, 2003.) on 11/4/04.

4 Our estimate of savings for drug buyers generally—1.7 percent— may be calculated as 40 percent price difference x 0.7 of all spending for drugs eligible for import x 0.12 of the drugs actually imported, x 0.5 of total potential savings going to drug buyers. Individual consumers as a group would realize savings equivalent to a small fraction of this amount.

5 Agency for Healthcare Research and Quality. "Prescription Medicines-Mean and Median Expenses per Person With Expense and Distribution of Expenses by Source of Payment: U.S., 2001," May 28, 2004, October 15, 2004. Accessed at http://www.meps.ahrq.gov/MEPSNet/TC/TC13.asp?File=HCFY2001&Table=HCFY2001_PLEXP on 11/4/04.

6 F.M. Scherer (2004) Scherer, F.M, "The Pharmaceutical Industry – Prices and Progress," *The New England Journal of Medicine,* 2004, 351(9): 927-932.

7 Danzon, Patricia M. and Furukawa, Michael F, "Prices and Availability of Pharmaceuticals: Evidence From Nine Countries," *Health Affairs Web Exclusive,* October 29, 2003. Accessed at http://content.healthaffairs.org/cgi/reprint/hlthaff.w3.521v1 on 11/04/04.

8 Food and Drug Administration, White Paper, "Generic Drug Prices in the U.S. Are Lower Than Drug Prices in Canada," November 2003. Accessed at http://www.fda.gov/oc/whitepapers/drugprices.html (hereinafter cited as FDA, 2003) on 11/4/04.

9 HHS Importation Task Force, Presentation of Patricia M. Danzon, Listening Session #4, April 27, 2004.

10 HHS Importation Task Force, Transcript of Listening Session #4, April 27, 2004.

11 Top-selling products are defined as products that are large sellers, in terms of sales. In addition, our top-sellers had to meet a number of other criteria that are specified in Appendix A. Based on these additional criteria, some top-selling products were excluded from our analysis; therefore, our list of top-selling products is not the definitive list of all U.S. top-sellers.

12 This estimate is based on data, excluding Japan, presented in Figure 7.2.

13 To compute a price index, we calculate, for the products common to the U.S. and another country, the ratio of the cost of buying the U.S. quantities of these products at foreign prices divided by the cost of buying them in the U.S. The mathematical expression for this index is

$$\text{Price Index} = \frac{\sum (Pi_{,C)} * (Qi_{,USA)}}{\sum (Pi_{,USA)} * (Qi_{,USA)}}$$

where $\sum$ denotes the sum over all common products (*i*), P is the price, *Q* is the quantity, and the subscripts $_{i,USA}$ and $_{i,C}$ represent molecule *i* in the USA or in foreign country C respectively. We define the product as the molecule and the quantity as kilograms (or IU). Appendix C explores several alternative definitions.

14 FDA, 2003.

15 We report elsewhere in this study evidence that some internet pharmacies describing themselves as Canadian, in fact, have no physical presence in Canada.

16 Washington Consumers' Checkbook, "Prescriptions for Less," Spring/Summer 2004, (13): 72-81.

17 In calculating the price index scores, equal weight was given to each drug regardless of its importance in the budget of representative consumers.

18 Kanavos, Panos; Costa-I-Font, Joan; Merkur, Sherry and Gemmill, Marin. "The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis." LSE Health and Social Care London School of Economics and Political Science, January 2004, Table 6.20, Page 181.

19 Ganslandt, Mattias and Maskus, Keith E. "Parallel Imports and the Pricing of Pharmaceutical Products: Evidence from the European Union," *Journal of Health Economics,* 2004, 23(5):1035-1057. Ganslandt and Maskus stand by this statement, which appears in their original paper, although it is absent from the version of the paper published in the *Journal of Health Economics.* (K. Maskus, telephone conversation, October 12, 2004.)

20 See Appendix D of this report.

21 NASs include all therapeutic drugs containing a new chemical entitity (NCE), new therapeutic biologics and

new vaccines. FDA defines an NCE as a new drug for which the active moiety has been previously approved or marketed in the U.S., but for which the particular new salt, new ester, clathrate or other noncovalent derivative or the unmodified base (parent) compound is not already approved or marketed in the U.S.

22 Scrip Magazine. PJB Publications Ltd, January 1994 - 1999 and February 2000-2003.

23 IMS Health, IMS National Sales Perspectives (TM), 2003, extracted September 2004.

24 Drug Topics, March 8, 2004.

25 CBO, 2003.

26 Yenra, "Pharmacist and drug shortages in Canada," November 21, 3003. October 15, 2004. http://www.yenra.com/internet-pharmacy/

27 Kaiser Network, "Prescription Drugs Supporters, Opponents of Prescription Drug Reimportation Make Case Before Federal Panel," Daily Health Policy Report, April 15, 2004, October 15, 2004. Accessed at http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=3&DR_ID=23210

28 Figure 7.2 presents the total quantity of drugs for all products using the 54 top-selling molecules. If instead we focus only on those drugs that might be eligible for import, dropping biologics, injectables, drugs inhaled during surgery, and controlled substances, etc. the volume of products sold in other countries relative to the U.S. consumption is virtually the same as presented here.

29 The peak in 2002 may be related to a recommendation by the Advocate General to the European Court of Justice to uphold an earlier Court of First Instance (CFI) decision restricting imports.

# CHAPTER EIGHT

# Impact of Importation on Research and Development and Consumer Welfare

## Chapter Highlights:

One of the most frequently debated issues surrounding drug importation is whether the legalization of importation would reduce research and development (R&D), including spending on discovery, development, and launching of new drugs. Based on both an empirical analysis of drug data and a review of previous studies, this report finds that, by shifting sales to countries with price controls for new drugs, importation would reduce overall U.S. pharmaceutical industry revenues. Since revenues would fall without a reduction in the cost to produce new medicines, profits would likely fall, as well as spending on R&D. Consequently, legalized importation would likely adversely affect incentives for R&D, thereby slowing the flow of new drugs. This report also finds that since annual R&D spending would drop, importation could result in between four to eighteen fewer new drugs introduced per decade, at a substantial cost to society. Furthermore, if there were a likely reduction in innovative new drugs, the foregone consumer benefits associated with loss or delay in new therapies may significantly offset any anticipated savings from legalized importation, depending on uncertainties.

## Key Points:

- Legalized importation would adversely affect incentives for R&D, thereby slowing the flow of new drugs and reducing benefits to future drug consumers and adversely affecting public health.
- Estimates of the reduced benefits to future drug consumers may range from $0.5 billion to $2 billion per year without including gains from having better generics in the future. Reduced benefits may significantly offset savings from legalized importation.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to assess the impact on the research and development of drugs—and the associated impact on consumers and patients—if importation were permitted.

### To further explore this issue, we also asked for comment on the following:

What would be the impact on research and development of drugs and the associated impact on consumers and patients, if changes in importation laws were to be implemented?

## II. WHAT THE COMMENTS SAID

Several comments stated that price controls, whether imported or mandated, would result in a reduced return on investment for American pharmaceutical companies and would adversely impact R&D. One comment stated that, for most of the past century, Europe led the world in pharmaceutical innovation. Within the last ten years, the U.S. overtook Europe, both in terms of investment and output of its innovative activity (e.g., NMEs). The comment argued that price control policies and cost-containment measures in Europe have led to a lack of competition, resulting in reduced R&D and fewer new drugs. This comment also cited studies on how pharmaceutical price regulation would affect future drug innovation. The studies cited confirmed a link between price controls and reduced innovation.

A pharmaceutical company cited academic research estimating that the R&D process for a drug generally costs over $800 million and takes up to 15 years. This comment stated that if U.S. pharmaceutical companies were forced to reduce their investment in R&D, the rate of development of new cost-saving pharmaceutical innovations, and new, more efficacious therapies would slow significantly.

A few comments stated that the perception of future profits greatly influences the amount pharmaceutical companies spend on R&D. If potential profits are reduced or eliminated, future development would be reduced. A comment noted that risky healthcare R&D projects must be justified by their potential payoffs in order to maintain capital flows into the industry.

Finally, several comments noted that, because U.S. pharmaceutical companies are the current world leader in innovation, American consumers benefit greatly by having earlier access to the best and newest treatments, and the American economy benefits as well.

## III. DISCUSSION

In this chapter we assess the likely magnitude of R&D that might be lost if drug importation were legalized. In our assessment, we consider the effects of legalized importation on R&D and future welfare in three parts: the effect of importation on prices, revenues and R&D spending; the effect of reduced R&D spending on discovery, development, approval, and launch of new drugs; and finally, the effect of new drugs on patient welfare. In presenting our assessment we also discuss the key uncertainties in our estimates. Our analysis is based not only on the public comments but also on a comprehensive review of the peer-reviewed and professional economics literature and on discussions with economic experts.

Our analysis shows that legalizing importation would adversely affect R&D of new drugs, causing future drug consumers to forego the health benefits associated with innovation. By shifting sales from countries with high prices to countries with low prices that are maintained through price controls, importation would reduce revenues. Since revenues would fall without any reduction in cost, profits and cash flow would be expected to fall, and spending on R&D would drop. Reduced R&D spending would delay the discovery and introduction of New Active Substances (NAS),[1] thereby depriving consumers of new treatments for disease. Based on this likely chain of events, we believe legalized importation would have a negative impact on R&D, drug development, and the welfare of future drug consumers.

We note that estimates of the impact on R&D from legalizing commercial importation may be too low because they do not reflect any costly defensive measures that drug companies might take in

response. The costs of such measures may make the development of innovative new drugs less financially attractive. We lack information to revise our estimates of the impact on R&D to take into account the costs of such potential defensive measures.

We also note that our estimates of the adverse effects of importation on R&D implicitly presume that drug companies do not take costly measures to curtail imports into the U.S. As the cost of such measures might further reduce the net returns to developing and marketing new drugs, the adverse effects of importation on R&D and future patient welfare may be larger than estimated here.

## A. Reductions in Revenue Reduce Spending on R&D

Our point of departure in analyzing the effects of reductions in drug companies' revenues on R&D spending is a convenient assumption that a reduction in spending on prescription drugs is one percent. According to CBO,[2] importation would reduce drug spending in the U.S. by one percent. While the effects of legalized commercial importation on spending on drugs may be slightly larger, as explained in the preceding chapter, R&D effects are essentially proportional to assumed changes in spending. Thus, R&D effects consistent with alternative estimates of consumer savings can be derived by rescaling appropriately the estimates described below. Our analysis identifies changes in global sales and profit resulting from legalized importation and the ensuing reduction in R&D spending.

According to the analysis in Chapter 7, drug company sales revenue will fall by more than the assumed one percent savings to drug buyers. Intermediaries—who move drugs from other countries to the U.S. —will bear the cost of any new safety measures, as well as the costs of collecting, storing, and shipping drugs, thereby earning a share of the gains from importation. Estimating the size of intermediaries' take is difficult because their activities will constitute an entirely new and different industry. As discussed in Chapter 7, we use a conservative estimate for the impact of intermediaries of 50 percent. This suggests that the decline in net revenue to pharmaceutical companies from legalized importation would be approximately two percent of U.S. sales revenue.

Published economics research suggests declines in revenues and expected profits will generally lower incentives for new drug development. In an assessment of severe declines in expected revenues, Ernst R. Berndt observes,

> …the likely result would be the termination of some existing R&D projects, especially those where, other things equal, the payoff is further in the distance. Preclinical research … would be particularly susceptible to reduced revenue expectations.[3]

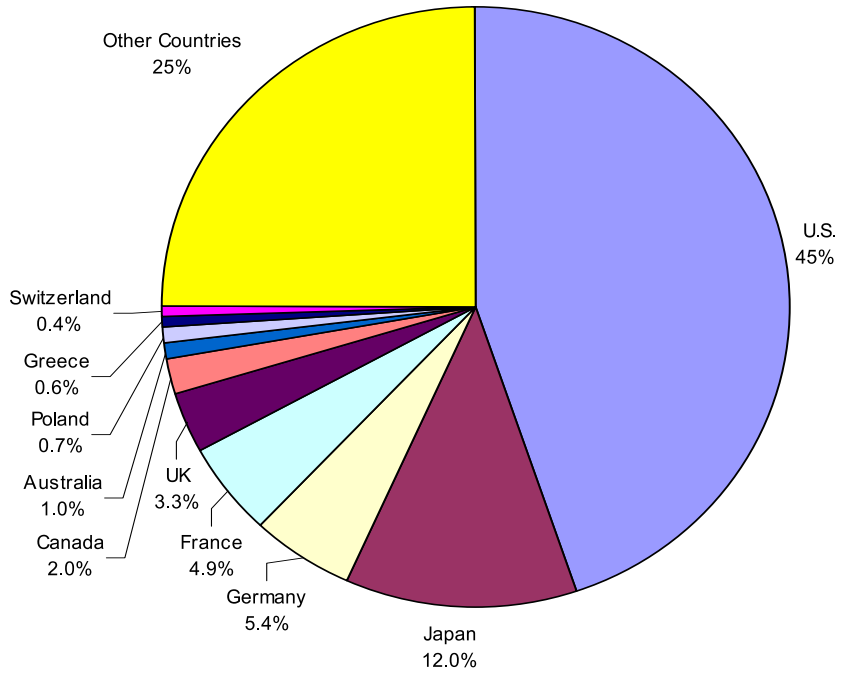
We therefore expect a decline in the return to industry investments to result in reduced R&D effort, including a reduction in preclinical research, although the magnitude of such reductions will vary with the size of any declines in revenues.

Since sales of pharmaceutical products in the U.S. represent approximately 45 percent of 2003 global sales (see Figure 8.1),[4] the loss in global sales is approximately 0.9 percent (0.9% = 45% x 2%). We note that U.S. drug manufacturers stand to lose at least 5.3 percent (5.3% = 0.9% / 17%) of global profits under this scenario, given the conservative assumption that long run profits in the drug industry average approximately 17 percent.[5] The economics literature has assessed the effect of changes in revenues on R&D spending, although there is still ongoing debate. To evaluate this effect, we reviewed three key peer-reviewed papers and conducted our analysis based on the different methodologies discussed in these papers. The results in these papers suggest that the potential response of R&D spending to changes in sales revenue may vary by a factor of two.

In the first paper, F.M. Scherer[6] finds that research expenditures vary predictably with changes in gross margins. In particular, a one percent change in gross margins (defined as revenues minus cost of goods manufactured, excluding depreciation, selling costs, and overhead cost allocations) has historically been associated with a 0.6 percent change in R&D outlays.[7] Scherer bases this conclusion on a time series

Figure 8.1

**Pharmaceutical Sales by Country* (2003)**
**Worldwide Sales = $492 B illion**




Source: IMS Health, IMS Country Sales Report (TM), 2004; IMS Health, World Review, 2001.
*Sales = Manufacturer sales; sales include audited and unaudited sales; ethical and some over-the-counter products

analysis of annual, industry-level data for the U.S. from 1962 through 1991. As gross margins are approximately 70 percent of revenues, the postulated percent decrease in revenues will result in a 2.9 percent decline (2.9% = 2% / 70%) in gross margins — assuming that all costs remain fixed. A 2.9 percent decline in gross margins would then generate an expected 1.7 percent (1.7% = 2.9% x 0.6%) reduction in R&D outlays.

In a more directly related study, Carmelo Giaccotto, Rexford Santerre, and John Vernon[8] find an elasticity of R&D intensity (defined as R&D as a percent of sales) with respect to real drug prices of 0.58, suggesting that a ten percent drop in real prices – and hence revenues (assuming that quantity is constant)[9] – would lead to a 5.8 percent reduction in R&D intensity. Thus a one percent decline in prices and, hence, spending would be associated with a 0.58 percent reduction in R&D intensity, and a 1.6 percent decrease in R&D spending. Under the current scenario, in which legalized importation could generate a one percent (direct) reduction in spending and a two percent (indirect) reduction in pharmaceutical company revenues, the Giaccotto *et al*. result would suggest a 2.6 percent reduction in R&D expenditures.

Finally, John A. Vernon,[10] expanding on previous work by Henry Grabowski and John Vernon,[11] finds a reduction in prices and revenues will influence R&D expenditures through two mechanisms: a cash flow effect and an expected profits effect. The empirical results obtained by Vernon[12] rely on the assumption that pharmaceutical prices and profit margins in the U.S. become equivalent, on average, to those found in non-U.S. markets. Vernon observes, "[a] new law legalizing the re-importation of pharmaceuticals into the U.S. would plausibly satisfy this requirement."[13] Applying similar assumptions and the results obtained by Vernon to our current example suggest that a two percent reduction in prices/revenues would generate a 3.2 percent reduction in R&D expenditures through cash flow and expected profits effects.[14]

To calculate the total change in R&D spending we need to apply these estimated percentage changes to total baseline spending on R&D. According to the Center for Medicines Research International (CMRI), worldwide pharmaceutical R&D spending was approximately $50 billion in 2003.[15] We note that estimates of expenditure on pharmaceutical research and development, especially global estimates, vary widely depending on the source of information. The variability comes in part from the lack of a consistent definition of R&D, and therefore what kinds of costs to include in the estimate. Accounting practices vary depending on company practice and the entities to which figures are reported. Some companies include marketing expenses apparently unrelated to research or development. Others report rather large estimates for "other" R&D without specifying what activities in fact are being funded. We also note that this estimate is for private sector R&D. Government entities such as the National Institutes of Health also contribute to R&D, but we are assuming this contribution would not be affected by legalized drug importation.

Because the MMA precludes the importation of injectable drugs and biologics specifically, we have not considered any potential impact on biotech R&D spending in this analysis. Based on the Goldman Sachs Global R&D Outsourcing Model, PAREXEL reports that total biotech R&D spending was $14.4 billion in 2003.[16] The elasticities derived earlier imply that the reduction in R&D spending as a result of legalized importation will range from about $850 million to $1.6 billion. Following Scherer,[17] legalized importation would generate an annual decrease in R&D of about $850 million ($50 billion x 1.7%), whereas applying results obtained by Giaccotto *et al*.[18] would generate an annual decrease in R&D spending of approximately $1.3 billion ($50 billion x 2.6%). Applying the assumptions and results from Vernon[19] suggests the decline in R&D spending associated with a two percent decrease in revenues would be about $1.6 billion ($50 billion x 3.2%).

Because Scherer[20] and Giaccotto *et al.*[21] relied on U.S. data (and not global data) to derive their coefficient estimates, our use of the $50 billion worldwide R&D spending estimate may overstate the impact of reduced U.S. sales to some degree. However, we assume that drug firms consider worldwide revenues in making their R&D decisions, regardless of location. As a result, the estimate of $50 billion for world-wide R&D spending figure is appropriate for estimating the impact of reduced U.S. sales on the R&D expenditures of all firms in the pharmaceutical industry.

The value of R&D spending may vary substantially with how it is spent. In particular, we note that not all R&D spending is for innovative NASs. Research by the Tufts Center for the Study of Drug Development (CSDD) suggests that approximately two-thirds of total out-of-pocket R&D spending is associated with the development of new medicines (an average of $282 million per new drug).[22] About a third is spent post-approval (an average of $140 million per approved drug) for long-term safety and efficacy studies in broader patient populations or specific patient groups, and the development of new indications and/or new formulations.[23] Post-approval R&D spending may increase sales, but does not generally produce products that offer therapeutic advantages comparable to those of NMEs. For purposes of this analysis we assume that diminished spending on R&D will be split between NASs and other purposes (such as new indications, dosing regimens, or formulations for approved active substances) in the same proportions as the current spending on R&D (i.e., 67% for NASs and 33% for other purposes). Thus, according to this analysis, legalized importation could reduce R&D spending on new drugs/NASs by between $570 million ($850 million x 67%) and $1.1 billion ($1.6 billion x 67%) annually.

## B. R&D Spending and the Development of New Drugs

There is relatively little information in the peer-reviewed literature—or in the comments submitted to us—concerning the relationship between pharmaceutical R&D spending and the rate of development of new drugs.

The most recent and oft-cited estimate of the cost of developing a new drug is by DiMasi *et al.*,[24] who estimated an average cost of $802 million (in 2000 dollars) per investigational, self-originated therapeutic compound reaching the U.S. market. The term "self-

originated" refers to a subset of drugs for which all steps in the development process were performed by the innovator firm or patent holder. This estimate reflects capitalization of the out-of-pocket costs to ten multinational pharmaceutical firms (eight in the top-20 worldwide) of developing self-originated compounds with a mean FDA approval date of 1997, including losses on unsuccessful research and the opportunity cost of capital. Assuming the same growth rates of 7.4 percent[25] in the inflation-adjusted capitalized costs of drug development between this most recent work and comparable earlier work, DiMasi estimated that the capitalized cost for a drug approved in 2001 would be approximately $1.1 billion[26] in 2002 dollars. Under these same assumptions, we estimate that the development cost of a drug approved in 2003 is approximately $1.3 billion (in 2003 dollars).

There are several reasons to be cautious in using this figure. This estimate may be high relative to the cost of developing all new drugs, because it applies only to self-originated new drugs marketed by large multinational pharmaceutical companies. The DiMasi estimate does not apply to all new drugs (NMEs and biologics) approved by FDA. Our own analysis of all 92 NMEs and biologics approved by FDA from 2001-2003 found that only 54 (59%) were developed by large multinational pharmaceutical firms. Furthermore, many of the kinds of compounds excluded from the DiMasi analysis are orphan drugs and/or drugs developed by relatively small entities. Orphan drugs, by definition, are used to treat very small patient populations and their clinical trials are generally much smaller and less expensive than those included in the DiMasi analysis. Thirteen (14%) of the 92 NMEs and biologics approved by FDA from 2001-2003 were orphan drugs. Thus, new compounds excluded from the DiMasi data set are likely to be less expensive to develop. Second, there may be varying returns to scale, so that the last new compound costs differ from the average, but we have little evidence concerning this aspect of R&D. Third, this estimate does not net out any revenues that drug companies may earn from licensing out the results of early drug research. Finally, the estimate capitalizes drug development costs to the point of FDA approval which, for slightly more than one-half of such products, is after approval elsewhere in the world.

Notwithstanding these cautions, the DiMasi estimate is credible enough to provide useful insights. It is derived using methods reviewed by the Congressional Office of Technology Assessment, which in 1993 concluded that an earlier report by DiMasi on the cash outlays required to bring a new drug to market and the time profile of those costs provided a reasonably accurate picture of the mean R&D cash outlays for new compounds first tested in humans between 1970 and 1982.

If we divide the reductions in new drug related R&D expenditures estimated previously by the $1.3 billion figure, we find a potential reduction of between 0.44 ($570 million / $1.3 billion) and 0.85 ($1.1 billion / $1.3 billion) fewer new drugs introduced per year as a result of legalized importation. In other words, this would translate into between approximately four and nine fewer new drugs over a decade, given the assumption that importation would provide consumer savings of one percent. If the savings from importation were larger than the one percent described here, the adverse R&D effects would increase proportionately, that is, the amount of money spent on R&D would decrease proportionately. Moreover, the decline in the number of new drugs introduced could essentially double to between eight and eighteen per decade if R&D expenditures are reduced by two percent. Given the uncertainty about the magnitude of consumer savings, an estimate for the number of new drugs that would not be introduced ranges from four to as many as 18 drugs per decade.

## C. Development of New Drugs, Public Health and Consumer Welfare

While some new drugs have obvious, enormous public health value — the Salk polio vaccine, the first anti-retrovirals, or statins — many others provide much more modest benefits. A few recent papers have tried to assess these benefits in a way that could generate an average value. This literature is split between those writers who seek to estimate quantitatively the effects of new drugs on public health, measured as declines in mortality or morbidity, and

those who instead focus on the value of new drugs in economic terms, i.e., in terms of what buyers are willing to pay for them. We turn briefly to the former, and then focus on the latter.

Frank R. Lichtenberg[27] has researched the effects of new drugs on human health and reported finding very large effects. In a 2004 paper, Lichtenberg attempts to measure the effects of new chemical entity (NCE) launches on longevity. Using data covering diseases borne by people in 52 countries from 1982 to 2001, Lichtenberg estimates that between the years 1986 and 2000, the average annual increase in life expectancy attributable to NCE launches was nearly 3 weeks. Moreover, he reports that NCE launches accounted for 0.79 years, or some 40 percent of the increase in longevity that these countries enjoyed from 1986 to 2000. These results suggest that a significant part of recent public health gains around the world may be attributed to access to new medicines. This result underscores the extent that other countries are benefiting from R&D efforts financed largely by U.S. consumers. These benefits are potentially very large, since recent economic research suggests that the value to consumers of improvements in health has in the U.S. historically been similar in magnitude to economic growth as conventionally measured.

These results are limited in their direct applicability to determining the impact on U.S. consumers alone, however, because Lichtenberg's estimate of the effect of NCEs on longevity is an average effect for all 52 countries in his sample. Since these countries have a wide range of incomes and levels of economic development, his estimates are not appropriate for an analysis of impacts in the U.S. Furthermore, since Lichtenberg provides no specifics as to how the U.S. differs from this average, we are unable to estimate the effect of NCEs in the U.S. based on his analysis. But even if the impact on life expectancy in the U.S. is a fraction of the overall global average, the adverse impact of reduced drug innovation on the health of Americans who use pharmaceuticals is significant.

An alternative approach would value new drugs in terms of their market impact, using economic measures of the benefits to consumers and producers. For goods and services unrelated to medicine, economists typically measure the value of such goods to consumers by their willingness to pay. While applying such measures to drugs is methodologically difficult, the authors of a recent study found under plausible assumptions, that total drug sales provide a lower bound estimate of total social surplus, i.e., the gains to both producers and consumers.[28] In addition, they find that one-third of this amount provides an approximate measure of the benefits to consumers of the new patented drug. Consumers benefit from new drugs by having a broader array of effective therapies and their spending on the new drug is thus a measure of the value of the new drug to them. This approach, however, can generate uncertain estimates of value. We believe that it may overstate somewhat the benefits of new drugs because it does not fully account for the substitution in drug use away from older products and towards newer ones. More importantly, it may significantly understate the total benefits to consumers of new drugs because it reflects only the gains from having access to the patented drug during its patent life. Of course consumers benefit after patent expiration from having access to inexpensive generic substitutes, and these benefits may in principle be relatively large.

Applying this research might provide one basis for describing roughly the value to consumers of foregone R&D in dollar terms. Based on data presented in an FDA report to Congress, the present discounted value of sales of a new drug over 15 years is approximately $5.4 billion.[29] We assume for the purposes of this analysis that the present discounted value of lifetime sales of a new drug is $5 billion, and that one-third of this amount, $1.7 billion goes to drug buyers—including households, government agencies, and private third party payers—in the form of consumer surplus. Combining this information with our previous estimates of 0.44 to 0.85 fewer NCEs might suggest a loss in consumer benefits of between $0.75 billion and $1.5 billion due to legalized importation that would reduce consumer spending by one percent. This estimate is likely to be significantly too low, however, because it ignores the benefits to consumers of lower prices associated with the generic drugs that enter the market after patent expiration.

## D. Social Welfare from Loss in R&D and Cost Savings

As noted previously, the analysis in this chapter assumes that the reduction in drug spending from legalized importation would be one percent—approximately $2 billion annually. This reduction in spending reflects not merely a transfer from drug companies to intermediaries and consumers, but also a real cost in the form of reduced future innovation. Our analysis suggests that the cost of this lost innovation may be worth between $0.75 billion and $1.5 billion per year, ignoring both potential delays between importation and reductions in R&D activity or new drug launches, and the benefits to consumers from future access to better generics. If the reduced revenues to drug companies from legalized importation affected sales of newly launched drugs with a seven-year lag, then the cost of the lost R&D would fall by approximately 30 percent, assuming a five percent discount rate. The results of the preceding analysis of R&D effects estimating one percent consumer savings are summarized below in Figure 8.2.

R&D effects for a scenario where savings to U.S. consumers are two percent would be double those presented in Figure 8.2. In these cases the reductions in spending and the consumer losses from not having access to new medicines would also be twice as large. Taking into account the uncertainty in the effect of legalized commercial importation on drug spending in the U.S., estimated reductions in the benefits to future drug consumers may range from $0.5 billion to $2 billion per year, without including gains from hav-

Figure 8.2

**Summary of R&D Impact Analysis Assuming One Percent Consumer Savings**

| Measure/Effect | Author/Result/Methodology | | |
|---|---|---|---|
| | Scherer (1996) | Giaccotto, *et al.* (2003) | Vernon (2004) |
| Decline in Annual R&D Spending[1] | $850 million | $1.3 billion | $1.65 billion |
| Decline in Annual R&D Spending on NMEs[2] | $570 million | $870 million | $1.1 billion |
| Annual Number of NMEs Lost[3] | 0.44 | 0.67 | 0.85 |
| Annual Loss to Consumers[4] | $0.75 billion | $1.1 billion | $1.5 billion |
| Discounted Annual Loss to Consumers[5] | $0.53 billion | $0.78 billion | $1.1 billion |

1. Assumes importation reduces U.S. drug spending by one percent, and global R&D is $50 billion annually.
2. Assumes 67% of R&D is spent on NCEs, and 33% of R&D is for joint products, new dosage forms, and other innovations.
3. Based on inflation-adjusted DiMasi *et al.*[30] cost estimate of $802 million to develop a new drug.
4. Following Berndt *et al.*,[31] gains to consumers can be roughly estimated to be about a third of the present discounted value of sales of NCEs.
5. Discounted at 5% interest over 7 years to account for delay between R&D expenditures and output.

ing access to future generic versions of new drugs. Thus, the reduction in drug spending due to legalized importation may be significantly offset by estimated losses to future consumers from reduced R&D.

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1 According to Scrip World Pharmaceutical News, New Active Substances (NASs) include all therapeutic drugs containing an NCE, new therapeutic biologics and new vaccines, but exclude non-therapeutic drugs. FDA defines an NCE (or an NME) as a new drug for which the active moiety has not been previously approved or marketed in the United States. These terms include non-therapeutic compounds used in diagnostic imaging but exclude biologicals. In this report we reference New Chemical Entities (NCE) and New Molecular Entities (NME) - the terms can be used interchangeably. In summary, the difference between NASs and NCEs/NMEs involve the inclusion/exclusion of biologicals and imaging agents. We have used all three terms in this study based on the sources of the information.

2 Congressional Budget Office, H.R. 2427, "The Pharmaceutical Market Access Act of 2003,"CBO Cost Estimate, November 2003.

3 Berndt, Ernst R., "Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price," *The Journal of Economic Perspectives,* Fall 2002, 16(4): 61.

4 IMS Health, IMS Country Sales Report (TM), 2004.

5 Average net income for branded pharmaceutical companies was 20 percent of revenue in 2001 according to The Centers for Medicare & Medicaid Services, "Health Care Industry Market Update; Pharmaceuticals," January 2003, Figure 8, Page 21. Accessed at http://www.cms.hhs.gov/reports/hcimu/hcimu_01102003.pdf on 11/4/04.

6 Scherer, F.M., *Industry Structure, Strategy and Public Policy*. New York: HarperCollins College Publishers, 1996 (hereinafter cited as Scherer, 1996).

7 Scherer, 1996: 388.

8 Giaccotto, Carmelo, Santerre, Rexford, and Vernon, John, "Explaining Pharmaceutical R&D Growth Rates at the Industry Level: New Perspectives and Insights," AEI-Brookings Joint Center for Regulatory Studies, Related Publication 03-31, December 2003. Accessed at http://www.aei-brookings.org/publications/abstract.php?pid=411 on 11/10/04. (hereinafter cited as Giaccotto *et al*. (2003)). Also forthcoming *Journal of Law and Economics* (2005).

9 We believe that the change in quantity will be negligible due to general price insensitivity on the part of insured, Medicare and Medicaid patients. We also believe supply constraints and the impact of intermediaries and restrictions on imports of certain types of drugs will limit potential savings.

10 Vernon, John A. "Examining the Link Between Price Regulation, Importation, and Pharmaceutical R&D Investment." *Journal of Health Economics.* Forthcoming 2004. Accessed at http://www.aei.brookings.org/admin/authorpdfs/page.php?id=930 (hereinafter cited as Vernon, 2004) on 11/4/04.

11 Grabowski, Henry and Vernon, John, "The Determinants of Pharmaceutical Research and Development Expenditures," *Journal of Evolutionary Economics.* 2001, vol.10: 201-215.

12 Vernon, 2004.

13 Vernon, 2004: 22.

14 The results obtained by Giaccotto *et al.* may be represented as:

$$\%\Delta\left(\frac{R\,\&\,D}{S}\right) = 0.58\ x\ \%\Delta P,$$

where R&D denotes research and development outlays, S denotes sales and P denotes real prices. From this relationship it can be shown that:

$$\%\Delta(R\,\&\,D) = 0.58\ x\ \%\Delta P + \%\Delta S$$

Legalized importation is expected to reduce drug spending/real prices by 1 percent (direct effect) and reduce pharmaceutical industry revenues by 2 percent (indirect effect) after taking intermediaries into account. Thus the implied impact on R&D is therefore:

$$\%\Delta(R\,\&\,D) = (0.58\,x1\%) + 2\% = 2.58\%$$

15 Accessed at: http://www.cmr.org/news.asp on 11/18/2004

16 PAREXEL International Corporation, "Pharmaceutical R&D Statistical Sourcebook 2004/2005," PAREXEL International Corporation, Waltham, MA, 2004.

17 Scherer, 1996.

18 Giaccotto *et al*. (2003)

19 Vernon, 2004.

20 Scherer, 1996.

21 Giaccotto *et. al*. (2003)

22 Tufts Center for the Study of Drug Development, "Therapeutic Class a Critical Determinant of Drug Development Time and Cost," *Impact Report*, Volume 6, Number 3, May/June 2004.

23 DiMasi, Joseph A, Hansen, Ronald W. and Grabowski, Henry G. "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economics,* 22(2), March 2003:151-185. Accessed at http://www.cptech.org/ip/health/econ/dimasi2003.pdf , (hereinafter cited as DiMasi, et al., 2003) on 11/4/04.

24 DiMasi et al., 2003.

25 DiMasi, et al., 2003 page 180.

26 DiMasi, et al., 2003 page 181.

27 Lichtenberg, Frank R., "The Impact of New Drug Launches on Longevity: Evidence from Longitudinal, Disease-Level Data from 52 Countries, 1982-2001,

*NBER Working Paper Series,* 2004. http://www.nber.org/papers/w9754 on 11/4/04.

28 Berndt, Ernst R; Gottschalk, Adrian H. B; Philipson, Tomas and Strobeck, Matthew W, "The Prescription Drug User Fee Acts: Towards an Economic Evaluation – I". Paper presented at NBER Frontiers in Health Policy Research, June 24th , Washington D.C. Accessed at http://www.nber.org/confer/2004/fhs04/berndt.pdf on 11/04/04.

29 DHHS, FDA, "The Pediatric Exclusivity Provision: Status Report to Congress", January 2001: 48-49. Accessed at http://www.fda.gov/cder/pediatric/reportcong01.pdf on 11/4/04. The cited data were reformatted to better reflect annual sales since initial marketing date and converted from 1999 to current (2003) dollars using the GDP deflator before estimating the present value using a five percent discount rate.

30 DiMasi *et al.,* 2003.

31 Berndt *et al.,* 2004.

# CHAPTER NINE

# Impact on Intellectual Property Rights

## Chapter Highlights:

Intellectual property rights have evolved over many years to strike a balance between, on the one hand, providing incentives for innovation through grants of exclusive rights over new ideas or products and, on the other hand, ensuring that knowledge and products are widely disseminated and accessible to provide the maximum benefit to society now and in the future. As with most new ideas and products, inventors of pharmaceuticals may obtain patents and other intellectual property protections for their products that provide certain exclusive rights. The challenge policymakers face is to ensure that intellectual property protection for pharmaceuticals provides adequate economic incentives to develop new drugs while facilitating access to affordable medicines.

An exhaustive legal analysis of the implications of allowing importation of patented pharmaceuticals to which intellectual property protections apply would require further study. However, it is clear that importation could impact the intellectual property rights of developers of pharmaceutical products and could be subject to challenge under domestic law, including possibly the U.S. Constitution, and international intellectual property rules.

## Key Points:

- Legalizing importation would impact the intellectual property rights of drug manufacturers.
- Unless intellectual property rights are statutorily changed if importation is legalized, importation of some products may be subject to legal challenge under patent, trademark, and/or copyright law.
- Legalization of importation could raise constitutional issues of "just compensation" under the Fifth Amendment.
- It is likely that intellectual property rights holders will exercise their rights to the fullest extent available under the law and the effects may impact the availability of imported drugs.
- Although states may have immunity from suits for patent infringement under the Eleventh Amendment, immunity may not extend to local governments.
- International agreements recognizing intellectual property rights may be affected by the legalization of importation.
- It is outside the scope of HHS's responsibility, expertise, and jurisdiction to protect intellectual property rights. Issues associated with intellectual property rights should be handled by those with current responsibility to do so.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to identify ways in which importation could violate U.S. and international intellectual property rights and to describe the additional legal protections and agency resources that would be needed to protect those rights.

### To further explore this issue, we asked for comment on:

- What kinds of protections from unapproved competitors would be available for generic manufacturers that have undergone the FDA abbreviated new drug application process?
- If foreign pharmacies export generics that are approved in their own countries but not in the U.S., will that undermine the incentive for generic companies to seek U.S. approval?

## II. WHAT THE COMMENTS SAID

Though the comments did not directly address the question of protections for generic manufacturers, several comments raised concerns about the erosion of the U.S. generic market and the U.S. generic approval systems. One comment suggested that legalizing importation would violate constitutional and North American Free Trade Agreement (NAFTA) rights.

A few comments suggested that importation would be a disincentive to challenge patents and bring generic products to market earlier, and would disrupt the balance created by the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Amendments.[1] Other comments suggested that generic production would be affected because Canada has a compulsory licensing scheme in the event of medical emergencies.

A number of comments noted that an importation system should take into account U.S. laws that provide incentives for innovation. One comment noted that the evidence suggests that the pharmaceutical industry is one in which patent rights are absolutely essential to supporting R&D and development of new products. One comment stated that one of the problems is lack of a private right of action to enforce various exclusivities and patent protections. The comment went on to suggest that any importation scheme would need to respect patent term restoration, pediatric exclusivity, 180-day exclusivity, data exclusivity for conducting clinical trials, exclusivity for orphan drugs, and exclusivity for a new chemical entity that does not have patent protection.

One comment stated that any drug developed on a government grant should not be priced more expensively in the U.S. than it is in foreign countries. Another suggested a set of additional exclusivities beyond the patent laws that reward companies for pediatric research or for introducing a new chemical entity in the U.S. that does not have patent protection or to restore market exclusivity lost in FDA review time.

## III. DISCUSSION

The protection of intellectual property rights in the U.S. is enshrined in the Constitution, Article I, § 8, clause 8, which grants Congress the power "To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." In addition to patent rights, Congress has exercised this authority to establish trademark rights to protect the owner's mark, and copyright protections for writings and certain other works. The challenge policymakers face with respect to pharmaceuticals is to ensure that intellectual property protection provides adequate economic incentives to develop new drugs while facilitating access to affordable medicines.

Several provisions in existing intellectual property law pose potential legal impediments to drug importation under the MMA. Importers and distributors could be exposed to patent infringement liability. Claims for trademark and copyright infringement might also be brought against them.[2] Under the Eleventh Amendment, states may be exempt from suit for some violations of these intellectual property rights, but local authorities may not be. In addition, under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS Agreement) and

other international agreements, the U.S. has made commitments that may preclude it from permitting the importation of products protected by these U.S. intellectual property rights without the permission of the right holder.[3] Also, regardless of the scope of protection afforded by U.S. intellectual property laws, manufacturers may include restrictions as part of licensing and other private arrangements with foreign entities to prohibit sales into the U.S. market. In short, implementation of section 1121 of the MMA may conflict with intellectual property protections and preexisting private agreements regarding intellectual property rights. Based on this assessment, unless these intellectual property protections can be reconciled with the MMA, they could complicate its implementation. Further, such limitations on current intellectual property protections may raise "just compensation" issues under the Fifth Amendment.

## A. Patent Protections

Throughout the history of the U.S., Congress has provided patent protection with varying changes to the terms and type of protection. Currently, the standard term of patent protection is twenty years from the date of filing with the U.S. Patent and Trademark Office (USPTO), the agency responsible for reviewing and issuing patents.[4] Extensions of the patent term may be granted based on unreasonable delays in issuing a patent and delays in approval for marketing of a pharmaceutical product.[5] To be issued a patent, an invention must be useful, novel and non-obvious.[6] A patent can be obtained for a process, machine, manufactured article, composition of matter (including mixtures of ingredients and new chemical compounds) and any new and useful improvements to them, as well as isolated microbes, cultured cells, genetically engineered animals, and asexually reproduced plants. If the USPTO issues a patent on an invention, the patent owner obtains the right to exclude others from making, using, selling, offering to sell or importing into the U.S. the patented invention.[7]

Patent laws are considered national in nature in that the patents are enforceable only within the country that issued the patent. At the same time, a U.S. patent does not grant its holder any legal rights that can be enforced in a foreign nation. To obtain intellectual property protection in a country other than the U.S., the inventor must obtain a patent in that country. It would be unusual for a pharmaceutical company to obtain a patent in only one country. In today's global economy, patent applications are filed in multiple countries for each innovative product. Although these patents may involve the identical product, such as the same active moiety, the resulting patents may not be precisely the same in each country depending on the legal effect of individual patent claims in each jurisdiction.

If a drug in the U.S. is the subject of a U.S.-issued patent and the first sale of the drug takes place abroad, anyone who imports the drug into the U.S. without the consent of the patent owner will be subject to possible patent infringement claims. For example, a distributor, drug store owner, or patient could be sued by the patent owner for patent infringement, even if the drug was sold legitimately in a foreign country, because the U.S. patent holder's ownership rights are not affected or "exhausted" by the foreign sale.

Under the "exhaustion" doctrine, the authorized sale in the U.S. of a patented product by the patent holder cuts off the patent owner's rights to control the subsequent sale of that product in the U.S. The purchaser of the specific product may use the product, charge others to use the product, or resell the product without any additional obligation to the patent holder. In effect, the patent holder's rights are "exhausted." Patent rights in the U.S. are not exhausted when the drug is first sold, if the sale takes place abroad. Therefore, anyone who, without consent of the patent owner, imports a patented drug into the U.S. could be liable for patent infringement in the U.S.[8] As a result, CBP, which works closely with intellectual property rights owners, may initiate enforcement actions to detain or seize the infringing product.

## B. Trademark Protections

Importation into the U.S. of drugs labeled for sale in a foreign country also could constitute an infringement of a trademark owner's mark if use of the mark is likely to cause confusion, or to cause mistake or to deceive the purchaser as to the origin of the mark, or

sponsorship, or approval by the trademark owner.[9] Trademarks are generally distinctive symbols, pictures, or words that sellers will use to identify their products.[10] Trademark status may also be granted to distinctive and unique packaging, colors or color combinations, and product styles. The trademark owner has the exclusive right to use the mark on the product it was intended to identify.[11] Trademarks may be protected by Federal statute under the Lanham Act,[12] and by state statutes and common law. [13]

Further protection of trademarks is provided by the Tariff Act of 1930.[14] Under the Tariff Act, it is generally unlawful to import into the U.S. any merchandise of foreign manufacture if the merchandise or any part, such as the label, package, or wrapper, bears a trademark owned by a U.S. company or citizen of, or by a corporation or association created or organized within, the U.S., and registered with the USPTO in accordance with the law and filed with the Secretary of the Treasury, unless the written consent of the trademark owner is produced at the time of import entry.[15] Such imports are subject to seizure at the time of importation.[16] There are certain personal and regulatory exceptions to seizure, but, generally, importation of pharmaceutical products that are protected by trademark would be a violation of the trademark.

The MMA requires that the manufacturer of a prescription drug provide an importer written authorization for the importer to use (at no cost) the approved labeling for the prescription drug. Accordingly, even if the U.S.-approved labeling is intended to include trademarks, liability for trademark infringement may not attach to the importer. This requirement may raise "just compensation" issues under the Fifth Amendment, since trademark holders have a property interest in their trademark. This requirement could raise questions under the TRIPS Agreement as well. In addition, if pharmacists who dispense imported drugs use the trademark on the container provided to the patient, they may be subject to liability to the extent the compulsory license does not extend to their use of the trademark.

Moreover, "when there are material differences between the domestic product and the foreign product bearing the same mark, most of the courts that have considered the issue have excluded the [imported] goods, even when the holders of the domestic and foreign trademarks are related companies, on grounds of both safeguarding the goodwill of the domestic enterprise, and protecting consumers from confusion or deception as to the quality and nature of the product bearing the mark." *Gamut Trading Co. v. U.S. Int'l Trade Comm'n.*[17] Thus, to the extent an imported drug may not be identical to an FDA-approved version marketed in the U.S., the case law suggests that the imported drug may be excluded on trademark grounds even when it bears the same valid trademark as the FDA-approved drug.

## C. Copyright Protections

The U.S. Copyright Act[18] also may protect the intellectual property associated with certain imported drugs. It is possible, although not as common as obtaining a trademark, to assert copyright protection for certain "writings" associated with drug products, including the labeling or other related materials.[19] The copyright owner has the exclusive right to reproduce, distribute, display, or license a work, in addition to other rights.[20] As a general rule, copyright protection for works created after January 1, 1978, lasts for the life of the author plus an additional 70 years.[21] For an anonymous work, a pseudonymous work, or a work made for hire, copyright protection lasts for a term of 95 years from the year of its first publication or a term of 120 years from the year of its creation, whichever expires first.[22]

Importation of copyrighted materials made in the U.S. is governed by the "first sale doctrine," which provides that the owner of a particular copy of a copyrighted item is entitled, without permission of the copyright holder, to sell or otherwise dispose of that copy as the owner of the copy sees fit.[23] However, under the MMA, the first sale doctrine may be inapplicable because under the requirements provided, the U.S.-approved labeling must be provided at no cost, and hence is not the subject of a sale at all. In any case, the MMA's requirement, under which imported drugs presumably must be relabeled to bear the U.S.-approved labeling, may preclude pharmaceutical companies from asserting copyright protections

to prevent the use of the labeling or to collect damages under copyright law. However, as with trademarks, this requirement raises Fifth Amendment takings issues of "just compensation" for the lost property right associated with the copyright.

## D. Importation by States and the Eleventh Amendment

Importation programs being set up by states and other local jurisdictions raise the question of potential liability of such governmental entities for infringement of intellectual property rights. The Eleventh Amendment of the U.S. Constitution provides that a federal court may not adjudicate a lawsuit by a private person against a state, except under certain limited circumstances.

Congress unsuccessfully attempted to abrogate the Eleventh Amendment immunity of states to patent infringement suits in 1992. The Supreme Court's opinion in *Florida Prepaid Postsecondary Education Expense Board v. College Savings Bank*[24] found that the challenged legislation did not meet the requirements of the Eleventh Amendment. As a result, this decision appears to uphold states' immunity to Federal suit for patent infringement if they choose to import patented drugs. However, under *Ex parte Young,*[25] a plaintiff may still obtain prospective declaratory or injunctive relief against individual state officers who violate federal laws protecting intellectual property while acting in their official capacities.

It is unlikely, however, that the state immunity to federal suit under the Eleventh Amendment would extend to local governments under *Florida Prepaid*. The Supreme Court has found that local governmental entities that act independently and raise their own funds are not an arm of the state for purposes of immunity under the Eleventh Amendment.[26] Although local governments may be able to claim immunity under the Eleventh Amendment if they are considered an "entity created by the state," such determinations would have to be made on a case-by-case basis [27]

## E. U.S. International Obligations to Protect Intellectual Property

The U.S. is party to numerous international agreements recognizing intellectual property rights, which establish certain governmental obligations. For example, the TRIPS Agreement among the members of the World Trade Organization (WTO) requires the U.S. (and the other member nations) to maintain national laws to comply with the basic principles that provide for the protection of intellectual property, including prevention of unfair commercial use of undisclosed data required as a condition of approval for drug applications.[28] In addition to the TRIPS Agreement, the U.S. continues to negotiate intellectual property agreements with groups of countries and individual nations that include, for example, more detailed obligations regarding protection of data required for drug marketing approvals and restrictions on importation into the U.S. without the authorization of the patent holder.

The TRIPS Agreement and other international agreements allow for the limitation of intellectual property protections under certain conditions.[29] These limitations have been cited as providing flexibility to promote public health initiatives, balancing innovator rights against the accessibility of less-expensive medications, and encouraging competition among companies. Such exceptions might provide some protection for a drug importation program. However, some countries may nevertheless question the consistency of allowing drug importation given the international intellectual property rules.

## F. Additional Protections

### 1. Label Licenses

A patent owner may use a "label license" to condition the sale of a patented (or unpatented) product. A label license can be used by a drug manufacturer to control the purchaser's use or distribution of the product in the U.S. or abroad under a patent infringement theory (if the drug is covered by a valid patent) or by a contract theory (if it is not).[30] For example, a manufacturer might condition the sale of its drug product to a distributor on an agreement that the

drug product only be sold in the country in which the distributor is located or that only a certain amount be sold in countries or areas other than that in which the distributor is located. These types of agreements are not unique to pharmaceutical products and are made for a variety of reasons including supply concerns, competitive advantage, or preferential treatment of certain distributors. Currently, some U.S. drug manufacturers have limited their supply of drugs to Canadian outlets. This practice has been defended as an effort to prevent the illegal importation of the drugs into the U.S. These particular actions have been challenged as antitrust violations by various parties, including State Attorneys General.[31]

Under a contract theory, a drug manufacturer has the ability to condition the sale of its product, assuming there are no other legal violations such as antitrust violations. *See Mallinckrodt, Inc. v. Medipart, Inc.*[32] Even if legislation were enacted, or a new court decision overturned *Jazz Photo Corp. v. ITC,* this may not prevent a manufacturer from restricting the distribution or importation of its product into the U.S by enforcing the contract created by a label license.

## G. Effective Enforcement of Intellectual Property Rights

The drug importation provisions of the MMA must be reconciled with existing intellectual property rights or those rights should be modified to allow for the legal entry, marketing, and use of the imported drugs, or the importers of such products could face liability. The same concerns extend to other intellectual property protections. Depending on how these issues are addressed, constitutional concerns may arise as well. For example, the MMA's compulsory license requirement for a drug's U.S.-approved labeling raises Fifth Amendment takings issues, potentially requiring compensation by the U.S. government for the rights holder under the Fifth Amendment.

Reconciling the legalization of drug importation and the intellectual property rights of innovator companies (and possibly generic companies) likely would require major changes in current U.S. laws and international agreements. These issues are considerably beyond the functions currently handled by HHS, and are not primarily within its public health expertise.

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1 Pub. L. 98-417.

2 There are other intellectual property rights provided under statutory marketing exclusivity provisions. Specifically, there are various exclusivity provisions generally administered by the FDA through its authority to approve a drug for marketing which limit FDA's authority to approve certain categories of drug applications submitted by third parties during a fixed period of time. Permitting a third party to import its own version of a drug (as opposed to permitting re-importation of an already approved drug, as provided for under the MMA) during the period of exclusivity might raise questions under marketing exclusivity rules in U.S. law and under provisions in U.S. trade agreements that codify similar rules.

3 TRIPS Article 28 states that a patent shall confer patent owners a set of exclusive rights, including the right to import. TRIPS Article 6, however, states that 'nothing in this Agreement shall be used to address the issue of the exhaustion of intellectual property rights.' Therefore, World Trade Organization (WTO) members are permitted to adopt a rule of international exhaustion, which would allow parallel importation, without being challenged under WTO dispute settlement rules.

4 35 U.S.C. § 154.

5 35 U.S.C. § 156.

6 35 U.S.C. §§101-103.

7 35 U.S.C. § 271(a).

8 *Jazz Photo Corp. v. ITC,* 264 F.3d 1094 (Fed. Cir. 2001). In the case of a patented drug that is exported from the U.S. and first purchased abroad, the Federal Circuit in *Jazz Photo* held that a patent owner's rights are not exhausted by that foreign sale. Accordingly, anyone who imports a patented drug into the U.S. without the consent of the patent holder could be liable for patent infringement in the U.S.

9 15 U.S.C. § 1125.

10 15 U.S.C. § 1127.

11 15 U.S.C. § 1115(b).

12 15 U.S.C. §§ 1051-1127.

13 Congress enacted the Lanham Act under Article 1, Section 8, Clause 3 of the Constitution, an exercise under its authority to regulate interstate commerce.

14 *See* 19 U.S.C. §1526.

15 19 U.S.C. § 1337(a)(C).

16 19 U.S.C. § 1337(d).

17 200 F.3d 775, 778-79 (Fed. Cir. 1999).

18 17 U.S.C. §§ 101 - 810

19 If copyright is available for such material under U.S. law, it would be important to confirm that such compulsory licensing is permissible under the TRIPS Agreement and other international intellectual property regimes.

20 17 U.S.C. § 106.
21 17 U.S.C. § 302.
22 17 U.S.C. § 302.
23 17 U.S.C. § 109(a); *Quality King Distributors, Inc. v. LAnza Research Int'l, Inc.,* 523 U.S. 135 (1998).
24 527 U.S. 627 (1999).
25 209 U.S. 123 (1908).
26 *See Mt. Healthy City Sch'l Dist. Bd. of Educ. v. Doyle,* 429 U.S. 274, 280 (1977) ("The bar of the Eleventh Amendment to suit in federal courts extends to States and state officials in appropriate circumstances . . . but does not extend to counties and similar municipal corporations.")
27 *See Florida Prepaid* at 631.
28 *See* TRIPS Agreement, art. 39, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Legal Instruments—Results of the Uruguay Round, 33 I.L.M. 81 (1994).
29 *See, e.g.,* Under the TRIPS Agreement for:
Copyright – Article 13 (allows limitations or exceptions for certain special cases which do not conflict with the a normal exploitation of the work and do not unreasonably prejudice the legitimate interests of the right holder)

Trademarks – Article 17 (allows exceptions, for example, for fair use of descriptive terms, provided that such exceptions take account of the legitimate interests of the owner of the trademark and of third parties)

Patents – Article 27 (allows exclusions from patentability for certain types of inventions, e.g., diagnostic, therapeutic and surgical methods for the treatment of humans and animals); Article 30 (allows limited exceptions to patent rights provided that such exceptions do not unreasonably conflict with the normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties); Article 31 (limitation permitting compulsory licenses to override patent rights under certain conditions)

30 *See, e.g., Pioneer Hi-Bred Int'l, Inc. v. Ottawa Plant Food, Inc.,* 283 F. Supp. 2d 1018 (N.D. Iowa 2003*).*
31 In re GlaxoSmithKline PLC, Case No. MC 03-015992 (MN Dist. Ct., 4th Jud. Dist.).
32 976 F.2d 700,(Fed. Cir. 1992)(upholding single use restriction on patented medical device.).

# CHAPTER TEN

# Liability Issues Related to Importation

## Chapter Highlights:

This report identifies the liability issues raised if importation is legalized for entities within the pharmaceutical distribution system. This report notes that allowing prescription drug importation would have uncertain effects on the litigation exposure of manufacturers, distributors, doctors, and pharmacists. To deal with these likely increased risks, entities in the pharmaceutical distribution chain may take additional costly defensive actions. Perhaps the largest source of additional liability and/or litigation risk under a drug importation system would be an increase in the number of injuries and poor disease outcomes if imported drugs are, as a class, less safe and effective.

## Key Points:

- Allowing prescription drug importation would have uncertain effects on the litigation exposure of manufacturers, distributors, doctors, and pharmacists.
- To deal with these increased risks, entities in the pharmaceutical distribution chain would likely take additional costly defensive actions.
- Perhaps the largest source of additional liability and/or litigation risk under a drug importation system would be an increase in the number of injuries if imported drugs are, as a class, less safe.
- Two new causes of action could arise: 1) against pharmacists for a failure to warn about the drugs, and 2) against state and other governmental entities for their roles in endorsing the importation of drugs that cause injury.
- Some potentially liable parties could be unavailable to U.S. courts and, therefore, to consumers, industry, or health care providers.

## I. WHAT WE SOUGHT COMMENT ON

Congress asked HHS to identify the liability protections, if any, that should be in place if importation is permitted for entities within the pharmaceutical distribution chain.

### To further explore this issue, we asked for comment on:

- What, if any, liability concerns would exist for entities in the U.S. drug distribution system if importation of drugs from another country were permitted?

## II. WHAT THE COMMENTS SAID

The majority of those who commented on this issue noted that plaintiffs' lawyers could use, but are not limited to, four legal theories against those that participate in the distribution of prescription drugs: strict liability, common law negligence, fraud/misrepresentation, and breach of implied warranty of merchantability. One comment noted that it is impossible to determine potential liabilities without knowing which model of importation to apply to the analysis.

Several comments noted that, in the strict liability context, courts have recognized that even when a defendant is not engaged in the distribution of a product, it may be held liable. Many comments noted that the creation by states of websites to facilitate importation raises an issue as to whether the facilitation puts the state in the same position as a seller or distributor.

Several comments expressed concerns over the ability of U.S. citizens to seek redress should they be defrauded or harmed by tainted foreign supply. These comments noted that many of the bad actors would be unknown or beyond the reach of the U.S. court system. The comments suggested that this will lead to U.S. residents being harmed by fraudulent, mislabeled or inappropriately shipped drugs - innocently or otherwise - and having no practical recourse.

## III. DISCUSSION

We were asked to identify the liability protections, if any, that should be in place if importation is permitted for entities within the pharmaceutical distribution chain. The comments we received discussed liability concerns rather than the protections that would be needed to alleviate these concerns. Thus, this discussion focuses on potential liability concerns for individuals and entities within the pharmaceutical distribution chain if importation is legalized.

Allowing prescription drug importation would have uncertain effects on the litigation exposure of manufacturers, distributors, doctors, and pharmacists. The primary factor in determining litigation risk – the number and severity of injuries – is not amenable to analysis at this time. Liability risk would change in small but significant ways due to importation, with the net effect on exposure unclear and somewhat dependent on the specific importation scheme adopted. Private contracting and litigation strategies and theories could decrease the impact of importation on the normal course of drug litigation.

Furthermore, many foreign internet pharmacies have disclaimers and waivers purporting to release them from liability, losses and damages, and all other claims. Websites established by U.S. cities and states that serve as a facilitator to these foreign internet pharmacies also attempt to disclaim liability because they view themselves as a provider of information and not as a dispenser of drugs.

### A. Current Tort Liability for Actors in the Drug Distribution Chain

In analyzing the question of what additional litigation or liability risk would result from an importation scheme, it is important to separate those elements of the risk that would be added by the legalization of importation from those that are already inherent in the manufacture, marketing, and distribution of prescription drugs. Because state tort law typically governs pharmaceutical personal injury cases, and tort law varies from state to state, the results of a given action could be vastly different depending on the state where it is brought and the choice of law

applied in that case. What follows, therefore, is a general statement of principles common to a majority of jurisdictions.

Pharmaceutical personal injury cases are most often heard by state, not federal, courts. Federal courts generally do not have jurisdiction to hear state-law claims unless there is complete diversity of citizenship between plaintiffs and defendants. In a given pharmaceutical personal injury case, a plaintiff will likely sue the manufacturer, all of the actors in the chain of distribution, the prescribing doctor, and the pharmacist. Because the doctor, hospital, or pharmacy is typically local, plaintiffs can dictate that cases will stay in state court by including credible claims against these parties.

In a given case, a plaintiff will assert (generally) strict liability theories against the manufacturer and distributors and (generally) negligence claims against the doctor and pharmacist.[1] Thus, a plaintiff would allege that the manufacturer incorrectly manufactured the product; that the distributor passed on the defective product and is strictly liable; and/or that the distributor improperly handled the product, compounding the manufacturing defect; that the doctor inappropriately prescribed the drug given the plaintiff's medical history and circumstances; and/or that the pharmacist improperly dispensed the product or dispensed the product with actual or constructive knowledge that it would cause harm. In the event of a judgment, a court in a comparative negligence state would allocate fault to each of the defendants, and to the plaintiff, if the plaintiff contributed to the injury. Payment of the judgment would then follow the state's joint and several liability rules. Each of these concepts is discussed in more detail below.

### 1. Negligence

Negligence liability in the pharmaceutical context creates the same obligations as negligence liability in any other context – there is a duty to act reasonably given all the circumstances. All of the actors in the drug distribution chain are currently subject to liability under negligence theories. The manufacturer, the distributor(s), the retailer, the doctor, and the pharmacist all have some duty toward the ultimate consumer. If that duty is breached, and the breach causes damages, each may be susceptible to negligence suits. Causes of action could include failure to manufacture the drug to specifications, failure to ensure safe storage or transportation of the drug, failure to include appropriate identification and tagging technologies, failure to adequately safeguard against counterfeiting or tampering, or failure to design systems to authenticate drugs through the chain of distribution. The potential defendants in each such cause of action vary with the specific facts. However, pharmaceutical manufacturers, with both the most resources and the most control over drug distribution, are usually the most vulnerable to lawsuits in the event of injury.

### 2. Strict Liability

Actors in the chain of distribution also can be held liable on theories of strict liability, or liability without fault. Under strict liability, an injured plaintiff does not need to show that the defendant's actions were unreasonable, only that the product caused the injury and that the product was defective. Strict liability is similar to a theory of implied warranty of merchantability, and the two actions have been consolidated by many states.

In general, strict liability attaches all the way down the chain of distribution. If the product is defective when it leaves an actor's hands, the actor is strictly liable, whether or not the actor has taken all possible care in handling and inspection. Thus, if a defective pharmaceutical product injures a consumer, the consumer has a cause of action against the manufacturer, any distributors, and, in some jurisdictions, the pharmacist. There are three commonly recognized product defects: manufacturing defects, design defects, and defects in warnings or instructions. Each of these theories is discussed in more detail below. As a general matter, however, the Restatement (Third) of Products Liability § 6(e) (1997) recommends that distributors and retailers of pharmaceutical products not be held liable for design defects or failure to warn. Moreover, there is usually a right to indemnity from the manufacturer if the downstream party can show the product was defective when it left the hands of the manufacturer.

### a. Manufacturing Defect

A defendant is liable for a manufacturing defect if the product was not manufactured in accordance with the manufacturer's standards, whether or not the manufacturer used reasonable care.[2] If a defectively manufactured product causes injury, there is liability through the chain of distribution.[3] Because of rigorous FDA regulation and monitoring of drug production facilities, manufacturing defect cases are quite rare in the pharmaceutical context.

### b. Design Defect

A defendant is liable for a design defect if the product poses an unreasonable risk of harm, and the harm could have been reduced by the adoption of a reasonable alternative design.[4] In the pharmaceutical context, however, most theorists and many jurisdictions have decided that such a standard is too difficult, given the inevitability of side effects from most pharmaceuticals. Thus, the Restatement endorses a standard where no cause of action arises for a design defect if the drug's benefits outweigh its harms for some class of patient – in other words, a drug does not give rise to liability if a reasonable physician would prescribe the drug in some circumstances.[5] This limited shelter does not protect a defendant from failure-to-warn or manufacturing defect cases, however. In fact, appropriate warning and assiduous manufacture are particularly important for such "inherently dangerous" products.[6] Design defect theories involving the packaging of the product can arise as well. If the design of the packaging is at issue, there is no special protection for pharmaceuticals from the normal application of products liability law.[7] Such design defect cases closely resemble negligence claims.

### c. Failure to Warn

Generally, a defendant is liable for failure to warn or instruct if warnings or instructions could have reduced the foreseeable risk of harm and if the absence of the warnings or instructions made the product unreasonably unsafe. Again, for pharmaceuticals, this general standard has been adapted to the unusual context. The Restatement applies the "learned intermediary" rule in the pharmaceutical context. Under this rule, manufacturers and distributors have no duty to warn individual consumers, as long as they warn the "learned intermediaries" – doctors and pharmacists – of any possible problems with the drug.[8] Nor are pharmacists generally liable for failing to warn, as long as they accurately fill prescriptions. The patient's recourse in a pharmaceutical failure-to-warn case, then, is typically against either the manufacturer for failure to properly warn intermediaries or the doctor for malpractice.

## B. Liability Concerns if Importation is Permitted

In a purely legal sense, the causes of action available to plaintiffs injured by pharmaceuticals will not change dramatically if importation is legalized. Importation would, however, likely introduce complications that would make the litigation of these claims more difficult. Perhaps the largest source of additional liability and/or litigation risk under a drug importation system would be an increase in the number of injuries if imported drugs are, as a class, less safe than U.S. products. Such an increase in injuries would presumably lead to a corresponding increase in the number of lawsuits and amount of liability. The assessment of the likelihood of injury, however, is not in most senses a legal question and is not thoroughly addressed here. What follows instead is an analysis of the changes in liability that would occur as a result of allowing drug importation.[9]

### 1. Substantive Changes

There are three different scenarios to consider in assessing the impact of importation on pharmaceutical liability: (1) drugs are defectively designed or improperly manufactured by a domestic or overseas manufacturer, resulting in litigation by the consumer against those in the chain of distribution; (2) drugs are mislabeled, misbranded, adulterated, improperly dosed, etc., within the chain of distribution from the manufacturer to the consumer, leading to litigation against those in the chain of distribution; (3) drugs are deliberately counterfeited or adulterated, leading to litigation against the party that counterfeited or adulterated the product, the manufacturer, and per-

haps others in the chain of distribution.
Legalized importation would affect each of these scenarios differently. In Scenario One, where the defect arises with the manufacturer, the importer and any other additional agents who distribute the product will be liable for defects under theories of strict liability in the same fashion as a current domestic distributor. In addition, if foreign manufacturers were allowed to sell unapproved drugs in the U.S., they would be strictly liable in the same fashion as a current approved manufacturer, assuming they are subject to U.S. law. Scenario Two may pose greater litigation exposure to manufacturers, since several of their joint tortfeasors might be unavailable for procedural or other reasons which follow, again, assuming they are subject to U.S. law.[10]

Scenario Three's effect on litigation risk is ambiguous. As a purely legal matter, if counterfeiting can be proven, manufacturers and distributors will generally have a strong defense to liability in such cases as most states do not impose a duty to prevent the criminal acts of others.[11] Proving the occurrence of counterfeiting in a specific case, however, is likely to be difficult and, therefore, entail significant litigation costs. Further, while this is a risk currently faced by manufacturers and distributors, the difficulty in proving counterfeiting may be exacerbated in cases involving imported drugs. Absent the availability of a sample of the drug at issue, counterfeiting or adulteration would have to be shown either through the manufacturer's records regarding the manufacture and testing of the product or, in the absence of such records, evidence regarding the chain of custody of the drug prior to sale. Depending upon the requirements imposed upon importers, evidence regarding the chain of custody may be more difficult to acquire for imported drugs, and would likely be significantly more difficult to obtain for personally imported drugs. Finally, if parties knew or should have known about the counterfeiting or adulterating, and could have acted reasonably to prevent such actions, then there is a chance they could be held liable.

An additional, and relatively novel, cause of action for failure to warn could arise under drug importation. Most states and the Restatement (Third) of Products Liability currently adopt the "learned intermediary" rule, which relieves manufacturers of the duty to warn consumers, so long as they warn doctors.[12] Similarly, pharmacists are generally not required to provide warnings because the law views the doctor as best situated to give advice about side effects and risk of injury. A few states have adopted an unusual exception to this no-liability rule for pharmacists, however. In these jurisdictions, pharmacists can be held liable for injuries resulting from an unwarned substitution of a generic drug for a brand name drug.[13] In such a case, the pharmacist is the only party able to warn of the harm, and so the logic of the learned intermediary rule does not apply.

The same rationale might be applied to create a new duty to warn in the case of importation. If, in fact, imported drugs are either categorically or occasionally more dangerous, courts could impose a duty to warn consumers that they are receiving imported drugs and to warn of the attendant dangers. The pharmacist (internet or otherwise), as the party most aware that the patient was receiving imported drugs, might bear the burden of warning of these dangers. Indeed, the logic used to justify an exception to the learned intermediary rule in generic substitution cases is even stronger in the case of the substitution of imported drugs. Generic drugs approved for sale in the U.S. have, under the FD&C Act, been shown to be therapeutically equivalent to the brand-name version of the same drug. Depending upon the type of importation scheme adopted, a similar showing may not have been made for imported drugs. This may be particularly true in cases of personal importation, which would be even more difficult to monitor and regulate than commercial importation.

Finally, several of the comments suggested that importation could cause companies to be held liable despite having done nothing wrong. For negligence actions, these suggestions are inapposite, since a negligence judgment by definition requires that the tortfeasor failed to exercise reasonable care under the circumstances. Strict liability theories are known as theories of liability without fault. However, even under strict liability, it is necessary to allege both that there was a defect in the product and that the defect proximately caused the injury. As a result, if a defendant truly has done nothing wrong, that defendant

should have a strong defense to liability under either negligence or strict liability theories. As discussed above, however, such a defense may be difficult to prove in cases involving counterfeiting in which no samples of the drug in question remain.

### 2. Procedural and Practical Hurdles

While prescription drug importation would lead to little substantive change in plaintiffs' causes of action, a variety of procedural and practical changes brought on by drug importation could alter the conduct and increase the cost of pharmaceutical personal injury litigation. Some of the more noteworthy changes are discussed here.

#### a. Personal Jurisdiction

For an American court to exercise jurisdiction over a defendant, it must have personal jurisdiction over that defendant. Personal jurisdiction is governed both by state statutes and the U.S. Constitution. Each state has a "long-arm" statute, which defines whether and when states can exercise authority over defendants with tenuous connections with the state. In addition, the Supreme Court has adopted a "minimum contacts" test which defines the outer limits of personal jurisdiction under the Constitution.[14] In the commercial context, the usual test for whether a business can be held to account in a court is whether the business has "purposefully availed" itself of the services of that state.[15] Mere placement of a good in the "stream of commerce," without more, does not subject a defendant to the personal jurisdiction of the state.[16] Many states' long-arm statutes take jurisdiction to the maximum extent allowable under the Constitution, although some states have narrower long-arm statutes.

Under a drug importation scheme, it is possible that some potentially liable parties would be out of the reach of U.S. courts. For example, a purely Canadian distributor who did not target advertisements or other business operations to the U.S. and who sold only to Canadian companies might be shielded from the exercise of jurisdiction by any state court. Similarly, a foreign drug manufacturer who did not target its business operations to the U.S. and who sold only to non-U.S. companies might also be shielded from the exercise of personal jurisdiction by a state court. Unless the other defendants in an action involving such a party could seek contribution[17] in foreign courts, the result of an unavailable defendant could be that all of the remaining defendants would carry greater litigation exposure. Even though courts routinely assess responsibility to absent defendants, a plaintiff cannot collect a judgment against a defendant if the court does not have personal jurisdiction over that party. In such a case, if permitted under the state's joint liability rules, a plaintiff may choose to collect the entire judgment from the present defendants and leave the paying defendants to seek contribution in a foreign court rather than trying to enforce the judgment in a foreign court themselves.

#### b. Choice of Law / Forum Non Conveniens

In cases involving foreign parties and foreign causes of action, state choice-of-law rules could select foreign tort law as the applicable law. While an analysis of Canadian or other foreign products-liability law is beyond the scope of this discussion, it is fair to note that many foreign countries are much less willing to assess product liability damages than the U.S.

Under some circumstances, courts will decide not only that they should use foreign law, but that the entire case should be moved to a foreign country. Such a decision could be made based upon the common law doctrine of forum non conveniens. As articulated by the Supreme Court in *Gulf Oil Corp. v. Gilbert*,[18] granting a forum non conveniens motion requires a balancing of the private and public factors involved in a suit. Private factors include access to sources of proof, ability to compel production of witnesses, and enforcement of a possible judgment. Public factors include congestion of the courts, concerns about imposing jury duty on a community, and the value of local courts deciding local controversies. Even if the appropriate forum substantially reduces the size and likelihood of a plaintiff's recovery, a court may, upon balancing the *Gulf Oil* factors, decline to take jurisdiction and send the case to another venue.[19]

Furthermore, contracts between manufacturer and distributor, distributor and pharmacy, and pharmacy

and consumer might specify that any disputes arising out of the sale of drugs be resolved in foreign courts. It is unclear whether or how many courts would be willing to enforce these contracts as, generally, courts are reluctant to allow parties to contract out of tort duties.

However, many courts do enforce reasonable forum selection clauses.[20] To the extent that successful forum non conveniens motions or contractual choice of law and choice of forum clauses would move some cases abroad or lead to the application of foreign law, manufacturers' liability is likely to be reduced. Many foreign courts, including Canadian courts, do not recognize any actions under strict liability, so fault must be shown for a recovery. This greatly decreases the likelihood that a manufacturer (either American or foreign) would be held liable for the wrongful actions of a foreign exporter/distributor. At the same time this may frustrate a plaintiff's ability to recover for injuries from imported drugs.

### c. Foreign Discovery

If importation is allowed, lawsuits involving imported drugs may well require foreign discovery of nonparties, since records and other evidence related to the suit would be located abroad. Such materials are generally beyond the subpoena power of American courts. Although the traditional mechanism of letters rogatory, with respect to discovery from a foreign entity that is not a party to the suit,[21] makes such discovery possible (with the cooperation of foreign courts), it is more time-consuming and expensive than domestic discovery. In theory, foreign discovery could greatly hamper the ability of both plaintiffs and defendants to marshal facts and evidence for their cases.

### d. Proximate Cause

One significant worry, related to the problems of foreign discovery, is that tort victims injured by foreign malfeasance will have a hard time pinpointing responsibility for their injuries. To prevail in a tort action under any theory of liability, the plaintiff must show proximate cause – that the defendant's act or failure to act was a cause, close enough in space and time, of the plaintiff's injury. In a suit where all actors along the distribution chain are alleged to have contributed to an injury, it is a common defense for each potential tortfeasor to blame the other potential tortfeasors. If the acts giving rise to the injury took place in a foreign country, with the associated difficulties in discovery and investigation, allocating liability and sifting through the various claims and cross claims could be very complicated. In some cases, the causal link between the tortious act and the eventual harm could be obscured, and the plaintiff could lose for failure to demonstrate proximate cause.[22]

Concerns about causation are particularly pressing in cases where a party inside or outside the chain of distribution intentionally tampers with a pharmaceutical product. As a general rule, actors are not liable for the intentional crimes or torts of third parties, even if the actor might otherwise have been held liable under strict liability or negligence theories.[23] Courts usually find that intervening intentional acts break the chain of proximate cause leading from the negligence to the injury. However, though this is the majority view, a minority of courts have found that the intervening act does not break the chain of causality, and that the negligent party can be held liable even though the most immediate cause of injury was the act of the intentional tortfeasor.[24] Thus, depending upon the jurisdiction, a manufacturer could potentially face a judgment even though the injury was primarily caused by the intentional wrongdoing of an absent third party.

### e. Preemption

Allowing the importation of prescription drugs may affect the analysis regarding the preemption defense sometimes available due to the FDA's extensive regulation of drugs and medical devices. The U.S. Constitution provides that the laws of the U.S. "shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding."[25] Thus, in some circumstances, federal statutes and agency regulations may preempt state law or preempt a state from allowing a common law right of action to private citizens.[26] Federal law contains express provisions preempting state law with respect to medical devices[27] and non-prescrip-

tion drugs,[28] making this defense is most relevant to cases involving those products. Nevertheless, preemption remains available as a defense in cases involving other products regulated by FDA. For example, it is possible for a manufacturer to show that the FDA has affirmatively spoken as to the precise aspect of the prescription drug challenged under state law such that a state-law remedy would be prohibited.[29]

The requirements imposed under a legal importation program could affect the viability of this defense. If importation is limited to drugs meeting all current FDA regulations, then presumably the preemption analysis would be the same. If, however, drugs which were not U.S.-approved drugs were allowed to be imported, the defense would likely no longer apply as to those drugs.

### f. Joint and Several Liability

Nearly all states recognize a doctrine of comparative liability. Thus, when several torts have combined to result in injury to a plaintiff, a finder of fact allocates responsibility among the tortfeasors, so that each receives a percentage of the liability. However, that allocation does not necessarily mean that each tortfeasor is only responsible for his or her portion of the debt. The traditional rule is one of joint and several liability, where the plaintiff could recover any portion of the judgment from any of the tortfeasors. Under such a system of pure joint and several liability, a plaintiff could collect one hundred percent of a judgment from a tortfeasor found to be one percent at fault. The tortfeasors are then left to pursue any available actions for contribution among themselves.

A system of pure joint and several liability has important implications for liability under a drug importation scheme. If drugs were counterfeited, contaminated, altered, misbranded, mislabeled, etc., by a foreign party, an even slightly negligent (or under a strict liability theory, slightly responsible) drug manufacturer, distributor, doctor, or pharmacist could be held to account for the entire wrong. While this problem is not unique to an importation system – the same problem would occur if a domestic wrongdoer were unreachable, either by reason of legal or practical unavailability or insolvency – it could be aggravated in a case involving foreign parties. In such a case, a deep-pocketed, slightly responsible party could bear the entire burden of payment despite bearing only a small portion of the legal blame.

In assessing the weight of this concern, however, it is important to note that, according to one comment, only seventeen states still have a system of pure joint and several liability. This comment finds that sixteen states have adopted pure several liability, where each tortfeasor is liable only for its comparative responsibility. Fourteen states have eliminated joint liability for defendants whose portions of the fault are less than some cutoff, often fifty percent. Under those systems, a defendant one percent responsible would never pay one hundred percent of the damages. Several other states have adopted other reforms. At the same time, such systems could leave an injured consumer with an incomplete recovery for injury resulting from imported drugs.

### g. Adaptive Behavior

While entities within the distribution chain might have strong defenses to claims under an importation regime, companies would still accrue substantial expense defending them. Composing answers to complaints, filing motions to dismiss, and participating in preliminary discovery certainly carries some expense, particularly in light of the complications discussed above.

It is possible, however, that parties will adjust to the new litigation environment in ways that mitigate some of these additional burdens. Manufacturers, distributors, and importers faced with exposure from the actions of downstream distributors or importers have powerful incentives to take preventive measures to minimize their liability. Indemnity and other risk-allocating agreements, as well as insurance, are pervasive in the pharmaceutical industry. Thus, among other options, entities in the pharmaceutical distribution chain could (1) choose to deal only with reputable downstream parties who will take adequate precautions to prevent litigation and/or maintain detailed records regarding the handling of the product; (2) do inspections and take other quality-control steps before and after the product leaves their hands; and/or (3) make sure that downstream parties are

solvent or carry sufficient insurance so that contribution actions are more effective.

Certainly, all of these steps are costly. Thus, in assessing liability risk under proposed drug importation schemes, it is important to consider the additional monitoring and other transaction costs involved in the potential options specified above as part of the overall increase in costs of importation, even though these costs will never be reflected in the form of settlements, judgments, or fees and expenses. Moreover, such private ordering would take place in the context of a complex legal regime. If, for instance, it were illegal or cumbersome for manufacturers to refuse to deal with underinsured or disreputable distributors and exporters, the private ordering system would be less effective in decreasing liability. Certain kinds of antitrust enforcement or legislative enactments may also affect the way companies deal with liability risk.[30] Finally, it is fair to note that such private ordering might be more complicated, less pervasive, and less effective in the context of personal (as opposed to commercial) importation.

### 3. Governmental Liability

Several states and municipalities have begun programs to buy, or to encourage their citizens to buy, pharmaceuticals from Canada. For example, Governor Doyle of Wisconsin provided testimony to the Task Force outlining the program created by Wisconsin to facilitate the importation of prescription drugs from Canada by creating a state-sponsored website linking Wisconsin residents to specific Canadian sellers. Further, if a federal importation scheme is adopted, the federal government could become involved in facilitating the importation of prescription drugs. In doing so, each of these governmental entities could be exposed to tort liability.

States as a general matter are immune from liability for acts they take as sovereigns. All states, however, waive their sovereign immunity under some circumstances, with the precise outlines of those waivers varying from state to state. Depending on the terms of a given state's waiver, it may expose itself to civil liability by participating in a drug importation scheme. In Wisconsin, and in every other state and municipality that has set up programs to encourage drug importation from Canada, the state has included a very detailed disclaimer of all liability associated with harm that may result from the drugs ordered.[31] In those cases in which sovereign immunity is found to have been waived, the effectiveness of the use of disclaimers in preventing state liability is unclear. The Uniform Commercial Code (U.C.C.) permits courts to disregard such disclaimers under fairly discretionary standards with respect to private parties.[32] Courts have in some cases ignored tort liability waivers, citing the need for protection of unsophisticated parties.[33] Even if courts were to enforce these clauses in cases involving state importation programs, the result would most likely not be a reduction in total liability, but simply a shift in liability from the state to private parties involved in the transaction.

Municipalities may also incur liability through participation in importation schemes. In some cases, the rules governing municipalities are the same as those governing states. These municipalities, having received delegations of state sovereignty, have the same immunity and offer the same waivers as the states. Other jurisdictions have found the opposite, that liability is the general rule for municipalities, with immunity the exception.[34] On average, then, municipalities should have more liability concerns than states, but the rule as to municipalities varies greatly from state to state.[35]

Finally, depending on the nature of the federal government's participation in implementing an importation scheme, it too might be subject to more protracted litigation. The federal government, in its waiver of sovereign immunity under the Federal Tort Claims Act,[36] retains immunity for suits arising from a discretionary function of the government or from misrepresentations by the government. In most cases, these exceptions to the U.S.'s waiver of sovereign immunity would preclude liability. The manner in which any importation statute and/or implementing regulations were drafted, however, would be important in retaining the applicability of these exceptions.

For example, in interpreting the discretionary function exception, the Supreme Court has held that if a regulation creates a "mandatory" duty, the government

cannot use the discretionary function exception as a shield.[37] The determination of whether a regulation creates a mandatory duty involves a close and sometimes subtle reading of the language of applicable laws and regulations to determine if the allegedly negligent government employee was indeed acting according to discretion or mandate. Thus, the specific wording of any statute or regulations would either preserve or waive federal sovereign immunity under the discretionary function exception.

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1 Several comments suggested that plaintiffs could also advance theories of implied warranty of merchantability or fraud/misrepresentation. State procedural or substantive law might encourage the phrasing of a case in these terms, but the cause of action in a pharmaceutical personal injury case, is, for purposes of this chapter, essentially one for either negligence or strict liability. Accordingly, these other causes of action are not addressed at length here.

2 Id. § 2(a).

3 Id. § 1.

4 Id. § 2(b).

5 Id. § 6(c).

6 *See* Restatement (Second) of Torts § 402A cmt. k (1977).

7 *See Elsroth v. Johnson & Johnson,* 700 F. Supp. 151, 158 (S.D.N.Y. 1988), at 158.

8 Restatement (Third) of Products Liability § 6(d) (1997).

9 Under current law, a significant portion of imported drugs are considered "unapproved." The analysis here does not address civil and criminal penalties that currently could apply for violations of the Food, Drug, and Cosmetic Act. *See 21* U.S.C. § 301 et seq. See Chapter 2 of this report for further discussion of some of the potential conflicts between these provisions and legalized importation.

10 This is a significant caveat. *See* discussion on personal jurisdiction in this Chapter.

11 *See generally* Restatement (Second) of Torts §314.

12 Id. § 6(d).

13 *See, e.g.,* W. Va. Code § 305-12(b).

14 *International Shoe Co. v. Washington,* 326 U.S. 310 (1945).

15 *World-wide Volkswagen Co. v. Woodson,* 444 U.S. 286 (1980).

16 *See Asahi Metal Industry Co. v. Superior Court,* 480 U.S. 102, 112 (1987).

17 Under the principle of contribution, a tortfeasor against whom a judgment is rendered may seek proportional shares of the judgment from other joint tortfeasors.

18 330 U.S. 501, 508 (1947).

19 *Piper Aircraft Co. v. Reyno,* 454 U.S. 235 (1981). Given the law on forum non conveniens, a manufacturing defect case with only one foreign defendant is unlikely to be moved to a foreign court. However, in a case where the central allegation is of negligence taking place abroad, where the witnesses and evidence were abroad, and where the negligent party was involved in drug distribution in a number of countries, one can easily imagine the case ending up in a foreign court.

20 *See, e.g., M/S Bremen v. Zapata Off-Shore Co., 407* U.S. 1 (1972).

21 A letter rogatory is a formal request from a court in one country to the appropriate judicial authorities in another country requesting compulsion of testimony or documentary or other evidence or service of process.

22 Proving proximate cause can in some cases be facilitated by the doctrine of res ipsa loquiter. When a party has exclusive control of an instrumentality that causes an injury usually the result of negligence, res ipsa loquiter creates a presumption of negligence. Thus, if a product were known to be safe prior to reaching a Canadian distributor, and the Canadian distributor had exclusive control of the product during the time it became unsafe, the court system could impute negligence to that distributor without the need for direct proof of negligence or intentional malfeasance. However, most pharmaceutical cases are poor candidates for the application of res ipsa loquiter, as it would often be difficult to prove exclusive control. Moreover, since most drugs can cause injuries even absent negligence, an inference of negligence may only be supported in cases involving an unusual pattern of symptoms.

23 *See Watson v. Kentucky & Indiana Bridge & R.R.,* 126 S.W. 146 (Ky. 1910).

24 *See, e.g., Brauer v. New York Central & Hudson River R.R. Co.,* 103 A. 166 (N.J. 1918) (negligence of railroad created situation where thieves were able to steal plaintiff's goods).

25 U.S. Const. art IV, cl. 2.

26 *See, e.g., Medtronic, Inc. v. Lohr,* 518 U.S. 470 (1996) (finding that provision of federal law preempting state law requirements regarding medical devices applied to some state common law damage actions); *Dowhal v. SmithKline Beecham Consumer Healthcare,* et al., 33 88 pP.3d 1 (Cal. 2004) (finding that state law suit challenging the warning label for non-prescription nicotine replacement products was preempted by the FDA's approval of the precise warning at issue and disapproval of various suggested changes).

27 *See* 21 U.S.C. § 360k.

28 *See* 21 U.S.C. § 379r.

29 *See e.g., Ehlis v. Shire Richwood,* Inc., 233 F. Supp. 2d 1189, 1196-1198 (D.N.D. 2002) aff'd, 367F.3d 1013 (8th Cir. 2004) (finding that federal regulation of the label for the prescription drug Adderall preempted state-law failure to warn claim).

30 Certain kinds of activity in response to importation could expose pharmaceutical companies and their distributors to antitrust liability, though it is beyond the scope of this discussion to speculate as to the likelihood or magnitude of this risk.
Section 1 of the Sherman Act prohibits "contract, combination . . ., or conspiracy, in restraint of trade. . . ." 15 U.S.C. § 1. Section 1 has generally been read to prohibit, per se, horizontal combinations of competitors to affect price or price related features. *See United States v. Trans-Missouri Freight Ass'n,* 166 U.S. 290 (1895); *Catalano, Inc. v. Target Sales, Inc.,* 446 U.S. 643 (1980). Commentators have worried that pharmaceutical manufacturers would respond to importation by reducing supplies to Canada, thereby preventing any significant level of importation. But see *United States v. Colgate & Co*., 250 U.S. 300 (1919) (noting that the Sherman Act does not implicate the rights of companies to choose to whom and under what conditions they will sell). Pharmaceutical companies could also attempt to regulate by contract the prices their distributors charge. Depending on how companies approached such price management, they could be exposed to liability. *See* Dr. Miles Medical v. John D. Park & Sons, 220 U.S. 373 (1911).

31 *See, e.g.,* http://drugsavings.wi.gov/medicinelist.asp?locid=2&linkid=17

32 U.C.C. § 2-302 (2003) (providing that courts may refuse to enforce unconscionable contracts), U.C.C. § 2-316 (2003) (limiting exclusions and changes in warranties).

33 *Henningson v. Bloomfield Motors, Inc*., 161 A.2d 69 (N.J. 1960).

34 *See, e.g., Kimps v. Hill,* 546 N.W.2d 151 (Wis. 1996).

35 It is worth noting that sovereign immunity for States is independent of State immunity from Federal suit under the Eleventh Amendment. This analysis focuses on sovereign immunity because tort law is grounded in the common law, and tort claims are typically adjudicated in State courts.

36 28 U.S.C. §§ 1346, 2671, et seq.

37 *See Berkovitz v. United States,* 486 U.S. 531 (1988) (finding that the discretionary function exception did not bar claims that the FDA negligently licensed certain polio vaccine which were premised upon the alleged failure to comply with mandatory regulations governing the licensing process.

# APPENDIX

## APPENDIX A: THE IMS DATASET

### I. Drugs

#### A. Brand Name Drugs

For brand name drugs, we started with 60 best-selling brand name products, according to U.S. sales in 2002. Because of data limitations, we dropped four products with more than one active ingredient, and found two products with the same active ingredient. This left us with 54 separate molecules used in 56 brand name products. A detailed explanation of the brand name drugs used in our analysis is below.

IMS Health provided sales and volume data on all comparable products marketed in ten countries based on the 60 top-selling products, judged by sales in the U.S. in calendar year 2002. These top-selling 60 products included four combination products (Advair Diskus, Augmentin, Lotrel, and Ortho-Tri-Cyclen). Additionally, there were two pairs of products (Epogen/Procrit and Flonase/Flovent) containing the same active ingredients (epoetin alpha and fluticasone).

For our analyses, we eliminated the four combination products, because we could not identify comparable combination products across countries, leaving the top 56 single ingredient products. Strength data were not available for all active ingredients in combination products. Since two pairs of these 56 products had the same active ingredients, we were left with products containing 54 different active ingredients. Thus, we are analyzing all single ingredient products in the ten countries having the same active ingredients as the top 56 single ingredient products marketed in the U.S. in 2002 based on retailer acquisition costs (or the value of wholesaler sales). The 54 active ingredients in these 56 products are listed in Figure A.1.

Figure A.1

## THE 54 ACTIVE INGREDIENTS RANKED BY IMS RETAIL ACQUISITION COSTS (FOR 56 PRODUCTS)

| 2002 | RANK | 2002 | RANK |
|---|---|---|---|
| 1 | atorvastatin | 32 | filgrastim |
| 2 | simvastatin | 33 | sumatriptan |
| 3 | lansoprazole | 34 | enoxaparin sodium |
| 4 | omeprazole | 35 | quetiapine |
| 5 | epoetin alfa | 36 | sildenafil |
| 6 | olanzapine | 37 | rabeprazole |
| 7 | celecoxib | 38 | ciprofloxacin |
| 8 | sertraline | 39 | rituximab |
| 9 | paroxetine | 40 | levofloxacin |
| 10 | amlodipine | 41 | ondansetron |
| 11 | gabapentin | 42 | fentanyl |
| 12 | esomeprazole | 43 | azithromycin |
| 13 | risperidone | 44 | fluticasone |
| 14 | rofecoxib | 45 | interferon beta 1a |
| 15 | pravastatin | 46 | etanercept |
| 16 | oxycodone | 47 | valproate semisodium |
| 17 | alendronic acid | 48 | ribavirin |
| 18 | clopidogrel | 49 | metoprolol |
| 19 | citalopram | 50 | docetaxel |
| 20 | loratadine | 51 | levothyroxine sodium |
| 21 | venlafaxine | 52 | fluconazole |
| 22 | fexofenadine | 53 | donepezil |
| 23 | bupropion | 54 | topiramate |
| 24 | pioglitazone | | |
| 25 | infliximab | | |
| 26 | zolpidem | | |
| 27 | montelukast | | |
| 28 | cetirizine | | |
| 29 | rosiglitazone | | |
| 30 | pantoprazole | | |
| 31 | estrogenic substances, conjugated | | |

Source: IMS Health, IMS MIDAS (TM), Q4/2003.

## B. Generic Drugs

For generic drugs, we started with a list from IMS of 50 top-selling active ingredient or combination products (based on global sales in the second quarter of 2003) that were widely available in the ten countries in our analysis. We dropped 21 products that were very old. The resulting data set of 29 molecules included two that also appeared on the list of branded products. These two were omeprazole and metoprolol. A detailed explanation of the generic drugs used in our analysis is below.

We started with a list from IMS of 50 drugs based on sales of all products regardless of ingredient mix. IMS highlighted those ingredients and combinations of ingredients where the three top-sellers were single ingredient products. Our assessment of the IMS list led us to realize that two important combination products should probably be included in our selected list - amoxicillin/clavulanic acid and levodopa/carbidopa. These fixed dose combination products are frequently sold in high volumes. For this reason, we chose them to be included in our final selection, but only as fixed combinations.

The existence of some over-the-counter (OTC) strengths/dosage forms tends to complicate cross-country price comparisons. Thus, if a generic entity was marketed as OTC, especially in the U.S., we excluded it from our list of generics to study.

From the IMS-provided list of 50 generics we selected 31, including the two important combination drugs noted above. In summary, the list of 31 drugs excludes very old drugs, drugs sold primarily in multi-ingredient products, and drugs often sold OTC. The list includes injectable drugs and drugs from most major therapeutic class-

Figure A.2 **THE TOP-SELLING 31 GENERIC DRUGS**

| No. | Generic | No. | Generic |
|---|---|---|---|
| 1 | omeprazole | 18 | vancomycin |
| 2 | amoxicillin/clavulanic acid | 19 | tramadol |
| 3 | metformin | 20 | metoprolol |
| 4 | nifedipine | 21 | lisinopril |
| 5 | propofol | 22 | diclofenac |
| 6 | salbutamol | 23 | lovastatin |
| 7 | tamoxifen | 24 | tizanidine |
| 8 | enalapril | 25 | cefalexin |
| 9 | diltiazem | 26 | amiodarone |
| 10 | atenolol | 27 | pamidronic acid |
| 11 | cefuroxime axetil | 28 | minocycline |
| 12 | levodopa/carbidopa | 29 | aciclovir |
| 13 | furosemide | 30 | doxazosin |
| 14 | warfarin | 31 | megestrol |
| 15 | verapamil | | |
| 16 | lorazepam | | |
| 17 | clindamycin | | |

Source: IMS Health, IMS MIDAS (TM), Q4/2003.

A few widely used generics appear to be excluded, usually because they were not available in all ten countries. Most notable is fluoxetine, which is not available in Japan.

All combination products, except the two listed above, were dropped from our analyses because of problems encountered when identifying strength. When two combination products were removed from the database, it was reduced to 29 generic entities. We analyzed all single ingredient products containing the 29 active ingredients listed above. Thus, innovator and branded products are included, but are identified as such based on our knowledge of the market.

## II. Countries

In its MIDAS™ database, IMS possesses drug-marketing data from over 60 countries, which could be used for price comparisons, but our budget limited the number of countries for which we could purchase data, as well as the time frame the data would cover.

Legislative proposals to legalize importation of finished pharmaceutical products have been limited to countries that are members of the Organization for Economic Cooperation and Development (OECD) with relatively sophisticated drug regulatory processes. We sought to include a variety of countries that have the following attributes:

- Are likely candidates for importation;
- Have well developed drug regulatory systems;
- Have varying kinds of drug price controls and price levels; and
- Are included in IMS's MIDAS™ database (for comparability).

## III. Adjusting IMS (Invoice) Price Data to Reflect Market Prices

The IMS manufacturers' sales data reflect invoice prices. These prices may not correspond exactly to market prices in the U.S. because they exclude discounts, rebates, and chargebacks, which U.S. manufacturers use as a matter of course. In most foreign countries, where the government controls prices and is the only important buyer, such discounts, rebates and chargebacks are thought to be negligible. To create a full and complete comparison of the prices of drugs in the U.S. relative to prices in other countries, we need to estimate the difference between the invoice prices reported by IMS and the actual prices received by manufacturers for U.S. sales after deducting off-invoice payments and making accounting adjustments.

CMS collects data on the average manufacturer price (AMP) paid by retail pharmacies, wholesalers, and other retail purchasers after discounts, rebates, and chargebacks are taken into account. Government agency and hospital sales are excluded. CMS provided these data for 2003 for products using the molecules in our dataset.

CMS identifies unique products in their data by the National Drug Code (NDC) number. Since our IMS data (IMS Health, IMS MIDAS (TM), Q1/2003 - Q4/2003) did not include NDC numbers, we combined the two datasets by use of an intermediary dataset, the National Sales Perspective (NSP) data that FDA purchases from IMS (IMS Health, National Sales Perspective (TM), 2003 extracted October 2004). The NSP data includes NDC numbers.

For some products in our MIDAS™ data set, we were unable to find matching products in the intermediary NSP dataset, or in the CMS data on average manufacturing price. For the branded drugs in our original dataset, we retained data on 40 of our 54 molecules and 66 percent of the data records. For the generic drugs, we retained 28 of our 29 molecules and 56 percent of the data records.

To compare the prices of drugs in the U.S. with the other countries, we constructed a set of price indices weighted by U.S. consumption. We did this two different ways:

- We used only the products where we were able to match IMS's data with CMS's data. In this case, we used CMS's average manufacturer price data and the corresponding IMS quantities in the index calculation. Price indices constructed using this method use only products for which the average manufacturers' price is available, but neglects the IMS data for U.S. products for which this information is lacking.

- Applying to all products in our MIDASTM dataset, the average discounts computed as the ratio of total manufacturer sales in the U.S. in 2003 based on CMS's prices and total sales of the same products based on IMS's prices. For the branded products, the CMS totals were about one percent higher than the IMS totals; for generics, they were 24 percent lower. We then applied these discounts (surcharges) to all the retail sales data in our original database. This method uses all the IMS data, but applies an average discount computed using a subset of the data.

Both methods give generally consistent results.

## APPENDIX B: PRICE DIFFERENCES AMONG INTERNET PHARMACIES

Retail cash prices for drugs – the prices that uninsured Americans pay using credit cards at their pharmacies – are difficult to compare internationally in a comprehensive and systematic way. All systematic prior research uses wholesale or manufacturer prices. As a result, our assessment of retail prices likely to be paid by uninsured people is limited to a relatively small number of drug prices that we can easily observe — those reported on the internet, especially prices for internet pharmacies describing themselves as American or Canadian. See Chapter 1 for a discussion on how some internet pharmacies describing themselves as Canadian have, in fact, no physical presence in Canada.) Of course these internet prices are not necessarily representative of average market prices in either country. Furthermore, we cannot apply standard methods of averaging price differences by weighting prices by quantities sold, because information on the volume of sales is unavailable. Despite these deficiencies, cash prices at internet pharmacies are of great importance to Americans whose budgets require them to search for the very lowest drug price. To best portray price differences for these consumers we present an analysis of internet drug prices.

The lowest internet pharmacy prices available to U.S. consumers for branded drugs are about 37 percent less at Canadian pharmacies, while generics sold at U.S. internet pharmacies are approximately 32 percent less than Canadian generic prices. We base this conclusion, which takes into account shipping costs assuming one prescription per shipment, on an assessment of the prices for 22 top-selling prescription drugs available from a single company, and five top chronic-use generics from U.S. and Canadian internet pharmacies. Our price information is from the website www.pharmacychecker.com. There is substantial variation around these averages. For some branded drugs, the U.S. price premium varies greatly for different strengths and package sizes of the same product.

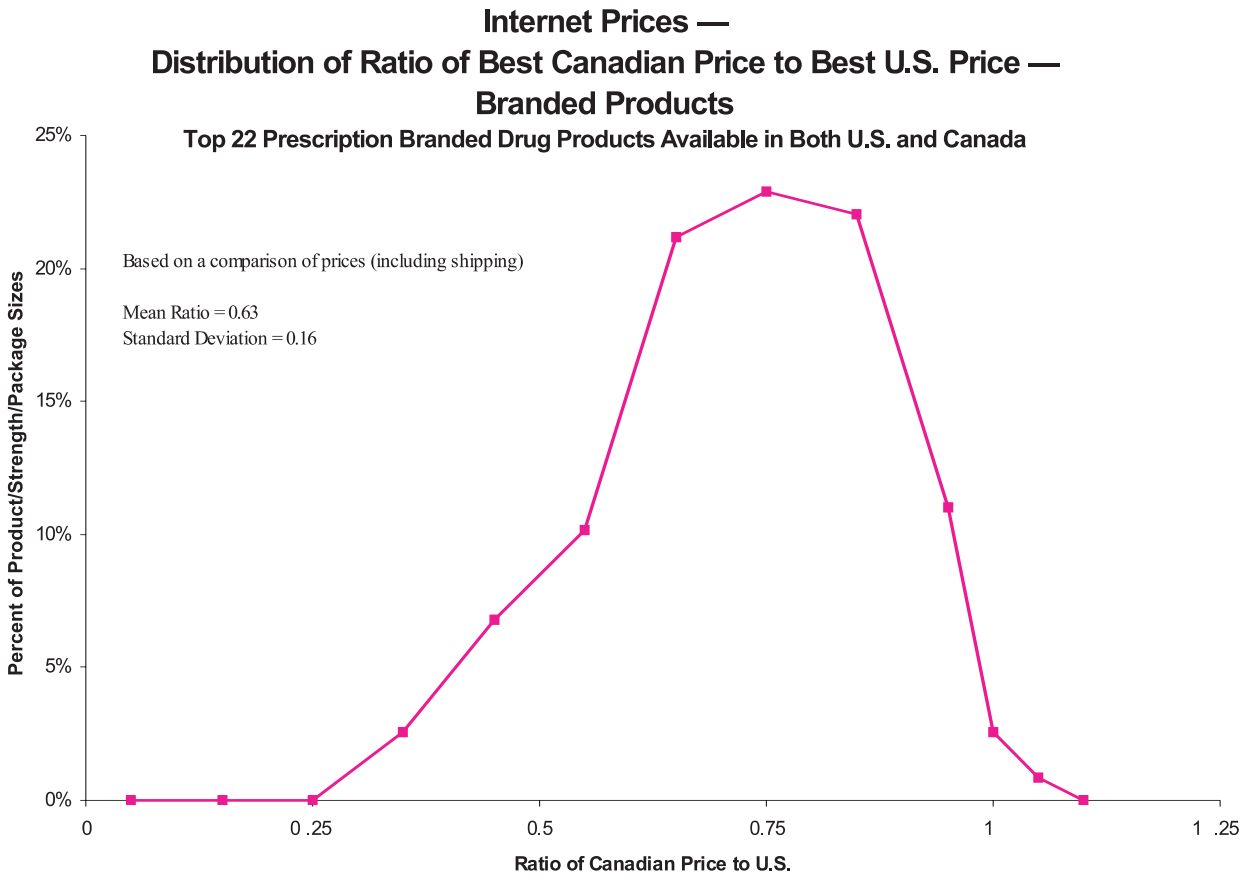
The source of our data, the PharmacyChecker.com website, collects and assesses prices for pharmaceuticals from 30 Canadian and six U.S. online/internet pharmacies. According to the site, "PharmacyChecker.com LLC ("PC") collects, evaluates, and reports credentials, prices, and customer feedback regarding pharmacies that operate online and through mail-order and fax (generally referred to as "online pharmacies" or "OLPs"). It is the leading independent source of information about online pharmacies."

### Prices on Branded Products — Internet Prices

Our analysis of branded drugs started with 30 top-selling drugs, based on U.S. sales and available from a single source. Five of these 30 drugs are either not available, or are not available via the internet, in Canada (Procrit, an injectable anti-anemia medicine for cancer patients, called Eprex in Canada; Epogen; Oxycontin, a pain reliever and Schedule II controlled substance; Remicade, an anti-inflammatory drug used against Crohn's disease and arthritis; and Ambien, prescribed to treat insomnia). We excluded Zyrtec and Allegra because they are available OTC in Canada, and Claritin, which is OTC in both countries. As a result, this analysis included 22 drugs.

For each pharmaceutical product, we identified all instances where the same combinations of strength and package size were available in both countries. In a few cases, identical package sizes were not available, but, if the sizes were similar (e.g., 28 tablets in Canada, 30 in the U.S.), we included the packages, but took the different numbers of tablets into account in computing unit costs. All prices used in this analysis include shipping costs; the prices are related to internet prices only. For drugs ordered from the Canadian pharmacies, shipping typically costs between 10 and 15 dollars. For drugs ordered from U.S. pharmacies, shipping typically costs between zero and two dollars.

Figure B.1

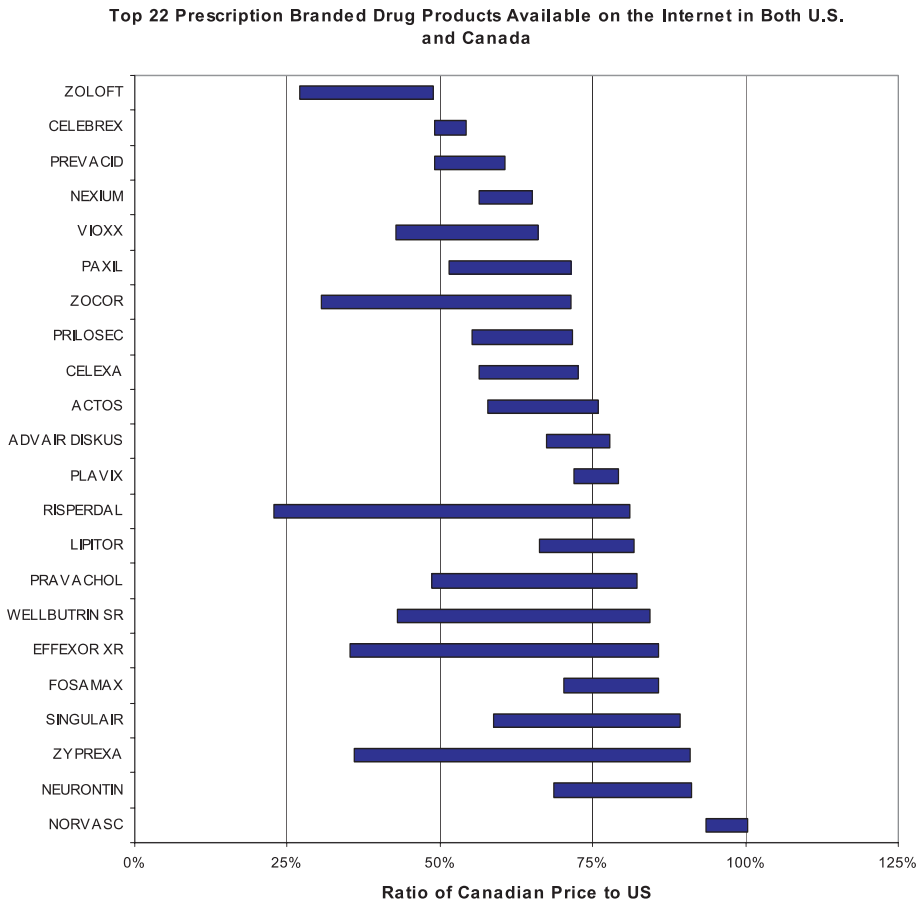



Source: Pharmacychecker.com March 10-11, 2004.
Note: Shipping costs are included assuming one prescription per shipment.

For each matching product (active ingredient, dosage form, strength, and package size), we recorded the lowest U.S. price and the lowest Canadian price. Then we took the ratio of the Canadian price to the U.S. price. In all, there were 118 matching products for the 22 drugs. For all but one of these, the U.S. price was higher than the Canadian price. Figure B.1 shows the distribution of the price ratios. On average, Canadian prices for branded products are 63 percent of U.S. prices (or 37 percent lower than U.S. prices), with shipping included. Figure B.2 shows the range of price ratios for each of the 22 drugs and includes the 118 matching products. Clearly, the difference in pricing between the U.S. products and Canadian products can depend on not only the drug, but also the dosage form, strength, and package size.

Figure B.2

**Internet Prices — Range of Price Ratios for Different Strengths or Package Sizes of the Same Product — Branded Products**



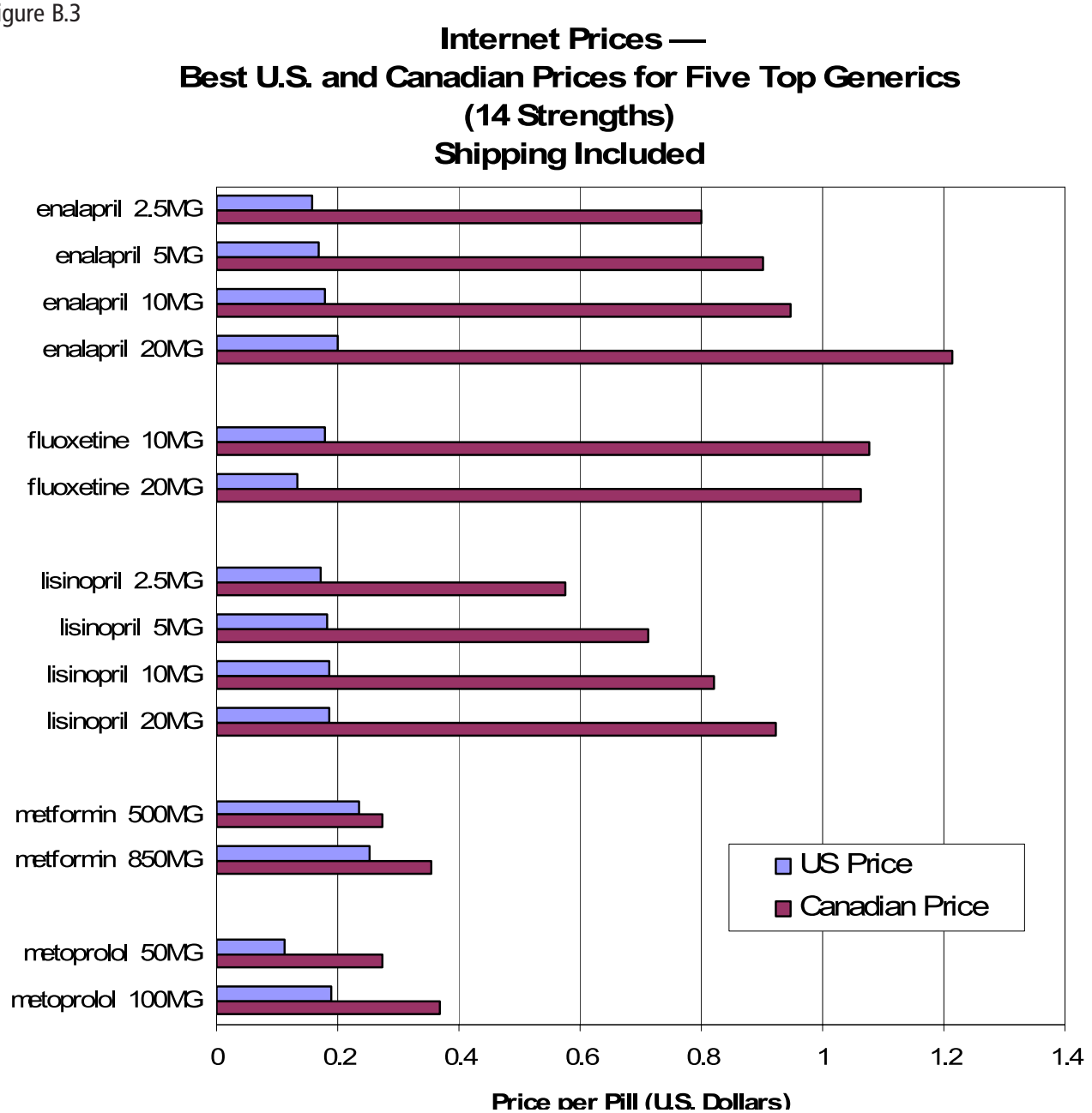

Source: Pharmacychecker.com March 10-11, 2004.

## Prices on Generic Products — Internet Prices

For the generic drugs, we started with seven top-selling chronic-use drugs for which the first U.S. generic entry occurred in the last ten years. Our set of seven drugs represents all the generic entities first entering the U.S. market in the last ten years that are sold in solid dosage form, not over-the-counter, and are not anti-infectives. Two of these, alprazolam and clonazepam, were available only in the U.S. The remaining five are listed in Figure B.3. Not all of these are available as generics in Canada. For each strength that is available in both countries, we calculated the lowest price per pill, regardless of the package size. As with the name brands, we included shipping costs in the prices.

For the five generic drugs (14 strengths) included in this analysis, we found that, on average, U.S. generic prices were 32 percent lower than Canadian generic prices, when the products were purchased from internet pharmacies in each country. This includes shipping costs.

Figure B.3




Source: Pharmacychecker.com March 10-11, 2004.
Note: For enalapril, which is not available as a generic in Canada, we use the price of the name brand equivalent.

## Caveats

Different shipping costs complicate this analysis. Shipping costs per shipment are much higher in Canada, but exactly how this fact affects the average cost of buying drugs from U.S. and Canadian internet sources depends on how many prescriptions are purchased with each shipment. The risks of buying drugs from foreign internet sources may be higher than from U.S. internet sources, but a comprehensive comparison of such risks is very difficult.

## APPENDIX C: METHODS OF COMPARING PRICES

To compare the prices of different drug products in different countries, we needed to determine what we meant by a 'product' and how to measure its quantity. We examined numerous different methods before settling on one that defines a product as the molecule and the quantity as the number of kilograms or international units (IU). We based this determination on the logical consistency of the comparison and the amount of data each comparison included or excluded.

Figure C.1, shows the results of four different methods of comparing prices:

- Defining a product as a molecule and using both kilograms (or IU) and standard units (SU) as the quantity measure (a standard unit corresponds approximately to a dose), and
- Defining a product as a molecule and dosage form (determined by the first character of the New Form Code (NFC123)) and using both kilograms (or IU) and standard units (SU) as the quantity measure.

Other comparisons we examined but do not display include:

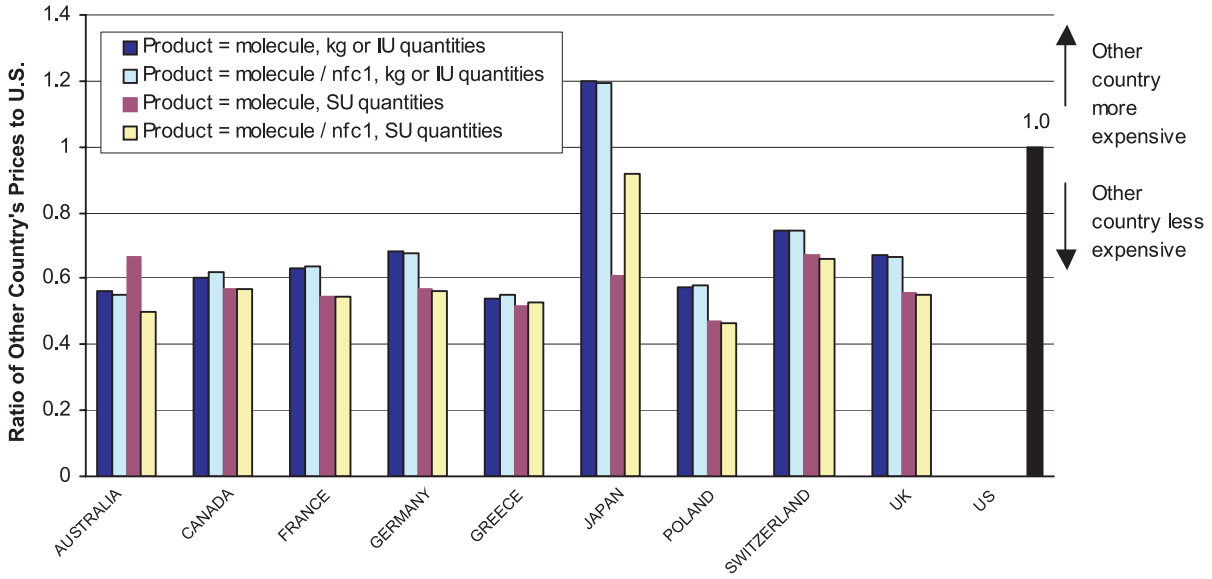
- Using 'counting units (CU)' as a quantity measure;
- Defining a product as the same molecule and 3-character New Form Code (NFC123);
- Defining a product as the same molecule, NFC123, and strength, and;
- Defining a product as the same molecule, NFC123, strength, and package size.

We decided against comparisons that use counting units or standard units as quantity measures and define product at the aggregated levels of molecule or molecule/NFC1 because they fail to differentiate among different strengths of the same drug. For example, they would equate, if all existed in a country, 10 mg tablets with 20 mg, 40 mg, and 80 mg. Using kgs or IUs avoids these invalid comparisons. We decided against using the more precise definitions of a product because they eliminated too much data. The three-character NFC lists as separate dosage forms, for example, tablets, tongue soluble tablets, and soluble tablets, or, alternatively, coated tablets, sugar-coated tablets, film-coated tablets, chewable-coated tablets, etc. Requiring, in addition, the same package size eliminated nearly all the cross-country comparisons. Figure C.2 and C.3 show the number of data records and molecules each different comparison included.

Figure C.1

**Comparison of Different Indexing Methodologies**

**All Comparable 54 Top-selling 2002 US Products, Innovators and Licensees only, Weighted by US Consumption, Adjusted US Prices***

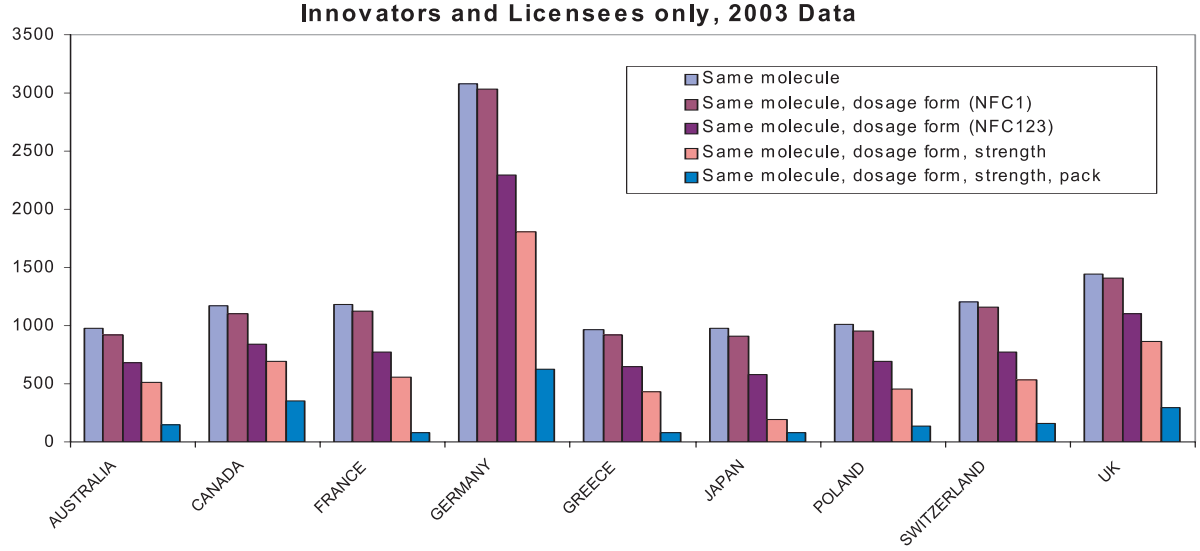



Source: Analysis completed by HHS based on data from IMS Health, IMS MIDAS (TM), Q4/2003; IMS Health, IMS MIDAS (TM), Q1/2003 - Q4/2003; IMS Health, IMS National Sales Perspective (TM), 2003 extracted October 2004; IMS Health, IMS National Prescription Audit (TM), 2003.
*US prices increased by 145 percent for non-Medicaid sales to account for differences between MIDAS's manufacturer prices and CMS's manufacturer prices and reduced by 46.75% for Medicaid sales which represent 15.2 percent of total sales for innovator and licensed branded products.

Figure C.2

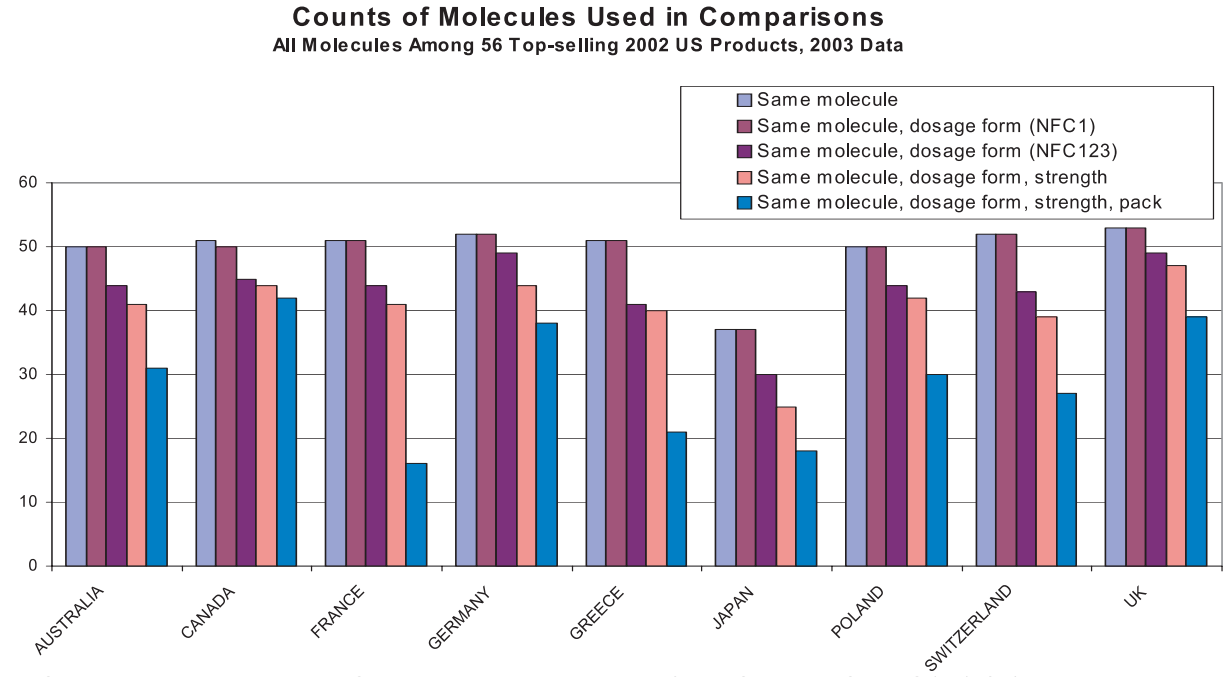
**Counts of Data Records Used in Comparisons**

**All Comparable of 56 Top-selling 2002 US Products, Innovators and Licensees only, 2003 Data**




Data Source: Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.

Figure C.3




Data Source: Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.

## APPENDIX D: IMPORTATION IN THE EUROPEAN UNION (E.U.)

Careful studies of the experience of the E.U. with legalizing trade in pharmaceuticals suggest that the practice has had small effects on aggregate drug spending, and that intermediaries get a large share of the total gains.

A recent paper by Kanavos et al.1 reports that savings to drugs buyers from commercial importation were very small because intermediaries retained most of the potential gains from trade. The authors studied drugs in six therapeutic categories that were treatments for chronic illnesses. Their data set, however, represented only 14 to 28 percent of the various countries' retail expenditures for prescription drugs.

In a separate study from the University of York, researchers calculated direct savings--excluding any savings from lower prices on domestic drugs--to government health funds from parallel imports for five European countries that are net parallel importers: Denmark, Germany, the Netherlands, Sweden, and the U.K.[2] IMS Health reviewed this study and suggested the savings values reported for Germany and the U.K. were misstated and should be, $126 million and $201 million, respectively.[3] Using total drug sales for each country (manufacturers' prices), we calculated the savings as a percent of total pharmaceutical sale.[4] Using these values, savings as a percent of sales range from 0.8 percent for Germany to 2.5 percent for Sweden.

Figure D.1

**Savings from Drug Importation for Selected European Countries in 2002**

| | Total Sales* ($ million) | Total Sales** (€ million) | Savings*** (€ million) | Savings as a percent of sales**** |
|---|---|---|---|---|
| Denmark (2001)***** | N.A. | N.A. | 15.7 | 1.2 |
| Germany | 20,278 | 16,425 | 194.0 | 0.8 |
| Netherlands | 3,090 | 2,503 | 31.6 | 1.3 |
| Sweden | 2,339 | 1,895 | 46.7 | 2.5 |
| United Kingdom | 13,660 | 11,065 | 342.0 | 1.8 |

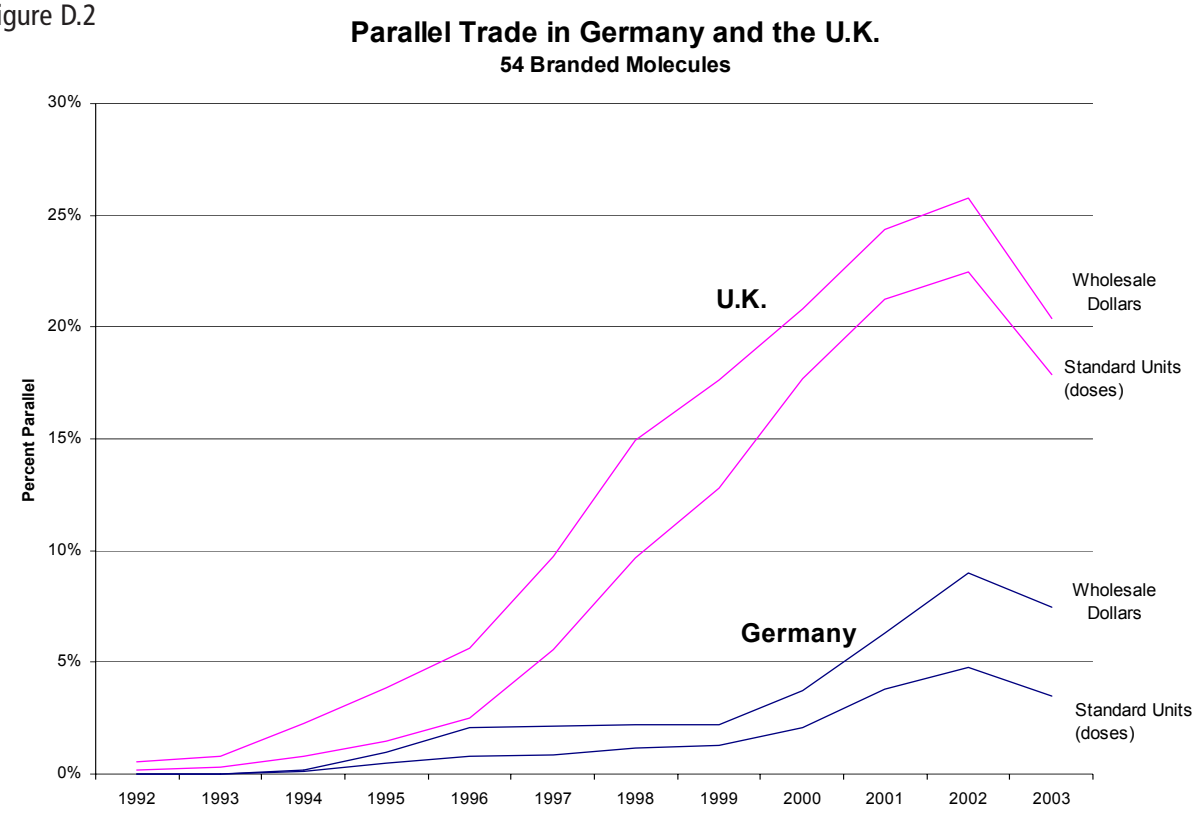
*Source: IMS Health, IMS Country Sales Report (TM), 2004.
**Conversion factor € 1 = $0.81;
***West and Mahon (2003, p. 67)
****Calculated by FDA
*****West and Mahon report total Danish drug bill of €1.3 billion in 2001, (p. 8)

Ganslandt and Maskus[5] report that parallel trade in Sweden reduced prices by between 12 percent and 19 percent, but the total savings to drug buyers are less than these estimates because there were no imports for many categories of drugs. In particular, the authors report that only 46 percent of the market captured in their data set experienced entry, largely because prices and volume of the other products did not attract parallel importers. Moreover, their dataset of the top 50 molecules represented about 37 percent of total Swedish wholesale sales in 1998. Assuming that parallel imports were negligible outside their data set, savings in Sweden from importation were approximately two percent and 3.2 percent of total drug spending.[6] Alternatively, an optimistic assumption that savings are proportional to regulatory decisions to authorize imports would imply that the imports outside the data set represent 42 percent of the total savings from imports, because their data on the top 50 molecules represented about 58 percent of the total approvals for parallel imports in 1998. Thus, this upper-bound estimate of savings in Sweden from imported drugs is between 3.5 percent and 5.6 percent of total drug spending.[7] We qualify this result by noting that the limited available supply of importable drugs has less of an effect on the small Swedish market than it would on the large U.S. market. If the Swedish market faced tighter supply constraints, the impact on drug spending would be smaller.

Using IMS data, we conduct two related analyses of the experience of importation in the E.U., focusing on two countries thought to be important importers, the U.K. and Germany.

First, we evaluate the volume of imported drugs. For each molecule, we measure the volume of imported drugs as the total doses (standard units) of all imported products divided by the total doses of all products. We find that the average volume of imports measured in this way peaked in 2002 and fell slightly in 2003 as illustrated in Figure D.2. The lack of continued recent growth in these estimates suggests that some supply constraints are limiting increases in the volume of imported drugs.

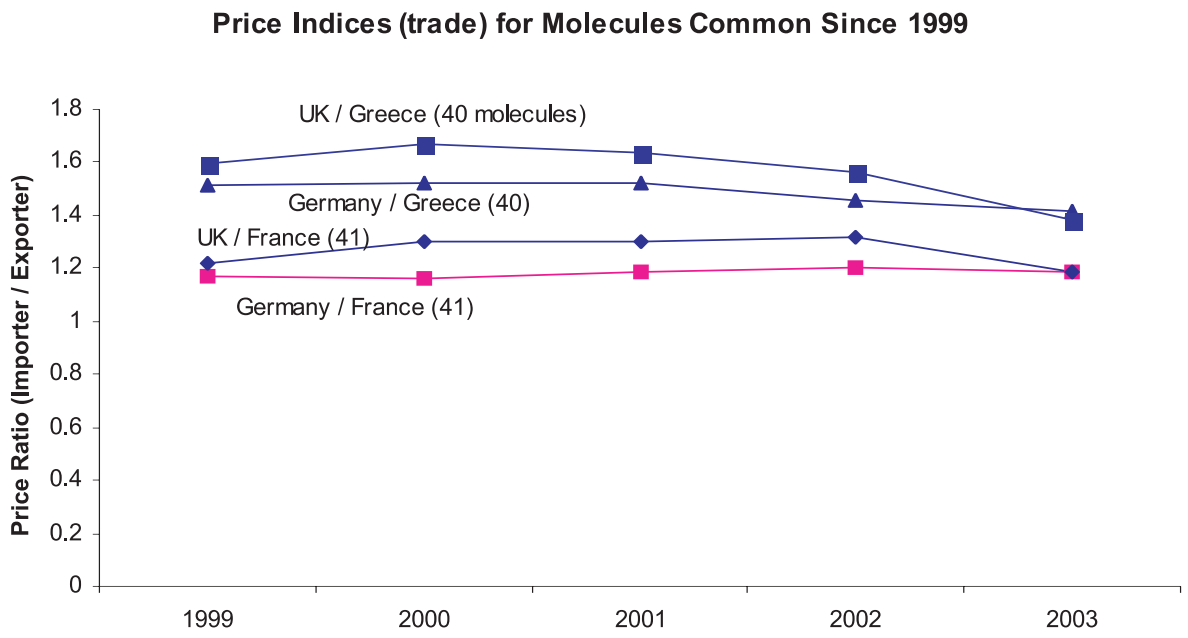
Figure D.2




Source: Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.

Second, we investigate whether increases in the volume of imports were associated with declines in the price of drugs when measured as retail acquisition costs. In particular we assess whether molecules for which the growth of import volume was high were also those for which the changes in wholesale price was modest or negative. We find no evidence that greater import volume reduced or avoided price increases. Our statistical analyses failed to show a relationship, because, as seen in the Figure D.3, rising imports did not seem to be associated with a declining premium of German or U.K. prices relative to those in the exporting countries.

Figure D.3




Note: These are indices of wholesale prices.
Source: Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.

Ultimately, however, the experience of E.U. countries is limited in its ability to predict the effects in the U.S. if importation became legal. All of the E.U. countries we researched have socialized healthcare programs that include some form of prescription drug coverage. In the U.K. and Germany, the two countries with the largest volume of imports, consumers pay fixed fees per prescription for the majority of drug products prescribed during the period our data covered.[8] Methods of reimbursing pharmacists in Germany are actually disincentives for use of parallel-sourced drugs.[9] Pharmacists are reimbursed at a fixed percent so they had a financial incentive to sell more expensive products.

1 Kanavos, Panos; Costa-I-Font, Joan; Merkur, Sherry; and Gemmill, Martin, "The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Stakeholder Analysis," LSE Health and Social Care London School of Economics and Political Science, January 2004 (hereinafter cited as Kanavos et al., 2004).
2 *See* Figure D.1; West, Peter and Mahon, James, "Benefits to Payers and Patients From Parallel Trade," York Health Economics Consortium, The University of York, May 2003 (hereinafter cited as West and Mahon, 2003).
3 IMS Health, "Parallel Trade in Europe –Assessing the Reality of Payer and Patient Savings," September 1, 2004.
4 Ideally the percent savings should be calculated using total sales at the retail level, however, we did not have consistent data for retail sales for the countries of interest. Using the manufacturer's price overstates the percent savings, so these estimates should be viewed as upper bounds.
5 Ganslandt, Mattias and Maskus, Keith E., "Parallel Imports of Pharmaceutical Products in European Union," The Research Institute of Industrial Economics (IUI) Working Paper No. 546, 2001.
6 The lower bound is .12 x .46 x .37, while the upper bound is .19 x .46 x .37.
7 The lower bound is .12 x .46 x .37 x (1+.42/.58), while the upper bound is .19 x .46 x .37 x (1+.42/.58).
8 Kanavos et al., 2004
9 West and Mahon, 2003; Kanavos et al., 2004; Tobin, Helena and Turner, Niel, "Parallel Trade 2003 A concise Guide," PPR Communications, Ltd., Cambridge, United Kingdom, 2003.

## APPENDIX E: POTENTIAL GENERIC SAVINGS

Consumers could save billions of dollars annually if they purchased generic versions of prescription drugs whenever these are available. Our examination of recent data on retail drug purchases estimates this potential savings. If consumers were to buy generic products whenever possible and no brand-name equivalents, we estimate savings to be approximately $17 billion.

For the 29 top-selling off-patent molecules described elsewhere, we obtained detailed 2003 retail price and quantity data for generic products and their branded equivalents.[1] We calculate potential savings as the difference between the price of a brand name product produced by an innovator or its licensee and the price of generic substitutes calculated as a weighted average of prices of generic products using a given molecule, dosage form and strength. Thus, for each molecule, dosage form, and strength, we have the branded product and its average retail price, plus the average retail price of a generic substitute.

The potential consumer savings from complete use of generic versions of products using these 29 molecules would be approximately $700 million. According to our data for 2003, consumers spent approximately $2.1 billion in retail establishments buying branded versions of single ingredient products using the 29 molecules when there was a generic equivalent available. If these purchases had been made at the prevailing average generic price, retail expenditures would have been $1.4 billion— $700 million less.

The set of 29 molecules includes the top-selling generics, but represents a fraction of all branded pharmaceutical products that face generic competition. One way to project the savings for the universe of such products is to use a 1998 report from the Congressional Budget Office that estimated that 27 percent of retail pharmacy sales went to innovator products with generic equivalents.[2] This estimate could be considered to be an upper bound because it counts an extended-release dosage form as having generic competition versions even if all generic products use only the original formulation. Consumers may be more reluctant to substitute in that instance because they would lose the additional convenience of the extended release product.

CBO's estimate that 27 percent of spending is on brand name products that face generic competition suggests retail sales of innovator versions of multiple source drugs would now be about $50 billion.[3] Complete use of generics whenever they are available in the same dosage form and strength offers savings of about a third in our data set ($700 million on spending of $2.1 billion on unprotected brand-name products). Applying this fraction to $50 billion suggests that complete use of generic substitutes for brand-name unprotected products could save $17 billion.

Although we conducted this analysis using data from retail pharmacies only, we find that we reach a similar conclusion when we repeated our analysis using sales data based on all distribution channels including hospitals, nursing homes, internet and mail-order.[4] We used manufacturer sales covering 28 of the 29 drugs in the first study. Across all distribution channels if branded multiple source drugs had been purchased at the average generic price, the savings would be approximately $1.4 billion. Reasonable extrapolations to the universe of branded drugs with generic equivalents would yield total savings in the billions of dollars. Thus, this finding supports our initial conclusion using retail level data.

1 Analysis completed by HHS based on prescription sales data provided by IMS Health, IMS National Prescription Audit (TM), 2003.

2 Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," page 15, 1998. In the report, if generic versions of an innovator drug were available in any

dosage form, then all sales of all dosage forms of the innovator drug were classified as being multiple source.

3 Estimated 2003 U.S. sales were $184 billion, according to Centers for Medicare & Medicaid Services (CMS) "Prescription Drug Expenditures; Aggregate and per Capita Amounts, Percent Distribution and Average Annual Percent Change by Source of Funds: Selected Calendar Years 1990-2013.

4 Analysis completed by HHS based on prescription sales data from IMS Health, IMS MIDAS (TM), Q4/2003.