

THE QUALITY QUANDARY

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ABSTRACT

America's physicians write over three billion prescriptions a year for patients¹—and they need to know that when patients fill those prescriptions, the drugs they take are safe. Physicians want their patients to be able to get those drugs at the lowest price possible. Patient safety and drug quality are the overriding issues, as physicians work with their patients to make prescription drugs more available and affordable. Patients are rightly concerned over the cost of prescription medication and are seeking alternative sources to fulfill their prescription drug needs. Many are turning to international pharmacy outlets as a resource and the Internet. The Internet option creates a special concern for physicians, as not all Internet sources are reliable or ethical. Further, importation creates safety issues. Using Canada as an example, there is considerable misunderstanding within the general public regarding the authenticity of medications imported or reimported from Canada. Many drugs sold there are manufactured in other countries where the U.S. Food and Drug Administration (FDA) has no authority. These issues and others become even more complex and are not easily addressed simply by contracting with an international pharmaceutical drug distributor, as many states have done or are considering. Therefore, to ensure that patient safety is the primary concern, drugs should be FDA-approved, the distribution chain should remain closed, products should be subject to track and trace technology, and FDA resources should be adequate to ensure authenticity and integrity of imported or reimported drugs.

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1. L. Michael Posey, *Prescriptions Top 3 Billion in U.S.*, PHARMACY TODAY (2001), available at http://www.pharmacist.com/articles/h_ts_0083.cfm.

INTRODUCTION

The United States appropriately takes great pride in its efforts to see that our citizens are the recipients of excellent medical care. With over 285 million citizens, this can be a daunting task. The lofty goal of providing quality medical care, including prescription medication availability, building modern facilities, promoting up-to-date technological advances, and community support for the sick and the ailing citizens of our country is commendable. Great sums of time and capital are invested in trying to reach these goals. The effort is a combination of public and private integration that is not seen in the rest of the world.

A major part of that effort is embodied in the availability and quality of prescription drug medication. American physicians write nearly 3.5 billion new prescriptions every year.² It is estimated that over forty percent of the population, i.e., 110 to 115 million people, take a prescription medicine every year. It is also widely accepted that the U.S. drug supply is among the safest, if not the safest, in the entire world.³ This has been an accomplished exertion, embracing cooperation of regulatory, legislative, and pharmaceutical manufacturing efforts over the past century. The twentieth century marked an evolution for the U.S. drug regulatory and manufacturing system, providing high levels of quality pharmaceutical products.

REGULATION

Regulatory efforts were often in response to a catastrophic event that highlighted the vulnerability of the manufacturing and distribution of drug products within the United States.⁴

In 1906, Congress passed the Pure Food and Drug Act that addressed adulteration of foods and drugs.

In 1938, Congress passed the Food, Drug, and Cosmetic Act (FDCA) that required the U.S. Food and Drug Administration (FDA) to validate the safety of the drug before the manufacturer could make the product commercially available for distribution. “[T]he FDCA was passed in response to the elixir of sulfanilamide disaster of 1937,

2. *See id.*

3. J. JAMES ROHACK, AMERICAN MEDICAL ASSOCIATION BOARD OF TRUSTEES REPORT: PRESCRIPTION DRUG IMPORTATION AND PATIENT SAFETY (2004) [hereinafter AMA REPORT], available at <http://www.ama-assn.org/ama1/pub/upload/mm/465/bot3i04.rtf>.

4. *Id.* at 2.

where 107 persons were killed by diethylene glycol (antifreeze) which was used as a solvent” in a drug product.⁵

In 1951, Congress passed the Durham-Humphrey Amendment that addressed the classification of drugs in prescription-only and over-the-counter medications. Since 1951, federal law requires that prescription drugs should only be dispensed by a licensed practitioner.

In 1962, Congress passed the Kefauver-Harris Amendments that addressed effectiveness and safety of drugs. The Act required pharmaceutical manufacturers to perform within good manufacturing practices (GMP), gave the FDA the authority to inspect the facilities where drugs are manufactured, and directed that a package insert providing full disclosure about the prescription drug be initiated.⁶

In 1987, Congress passed the Prescription Drug Marketing Act in response to concerns about counterfeit drugs entering the U.S. drug supply. This law addressed the importation of pharmaceuticals, allowing a personal use exemption but restricting importation to pharmacy wholesalers and distributors only.

In 2000, Congress passed Section 804 of the FDCA, which allowed wholesalers and pharmacies to reimport drugs from Canada that were already available in the United States. It also required Health and Human Services (HHS) to demonstrate to Congress that importation and reimportation pose no additional risk to the public health or safety and would reduce the cost of prescription drugs.⁷

In 2003, Congress passed the Medicare Prescription Drug Improvement and Modernization Act, which, among other things, established a task force to address importation issues.⁸

ISSUES

Drug importation and reimportation has surfaced as a major topic before Congress and in the minds of people across the nation. In part, current discussions dealing with importation and reimportation of medications are being debated in Congress, in the legislative and administrative arenas of state governments, and in the homes of citizens throughout the United States. These discussions are being fueled by the increasing cost of prescription medication, the increased use of potent medications in the treatment of major medical problems, and the

5. *Id.*

6. *Id.*

7. *Id.*

8. *Id.* at 16.

increasing use of medications by all ages of the population in the United States.

There are a number of significant issues that are driving the discussion of importation and reimportation of prescription drugs in the United States. Safety and the quality of prescription medications are the overriding issues that face our patients. Patients are rightly concerned and grieved over the cost of prescription medication and have been seeking alternative sources in the acquisition of prescription drug needs. Many patients have turned to importing drugs from Canada and other countries, and frequently use the Internet as a resource. Cost concerns primarily have created the impetus for patients to find their prescription medications from alternative sources other than the U.S. distribution system. Cost concerns and the opportunity to use alternative resources pose significant challenges, which is the focus of this discussion.

Fine-tuning the issues should facilitate an understanding of the critical variables and perhaps provide a construct for conclusions and provide direction in developing a template for solutions to the challenges of quality and cost appropriateness. Two terms that need defining are reimportation and importation. In this discussion, reimportation is meant to cover those prescription pharmaceuticals that are manufactured in the United States or manufactured in another country by an FDA-certified manufacturer or manufacturing process, and then shipped to the manufacturer in the United States. The drug or drug product is then sold and distributed to an authorized purchaser in another country and then reimported to the United States. This is generally considered a closed distribution system.

Importation of pharmaceuticals in this discussion are those prescription medications that are manufactured in another country and are not part of a FDA-approved manufacturing process, and then are shipped to the United States either through an Internet source or a distributor from the country of shipment. These imported medications cannot be guaranteed to be FDA equivalent.

Another significant issue is the cost of medication. There is a difference in prescription cost of generic versus brand name drugs. A recent survey of my practice for a typical Medicare patient over the age of sixty-five with coronary artery disease, hyperlipidemia, hypertension, diabetes, and arthritis is presented in the following table which outlines the cost of similar medications to treat the same illnesses. Recognizing its limitations, the table illustrates the cost differential between using generic and brand named products for a typical patient. Our seniors, as well as other people in the community, are quite sensi-

tive to the price differential and the opportunity to treat them in a cost effective manner. It is recognized that not every patient fits this template, but there is opportunity to address significant medication savings in treating patients.

<u>GENERIC</u>	<u>BRAND NAME</u>
Isosorbide 20mg \$9.17	Imdur 30mg \$49.59
Lovastatin 20mg \$60.29	Lipitor 20mg \$120.99
Lisinopril/Hctz 20/12.5 \$27.17	Avalide 300/12.5 \$77.59
Metoprolol 50mg(BID) \$16.73	Toprol XL 50mg \$35.49
Glipizide 10mg(BID) \$28.99	Amaryl 4mg \$35.00
Metformin 1000mg(BID)\$38.69	Glucophage 1000(BID)\$107.00
Ibuprofen 600mg(BID) \$5.00	Celebrex 200mg(BID)\$193.99 ⁹

Prescription drug coverage is an issue for our senior citizens. A recent survey of patients in my practice revealed that only forty percent of them had any type of prescription coverage. Only five percent of them participated in the 2004 approved Medicare Discount Drug Program, as penetration of the program in the Medicare population has been disappointing.

There are also diminishing benefit options for patients under sixty-five. The following table, published by Modern Healthcare in April 2005, demonstrates a decreasing percentage of Americans who have employer-based health insurance.¹⁰ Coverage dropped from 67.2% in 1999 to 63.8% in 2003. There is the perception that this trend is continuing into 2005 and perhaps at an accelerated rate. It is not just the seniors who are being impacted by diminishing health care coverage. At any one time, there are fifty-eight million people in the United States without health care coverage,¹¹ most of whom are employed but without employer-based health insurance and, consequently, do not have prescription drug benefits as well.

9. This table represents the average cost of a one-month supply of medicines from a group of community pharmacies that the author's patients utilized in Lafayette, Indiana.

10. Laura B. Benko, *Is the Worst Yet to Come?*, MODERN HEALTHCARE, Apr. 25, 2005, at 6.

11. Charles Marwick, *A Total of 58 Million Americans Lack Health Insurance*, 325 BRITISH MED. J. 678, 678 (2002), available at <http://bmj.bmjournals.com/cgi/content/full/325/7366/678/d>.

Percentage of Americans Under Age
65 with Employer Based Health Insurance

YEAR	% of AMERICANS
1999	67.2
2000	67.7
2001	66.4
2002	65.0
2003	63.8 ¹²

Counterfeiting of prescription drugs is a major issue. The World Health Organization estimates that at least 10% of the world drug supply is counterfeit.¹³ When one considers the high prescription drug use within the United States, it can be inferred that the counterfeit volume in the rest of the world is substantially higher than 10%. Without having a closed system for distribution, this poses a quality risk factor for U.S. citizens who are seeking alternative sources for prescription medications outside of a closed system.

Adulterated drugs and unapproved drugs entering the distribution system are a major concern. The FDA conducted spot checks in 2003 and 2004 that demonstrated major problems of unapproved, mislabeled, inappropriately packaged, and veterinary drugs being shipped into the country for distribution.¹⁴

Personal importation via the Internet is a major issue and concern. Although on the surface it is quite appealing, it represents a risk for our patients because rogue pharmacy Internet sites are not what they appear. Many appear to represent pharmacies in Canada or perhaps the United Kingdom, where a certain sense of safety prevails. Unfortunately, many of these are rogue sites located in various countries all over the world, dealing in counterfeit and adulterated drugs, which are then shipped to unwary patients at a price that seems appealing.

All these factors have culminated in a number of focused Federal Task Force evaluations over the past two to three years. In July 2003, the FDA Commissioner established a Counterfeit Drug Task Force and submitted a report in 2004 entitled *Combating Counterfeit Drugs*:

12. Benko, *supra* note 10.

13. *Importation of Prescription Drugs into the United States: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 108th Cong. (2004) [hereinafter Taylor Testimony] (statement of John M. Taylor, Assoc. Comm'r for Regulatory Affairs, FDA), available at <http://www.fda.gov/ola/2004/importeddugs0520.html>; AMA REPORT, *supra* note 3, at 7.

14. AMA REPORT, *supra* note 3, at 8.

*A Report of the Food and Drug Administration.*¹⁵ The Task Force recommended a multi-pronged approach to combat the growing trend of counterfeiting and its impact on our domestic supply chain:¹⁶

1. The adoption of a reliable “electronic track and trace technology.” Radio frequency tagging would facilitate an accurate drug pedigree, i.e. a record of distribution of the drug from the sale by the manufacturer through the acquisition and distribution by any wholesaler, repackager, or pharmacy to insure authenticity and integrity of the drug product throughout the drug distribution chain. This would require acceptance, not only within the borders of the United States, but by international manufacturers as well to have any major impact. Unfortunately, there is no widespread acceptance of the technology, nor any enforcement mechanism to require its implementation or assure its utility.
2. The use of overt and covert authentication technology, such as color shifted inks and holograms for pharmaceuticals.
3. Increased regulatory enforcement of wholesale distributors by state governments who have the responsibility for licensing.
4. Increased criminal penalties to deter counterfeiting and to more adequately punish those who are convicted.
5. Adoption of more secure business practices by all participants in the drug chain (difficult to get widespread acceptance).
6. Development of a more effective reporting system for counterfeit drugs, including a counterfeit alert network.
7. Education of consumer and health professionals about the risks of counterfeit drugs and how to protect against those risks.
8. And finally, collaboration of foreign governments to develop strategies to deter and detect counterfeit drugs globally.

The Task Force noted that counterfeiting is a major issue internationally and the issue has to be addressed from a global perspective to have any hope for success.

15. FDA, COMBATING COUNTERFEIT DRUGS: A REPORT OF THE FOOD AND DRUG ADMINISTRATION (2004), available at http://www.fda.gov/oc/initiatives/counterfeit/report02_04.html.

16. *Id.*

The HHS Task Force Report on Drug Re-importation was released in December 2004.¹⁷ This Task Force identified different categories of imported drugs that potentially have different levels of associated risks. Currently, the only types of imported drugs are:

1. Those manufactured in foreign FDA-inspected facilities adhering to FDA standards.
2. Drugs approved by the FDA and manufactured here, sent abroad, and then reimported back into the United States by the manufacturer in compliance with the Food, Drug, and Cosmetic Act. These are truly drugs that are “reimported” and are part of a closed drug distribution system.
3. Imported drugs are those that are manufactured in a foreign facility that may manufacture U.S.-approved versions of the drugs, but the imported drugs are produced in unapproved manufacturing lines, i.e. a foreign version which may differ in certain aspects from the FDA-approved version. The foreign version cannot necessarily be considered equivalent to the U.S.-approved version of the drug.
4. The final category of imported drugs, which are unapproved, are those produced in foreign facilities that the FDA has not inspected. The FDA cannot assure the safety and effectiveness of these drugs. They pose the greatest concern because little is known by U.S. regulators about how they have been made or the process used to ensure their safety.

The Report estimates that in 2003 alone, cross-border sales from Canada resulted in nearly five million shipments containing twelve million prescription drugs with an approximate value of \$700 million entering into the United States.¹⁸ It is assumed that these numbers have grown substantially in 2004.

The Report also expresses concern regarding at least an equivalent amount of drugs that are being imported from the rest of the world through mail order and courier services. The safety and validity of these drugs cannot be ensured. Spot checks of drugs in 2003 by inspectors found that the majority of packages examined in these blitz inspections contained illegal and unapproved drugs.¹⁹ FDA and customs inspectors examined mail shipments in Miami and New York in

17. U.S. DEP'T OF HEALTH & HUMAN SERVS., HHS TASK FORCE ON DRUG IMPORTATION: REPORT ON PRESCRIPTION DRUG IMPORTATION 37-38 (2004), *available at* <http://www.hhs.gov/importtaskforce/Report1220.pdf> [hereinafter HHS TASK FORCE].

18. *Id.* at 11-12.

19. *Id.* at 13.

July of 2003, and in San Francisco and Carson, California facilities in August of 2003.²⁰ They examined 1153 shipments, of which 88% contained unapproved drugs,²¹ arriving from many countries including 16% from Canada, 14% from India, 14% from Thailand, and 8% shipped from the Philippines.²² In November of 2003, a similar blitz examined 3375 products and found 2256, or 69%, of them violated drug laws.²³ The FDA found recalled drugs, drugs requiring special storing conditions, and controlled substances.²⁴ Animal drugs not approved for human use were part of the shipments, as were drugs with inadequate labeling, missing dosage information, or labeling not in English. Further, inadequately labeled drugs that require risk management or restricted distribution programs here in the United States were also found.²⁵ Improperly packaged drugs shipped loose in sandwich bags, tissue paper or envelopes, drugs withdrawn from the U.S. markets for safety reasons, and unapproved drugs were also found in these blitzes.²⁶

Not only has the FDA been involved in issues regarding safety concerns and importation, but the federal courts have been involved as well. On November 6, 2003, the Federal District Court of the Northern District of Oklahoma issued the decision *United States v. Rx Depot, Inc.* granting an injunction to prevent importation of unapproved drugs in violation of the FDCA.²⁷ The judge stated, “[b]ecause the drugs are not subject to FDA oversight and are not continuously under the custody of a U.S. manufacturer or authorized distributor, their quality is less predictable than drugs obtained in the United States.”²⁸

A report documented Minnesota’s evaluation of Canadian pharmacies that were involved in distribution of medications to citizens of the United States.²⁹ The report found several pharmacies using unsupervised technicians in prescription filling and involved in trying to clarify prescription questions. One pharmacy utilized a high volume prescription filling process allowing 100 new or 300 refill prescriptions per hour, “a volume so high that it would have been impossible

20. *Id.*

21. *Id.*

22. Taylor Testimony, *supra* note 13.

23. HHS TASK FORCE, *supra* note 17, at 13.

24. *Id.* at 13-14.

25. *Id.* at 14.

26. *Id.* at 13.

27. *United States v. Rx Depot*, 290 F. Supp. 2d 1238 (D. Okla. 2003).

28. *Id.* at 1241.

29. Taylor Testimony, *supra* note 13.

to assure safety.”³⁰ Drugs shipped in containers without labels attached and drugs requiring refrigeration being shipped in unrefrigerated containers were also discovered. One of the pharmacies was found to be sending drugs that were not even of Canadian origin, and many were obtained from scripts that had been written and rewritten across multiple Canadian provinces.³¹

The HHS Task Force also expressed grave concerns about “rogue” Internet pharmacies masquerading as legitimate pharmacies and yet operating behind improper facades.³² The Task Force concluded that “American consumers currently purchasing drugs from overseas are generally doing so at significant risk.”³³ But it is recognized that there are numerous pharmacies in Canada that are providing approved drugs to fill prescriptions for American consumers. The challenge for the American patient is verifying that the pharmacy with which they are dealing is legitimate.

The Report also summarized by suggesting that it is important to:³⁴

1. Maintain the integrity of the distribution system.
2. Exclude personal prescription importation because of the risk to the American consumer.
3. Drugs should be limited to those most likely to provide acquisition savings.
4. Importation and reimportation should come from countries in which the FDA has confidence in their comparability to the FDA regulatory system.
5. Restrict the distribution of drugs that could pose increased safety risks, such as controlled drugs and those requiring refrigeration and other special labeling and distribution issues.
6. Prescriptions must be dispensed pursuant to a valid prescription.
7. The purchaser must receive assurance and documentation of the source of drugs and meet FDA requirements.
8. Any program implemented must ensure oversight by the government. Adequate resources must be supplied to the oversight organization to address that responsibility.

30. *Id.*

31. *Id.*

32. HHS TASK FORCE, *supra* note 17, at 7.

33. *Id.*

34. *Id.* at 37-38.

9. Reimportation and importation would require increased streamlining of inspection procedures and reporting of adverse events of imported drugs.

The Commerce Department submitted a report in 2004 entitled *Pharmaceutical Price Controls in OECD Countries: Implications for U.S. Consumers, Pricing, Research and Development, and Innovation*.³⁵ The Commerce Department concluded that one of the reasons for the elevated prices for medications in the United States is because many foreign governments have price controls on prescription drugs within their borders.³⁶ Therefore, there is pressure on the U.S. market to make up the lost revenues. Addressing price issues in the United States would, in fact, require global cooperation. The Commerce Department was concerned that price control programs reduce research and development in countries, and they also reduce competitive market forces for generic medications.³⁷ The Commerce Department determined that generic drugs would frequently cost fifty percent more in foreign countries than they do in the United States.³⁸

DISCUSSION

The average cost of a prescription medication in the United States is approximately seventy-two dollars.³⁹ The average price is rising faster than the inflation rate on an annual basis, particularly over the last three to five years. But prescription medications provide an important and significant therapeutic tool in the treatment of major disease processes for the American consumer.

The pharmaceutical products on the market today have been designed based on the science and physiology of the human body, resulting in medications that are specifically tailored to treat a specific medical problem. But along with the specificity of the treatment with medications and the increased potency of the medications, there are increased potential side effects. Therefore, it is incredibly important

35. U.S. DEP'T OF COMMERCE, PHARMACEUTICAL PRICE CONTROLS IN OECD COUNTRIES: IMPLICATIONS FOR U.S. CONSUMERS, PRICING, RESEARCH AND DEVELOPMENT, AND INNOVATION (2004), available at <http://ita.doc.gov/td/chemicals/drugpricingstudy.pdf>.

36. *Id.* at viii.

37. *Id.* at x.

38. *Id.* at 22.

39. NAT'L INST. FOR HEALTH CARE MGMT., PRESCRIPTION DRUG EXPENDITURES IN 2001: ANOTHER YEAR OF ESCALATING COSTS (2002), available at <http://www.nihcm.org/spending2001.pdf>.

that the American consumer obtains the appropriate medication to treat a specific medical problem.

The United States has been blessed with the safest distribution system in the world. Any altering of that system must be considered thoroughly and critically to protect the American consumer. Not only does it impact the specific care of an individual patient, but when counterfeit or adulterated medications are improperly introduced to the distribution system, it creates problems not only for the patient, but it creates liability and further cost issues for pharmacies, manufacturers, and providers.

Therefore, should reimportation or importation of medications occur and be facilitated by federal legislation or regulation, the following criteria should be seriously considered:

1. All drugs should be FDA-approved and meet all regulatory requirements for safety and purity. This approval process includes the inactive ingredients within the medications, as well as label, storage, and distribution issues.
2. The distribution system must be a closed chain system. One of the hallmarks of our system in the United States has been the integrity of that closed chain, which has undergone significant challenges in the last decade. The chain must be closed from the manufacturing site to the dispensing sites to assure that our patients are receiving medications that are safe and effective.
3. Products should be subject to some type of reliable tracking and traceable technology. This would require a global effort because of the issues associated with importation and reimportation of medication.
4. There should be appropriate funding available to the FDA to address the issues involved in drug reimportation or importation; there must be enough inspectors. The FDA must have support in developing technologies and tracking processes as well as the opportunity to track and address any adverse efforts associated with reimported or imported medication.
5. Internet pharmacies pose significant challenges for the safety of the American consumer. Consideration of the following recommendations would assist in assuring appropriate Internet pharmacy distribution:
 - A. Require that pharmacists who do the direct dispensing or supervise the dispensing process be licensed in the United States.

- B. Require a valid prescription written by a licensed physician from the United States (congruent with the Humphrey-Durham Amendment).
- C. Consider having mandatory certification for Internet pharmacies that can be verified through an appropriate process such as the VIPPS (Verified Internet Pharmacy Practice Sites) program of the National Board of Pharmacy⁴⁰ or similar programs developed by HHS.
- D. Mandate pharmacy disclosure and make information available to the consumer that lists identifying information accessible on the Internet to validate and verify the pharmacy with regard to location, license, and listing of appropriate state licensing requirements.
- E. Internet service provider issues: the federal government could require that Internet service providers not provide access to non-certified Internet pharmacy sites selling prescription drugs (for example, credit cards could not be used to buy medications from a non-certified pharmacy).

CONCLUSION

There are many more variables surrounding the issue of importation and reimportation of prescription medications. This discussion and presentation attempts to outline some of the major issues and concerns from a practicing physician's perspective. There are no easy answers. The cost of prescription medications must be addressed. The maintenance of a secure distribution system is imperative. But safety must be the overriding concern.

40. For more information on VIPPS, see <http://www.nabp.net/vipps/intro.asp>.

