

PEW
HEALTH GROUP

After Heparin:

Protecting Consumers from
the Risks of Substandard
and Counterfeit Drugs



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Executive Summary

In late 2007, U.S. health officials began receiving reports of unexpected allergic-type reactions in patients undergoing dialysis.¹ The reactions were linked to a widely used blood thinner—heparin²—and specifically to an adulterant that had been introduced during manufacture of the drug in China.³⁻⁵ The U.S. Food and Drug Administration (FDA) believes the adulteration of heparin was an economically motivated act—a clear breach of the U.S. pharmaceutical supply chain.⁶

Pharmaceutical manufacturers and distributors work together in a robust system to deliver high-quality products, but drug manufacturing and distribution have become increasingly complex in recent years. Prescription and over-the-counter (OTC) medications originate in factories all over the world, moving into the American marketplace through supply chains that can involve numerous processing plants, manufacturers, suppliers, brokers, packagers and distributors.

The number of drug products made outside of the United States doubled from 2001 to 2008, according to FDA estimates.⁷ The FDA estimates that up to 40 percent of finished drugs used by U.S. patients is manufactured abroad,^{8,9} and 80 percent of active ingredients and bulk chemicals used in U.S. drugs comes from foreign countries.¹⁰ Increasingly, the United States relies on drug manufacturing in developing countries—mainly China and India. Globalization, increased outsourcing of manufacturing, the complexity of pharmaceutical distribution and the existence of criminal actors willing to capitalize on supply chain weaknesses has created the potential for counterfeit or substandard medicines to enter the system and reach patients. As evidenced by the adulteration of heparin and other case studies outlined in this report, these rare but potentially serious events can have grave consequences.

For economic reasons, the movement of manufacturing from the United States to foreign countries is likely to continue. However, industry and regulatory bodies have failed to adapt adequately to these changing circumstances.

Drawing on public documents, peer-reviewed publications and dozens of interviews with industry stakeholders, regulators and supply chain experts, this Pew Health Group white paper provides an overview of the complex, modern pharmaceutical supply chain and its risks from manufacturing through distribution of the finished drug. A discussion draft of this document was developed to inform a Pew Health Group stakeholder conference on ensuring the safety of the U.S. drug supply that was held on March 14

and 15, 2011, in Washington, D.C. Conference participants included leadership from the FDA, the United States Pharmacopeial Convention (USP), major pharmaceutical manufacturing and distribution trade associations, pharmacy organizations and medical professional groups, individual supply chain experts and consumer organizations. This paper has now been revised to incorporate outcomes and stakeholder discussion from that meeting.

This report concludes that more can—and must—be done to ensure the safety of “upstream” pharmaceutical manufacturing (chapter 1), to provide the FDA with essential authorities and resources to exercise effective oversight (chapter 2) and to improve the security of “downstream” pharmaceutical distribution (chapter 3).

In a world where drug manufacturing is increasingly outsourced and offshored, robust supply chain management is critical. Pharmaceutical companies have the ultimate responsibility for drug quality and safety, but some companies may not be adequately verifying the quality of their suppliers.^{11,12} Ensuring drug-ingredient manufacturers meet quality standards is critical to ensuring the quality of the product itself. However, chapter 1 reviews numerous situations in which foreign producers and traders have misrepresented the source drug ingredients from the United States and other purchasers, in some cases concealing substandard products that harmed consumers. It is essential that manufacturers look beyond current manufacturing quality standards (known as good manufacturing practices, or GMPs) in their own facilities to ensure appropriate supplier qualification, through risk-based assessments, quality agreements and physical audits, where appropriate.

The FDA and its counterpart agencies worldwide monitor the quality and safety of drug manufacturing by inspecting plants and validating compliance with GMPs. However, the FDA lacks the resources, capacity and authority to effectively inspect foreign facilities and assess risk. In contrast with U.S. manufacturing facilities, which are inspected every two to three years, the FDA currently inspects foreign facilities once every nine years on average.¹³ Improved oversight of foreign manufacturing is essential and will require increased resources for the FDA, some of which could be obtained through industry fees. In addition, the agency will have to make additional use of third-party inspections, including those by other regulators and, potentially, private entities. The FDA also requires certain new authorities to enable effective oversight and must more effectively use its existing authorities and resources. The agency should have the power to mandate recalls, subpoena witnesses and documents and destroy at the border any products that present public safety risks. In the long term, ameliorating risks to the U.S. and global drug supply requires international cooperation, harmonization of standards and steps to improve the capacity of regulatory bodies in the developing countries where manufacturing increasingly takes place.

The movement of finished drugs from manufacturer to the consumer is also a complex process involving many intermediate players. The past decade has seen several instances of adulterated and counterfeit drugs infiltrating U.S. distribution. In 2002, counterfeit vials of the anemia drug Epogen[®] entered the distribution supply chain through licensed wholesalers and were sold by U.S. pharmacies.^{14–16} A shipment of 129,000 vials of insulin, stolen in June 2009, was stored under unknown conditions before

eventually being sold to legitimate pharmacies and, ultimately, to patients.¹⁷ Pharmaceutical cargo theft is substantial, and much of the stolen product is never recovered. Manufacturers, wholesalers and pharmacies have taken steps to secure the distribution pipeline, but risks persist. No national system exists for tracing the provenance of finished drugs as they are bought and sold. Requirements for drug pedigrees and wholesaler licensure vary widely among states. Drug distribution tracking and regulation must be improved; methods of documenting the movement of drugs at the individual package level have been attracting support, and a universal system should be implemented. Legislators, the FDA, consumer organizations and industry recognize the need to strengthen control of the pharmaceutical supply to safeguard public health. Based on the outcomes of Pew’s stakeholder conference, as well as extensive review of the public literature and background interviews, this paper concludes that Congress must institute reforms to ensure that the FDA’s oversight of overseas manufacturing is increased, and that industry is held accountable for the security and safety of increasingly globalized and outsourced supply chains. This report makes the following key policy recommendations:

Ensure meaningful oversight and quality management of globalized pharmaceutical manufacturing

- Require 21st-century quality systems to protect drug safety through statute and regulation
- Strengthen industry oversight of contract manufacturers and suppliers
- Enhance documentation and transparency of upstream manufacturing supply chains through legal requirements
- Improve testing standards

Eliminate barriers to FDA oversight

- Increase FDA oversight of overseas manufacturing
- Ensure adequate FDA resources
- Improve the FDA’s infrastructure and tracking systems
- Strengthen oversight of drugs and bulk drug substances at import
- Empower the FDA with regulatory authorities it needs to fulfill its mission
- Strengthen the FDA’s enforcement ability through stronger penalties and clearer accountability for industry
- Improve FDA access to information from other regulatory bodies and industry

Secure pharmaceutical distribution

- Improve drug distribution security through a federal serialization and verification system
- Strengthen wholesaler regulation and oversight

Methodology

This white paper provides an overview of the complex, modern pharmaceutical supply chain from manufacturing through distribution of the finished drug, and advances proposed policy solutions to help reduce the risks of counterfeit, adulterated and substandard drugs. It was prepared to inform, and incorporates the outcomes of, a Pew Health Group stakeholder conference on policy reforms to ensure the safety of the U.S. pharmaceutical supply, held on March 14 and 15, 2011, in Washington, D.C.

The paper draws on publicly available sources of information, including FDA documents, U.S. Government Accountability Office reports, Congressional testimony, peer-reviewed journal articles and commercial publications, as well as in-depth background interviews with a wide range of supply chain experts and stakeholders. Roundtable participants included representatives of the U.S. Food and Drug Administration (FDA), state regulators, the United States Pharmacopeial Convention (USP), pharmaceutical manufacturing and distribution trade associations, the retail pharmacy industry, medical and pharmacy professional associations, consumer groups and individual supply chain experts. The final paper has been reviewed by nine external reviewers.

Complete lists of roundtable participants, expert interviews and reviewers, as well as the conference agenda, are appended. Video of the conference presentations and discussions is available on the Pew Prescription Project website.

The conclusions and recommendations herein are those of The Pew Charitable Trusts and may not reflect those of individual sources, reviewers, or roundtable participants.

Introduction and Background

U.S. pharmaceutical manufacturers and distributors work together in a robust system that delivers high-quality products. Nevertheless, complex supply chains and increased reliance on outsourced manufacturing create the potential for counterfeit or substandard medicines to enter the system and reach patients. The adulteration of the commonly used blood thinner heparin, outlined below, is a sentinel failure that demonstrates the weaknesses of today's pharmaceutical supply chains—particularly the risks of an increasing reliance on production outside the United States without sufficient levels of oversight. Heparin and the other case studies outlined in this paper have also become a catalyst for reform. The U.S. Congress, the U.S. Food and Drug Administration (FDA), the pharmaceutical industry and other organizations have renewed their commitments to remedy existing weaknesses. This white paper seeks to inform these efforts by presenting a holistic picture of the pharmaceutical supply chain and its problems (illustrated by case studies), and to propose a set of meaningful reforms that will better protect patients.

The exact prevalence of substandard* and counterfeit drugs in the United States and elsewhere is not known. The FDA estimated in 2004 that less than 1 percent of drugs in the United States are counterfeit.¹⁸ For prescription drugs alone, even a fraction of 1 percent of the nearly four billion prescriptions filled in 2010¹⁹ would still equate to millions of dispensed medications. It should be noted that differing definitions of “counterfeit” complicate the use of the term as it applies to pharmaceuticals,[†] with some stakeholders concerned that overly broad application of intellectual property regimes may impede global access to medicines.^{20,21,‡} The World Health Organization's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) has estimated that fake drugs may account for approximately 30 percent of the market in parts of Africa, Asia and Latin America.²² Drug contamination, adulteration or the insertion of counterfeits can occur at any point during manufacturing or distribution, from the sourcing of

* Substandard medicines are legitimately marketed products that contain adulterants or improper amounts of active ingredients, or were compromised by improper manufacturing, handling and storage. Whether the result of deliberate or unintentional acts, substandard products have the potential to cause serious harm or to deny patients the therapy they need to preserve health or life.

† For the purposes of this report, the term counterfeit is used to apply to finished drugs only, consistent with U.S. statute:

“...a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.” [21 U.S.C. 321 (g)(2)]

Thus, the contamination of heparin (see case study 1), which involved a presumed act of economically motivated adulteration and deliberate misrepresentation of an ingredient, resulted in an adulterated drug, not a counterfeit one.

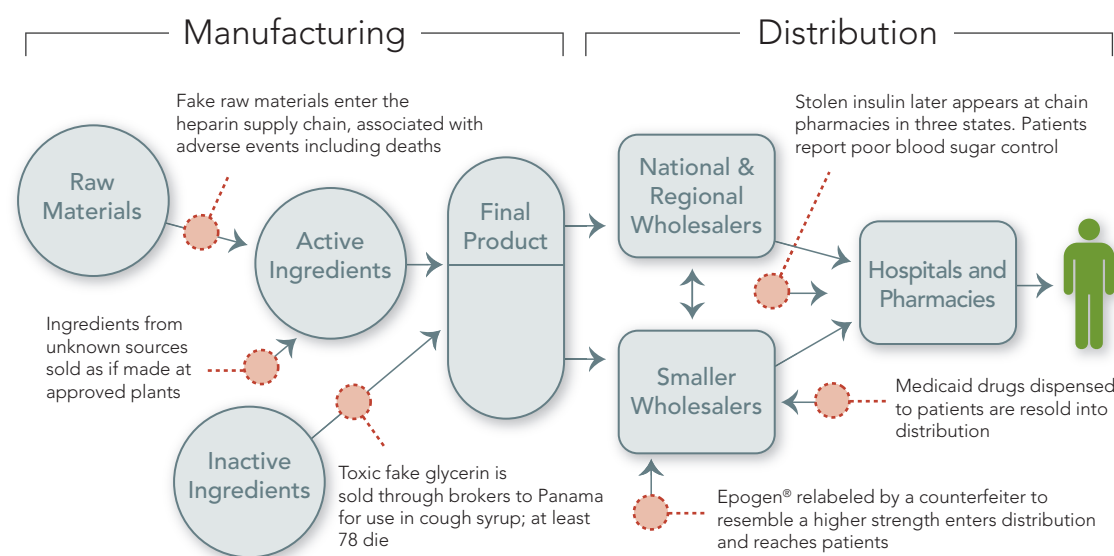
‡ For example, regulatory authorities in Europe have seized drugs within their customs zones that they consider to be in violation of European intellectual property laws, even when those drugs are in transit to developing countries and are considered by some to be lawful generics in their country of destination.

raw ingredients through the delivery of a finished drug to the patient (see figure 1). Substandard and counterfeit products may reach patients through legitimate supply chains as happened with heparin (see case study 1) or through illicit routes.

Every step in the complex pathway of the pharmaceutical supply chain—from raw materials (see sidebar 1) to finished products to patient delivery—is an opportunity for adulteration. A typical pharmaceutical supply chain might proceed as follows: raw materials for a drug's active ingredient are purchased from suppliers and undergo initial processing. Processed raw materials then move to an active active-ingredient manufacturing site, sometimes through consolidators or brokers. This site prepares the finished active ingredient and sends it to another plant, where active and inactive ingredients, provided by yet other suppliers, are combined to create the finished drug. After the finished drug is packaged and enters distribution, it may change hands between brokers and wholesalers, be repackaged into different quantities and then stored for periods of time. Eventually, the product arrives at hospitals, pharmacies and doctors' offices, where it is dispensed to patients.

Figure 1

The pharmaceutical supply chain with examples of vulnerabilities



Several factors offer opportunities to adulterate a product or ignore quality controls (see sidebar 2). In regions where regulation, compliance and vigilance are weak, the quest for lower-cost materials can drive the trade of substandard or falsified drug ingredients. These may be introduced into manufacturing processes or sold as legitimate products by distributors and brokers. In countries with less developed regulatory systems than that of the United States, manufacturing standards may also be less rigorous—or

less rigorously observed. Those same countries receive much less FDA oversight than U.S. manufacturing facilities, creating additional potential for poor quality medicines to reach U.S. consumers (see section 1.3).

The Federal Food, Drug, and Cosmetic Act (FDCA) penalizes adulteration, misbranding and counterfeiting at a maximum of \$10,000 or three years in prison.²³ These penalties may be too low to present meaningful deterrents to violations and crime, particularly for pharmaceutical counterfeiting, which is additionally incentivized by high profitability. By one estimate, the return on counterfeit prescription drugs may be 10 times greater than that of the sale of illegal narcotics.²⁴ In the United States, the penalties for trafficking drugs such as heroin and cocaine can have jail sentences up to life and fines in the millions of dollars.²⁵ Although counterfeiting can be prosecuted under trademark law, with a maximum sentence of 10 years, the FDCA, with its lower penalties, is the most common statute used for prosecuting counterfeit drug cases.²⁶

The FDA regulates many thousands of drugs and medical devices intended for the U.S. market. The various entities involved in the manufacture of these products may be located within U.S. borders, or partly or completely overseas—and the overseas component is growing. The United States imported 393 million kilograms of pharmaceuticals and medicines in 2009 (see section 1.2.1).^{*} FDA-regulated imports represented 20 million shipments into the United States in 2010, a threefold increase over 10 years.²⁷ Human drugs, though a small percentage of the total, amounted to over 300,000 shipments of pharmaceuticals in 2007, more than double the volume in 2002.²⁸ The number of foreign establishments named in U.S. drug marketing applications more than doubled over a seven-year period (779 vs. 2,019 in years 2002 and 2008, respectively).²⁹ Imported drugs and their ingredients, each with intricate manufacturing, packaging and distribution supply chains, are made at thousands of sites around the world,³⁰ and arrive at any one of hundreds of U.S. points of entry every day.³¹

* From a dataset provided by the U.S. Census Bureau, Foreign Trade Division.

SIDEBAR 1

COMPONENTS OF A DRUG PRODUCT

A finished drug, also known as a drug product, may take many forms, including tablets, capsules, injectables, ointments or solutions. Drug products contain both active and inactive ingredients. Inactive ingredients (also called inert ingredients or excipients) act as carriers for the active components, and include syrups, binding agents and fillers for tablets, capsule coatings, sweeteners and colorings, as well as solutions used in the formulation of injectable products. Some are specifically processed for use in pharmaceutical products, but many are not, and have applications in other market sectors. Excipients often make up the bulk of a finished drug product, while representing just a fraction of its value. Excipients have no therapeutic effect of their own, but can significantly affect the absorption of drugs by the body. As with any other ingredient, adulterated or substandard excipients can be harmful to patients.

A drug product's therapeutic effect comes from its active pharmaceutical ingredient (API).³² Materials in bulk form that become either the API or the finished drug when manufacturing is complete are called bulk drug substances.³³ In many cases, the terms API and bulk drug substance are used interchangeably. Traditional small-molecule APIs may be synthesized by multistep chemical reactions and a series of purification/isolation steps or through synthetic modifications to a naturally occurring structure. APIs may also be derived from animal or plant sources or produced through biotechnology.³⁴ According to the FDA and international guidance, an API must be manufactured in accordance with good manufacturing practices (see sidebar 2) and under procedures that ensure the product meets specifications³⁵ that are set by industry in a marketing application or exist in public monographs. Substantial deviation from the approved set of conditions and procedures could prevent assurance of API quality and purity,³⁶ which could result in harm to patients. Because APIs are the most therapeutically important (and often the most expensive) drug ingredients, industry and regulatory bodies often give them greater, and sometimes exclusive, scrutiny over inactive ingredients in terms of oversight of manufacturing processes.

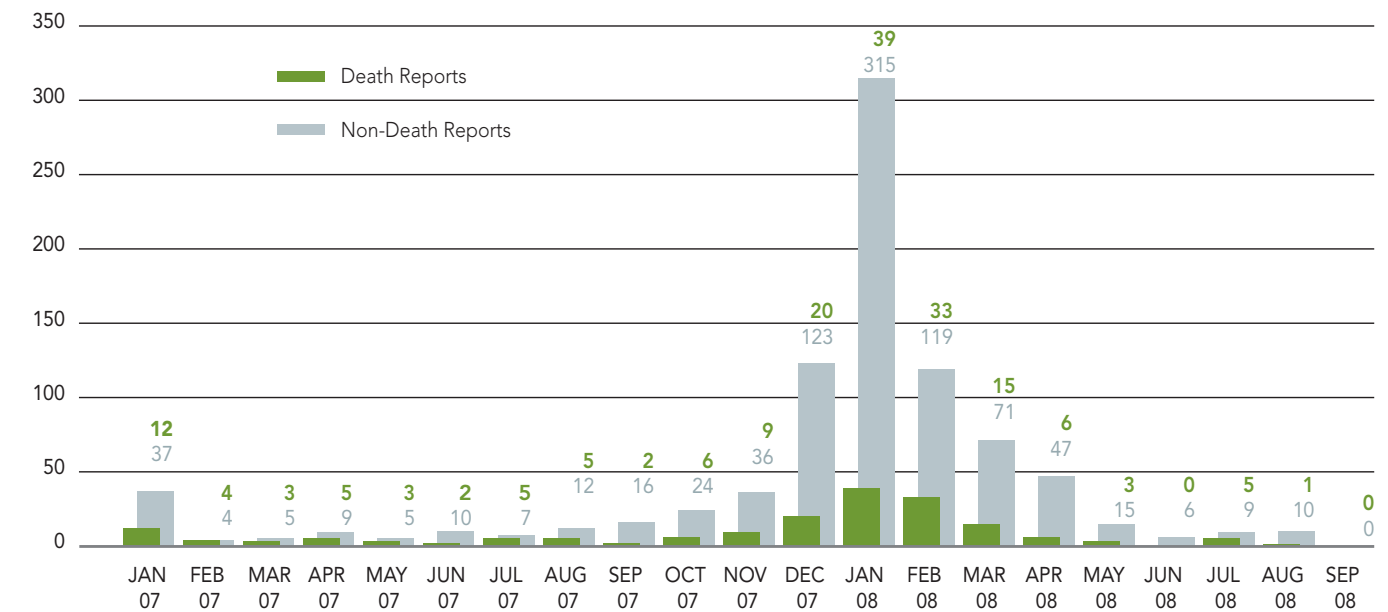
Case study 1: Adulteration of heparin

In late 2007, health authorities at the U.S. Centers for Disease Control and Prevention (CDC) and the FDA began receiving reports of unexpected allergic-type reactions and hypotension in patients undergoing dialysis.³⁷ Reported events sharply increased from December 2007 to January 2008, a clear spike over baseline levels in 2007 and the first eight months of 2008 (figure 2). The events were subsequently linked to heparin, a widely used blood thinner made by Baxter International Inc.³⁸ Additional analysis led to the identification of oversulfated chondroitin sulfate (OSCS), a substance that standard tests were unable to detect³⁹ and whose biological properties can cause the reported reactions.⁴⁰ Although the available data do not permit clear determination of causality for any individual death, the FDA examined a subset of 574 adverse events, including 68 deaths, submitted between January 1, 2008, and March 31, 2008—a period that corresponded with the heaviest reporting.⁴¹ The FDA determined that three deaths were likely caused by OSCS, six were possibly caused by the adulterant, 24 were unlikely and 35 were

unassessable.^{42,43} Once the products were removed from the market, reports of unusual adverse reactions essentially ceased.⁴⁴ It was later discovered that the adulteration of heparin had occurred during manufacture in China.⁴⁵

Figure 2

Adverse event reports in patients receiving heparin and exhibiting allergic-type symptoms, January 2007–September 2008



Source: FDA Adverse Event Reporting System.⁴⁶ Also includes reports that did not specify a month and were assigned to January of that calendar year.

Heparin is derived from animal mucosal tissues, almost exclusively from pigs. In China, numerous workshops harvest basic heparin material (heparin crude) by cooking and drying pig intestines collected from local slaughterhouses (figure 3). These workshops are often run by small farmers and are subject to limited regulatory scrutiny.⁴⁷ Heparin crude is then sold, often through consolidators, to other plants that further refine the material into an active ingredient. In 2004, one such Chinese factory, Scientific Protein Laboratories–Changzhou (SPL-CZ),^{48,*} became part of the heparin active-ingredient supply chain for Baxter International Inc.⁴⁹ At the time, Baxter provided approximately 50 percent of the U.S. supply of heparin vial products.^{50,†}

* SPL-CZ is a joint venture of Wisconsin-based Scientific Protein Laboratories (SPL) and Techpool Bio-Pharma Co. Ltd. SPL had provided Baxter with heparin active ingredient prior to opening its Changzhou plant.

† There are other types of heparin products, including premixed IV bags and prefilled syringes.

Figure 3



Processing pig intestines to extract material used to create heparin crude.

Photo credit: Wall Street Journal. Used by permission.⁵¹

OSCS is a synthetic material that costs nearly 100 times less to produce than actual heparin.⁵² Because it mimics some of heparin's chemical properties, it was not detected as an adulterant by standard assays⁵³ or by additional tests used by Baxter when the product reached the United States.⁵⁴

OSCS was identified in the finished heparin active ingredient made in China by SPL-CZ and in the crude material provided to SPL-CZ from consolidators.⁵⁵ This evidence suggests that in the case of Baxter's heparin, the OSCS was introduced upstream of SPL-CZ, possibly during crude heparin consolidation. Both Baxter and the FDA remain unable to pinpoint the exact source, or sources, of the adulteration.

Baxter was the major U.S. manufacturer of heparin, but other companies also executed heparin product recalls. In the United States, 15 companies recalled at least 11 heparin drug and 72 medical device products (heparin is used to coat stents and in other medical devices).⁵⁶ According to local health agencies and news reports, products containing heparin were also recalled in 2008 in Australia, Denmark, France, Germany, Italy, Japan, Sweden, and Switzerland.^{57–60} Chinese authorities have acknowledged that heparin produced in China contained OSCS, although they question whether data have conclusively linked the adulterant to the adverse allergic reactions.⁶¹ The FDA and others believe that persons

in China added cheaper OSCS to crude heparin to cut costs.^{62,63} One industry insider estimates that to achieve this volume of distribution, from one to three tons of OSCS must have been produced and used to dilute real heparin, which would have generated \$1 million to \$3 million in profit for the individuals or companies that sold it.⁶⁴

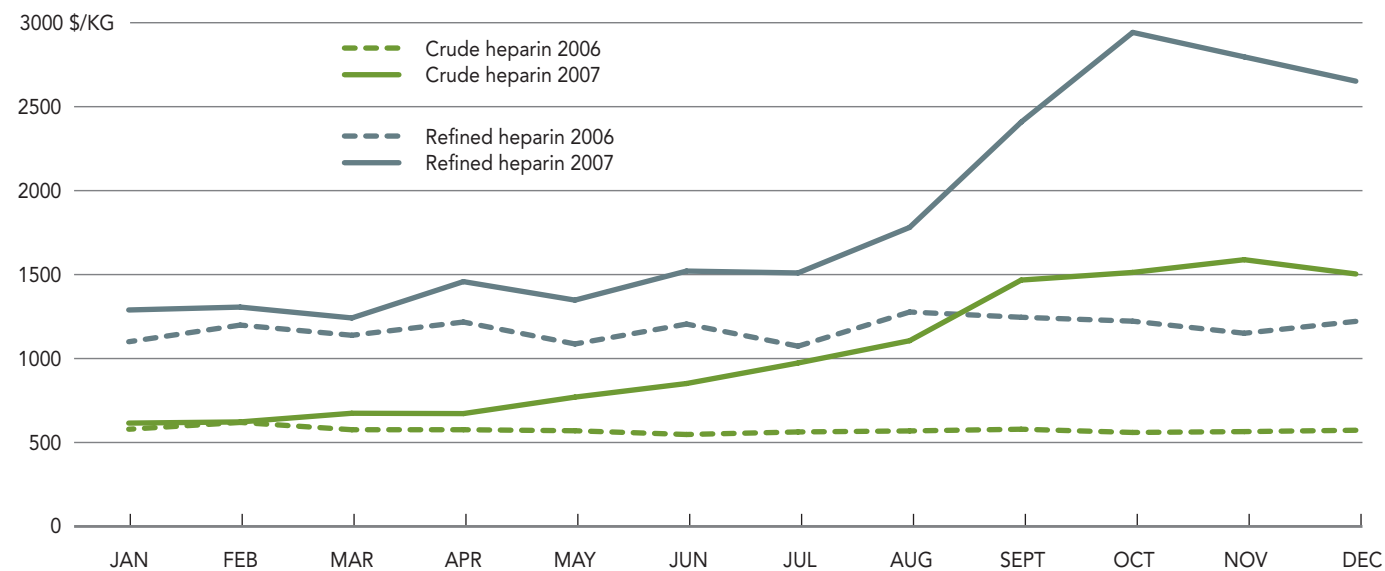
Laboratory tests for many off-patent medications, including heparin, are established and updated by the U.S. Pharmacopeial Convention (USP), a nongovernmental standards-setting authority for prescription and over-the-counter (OTC) medicines manufactured or sold in the United States. Prior to the adulteration, assays for heparin were based on a USP monograph from the 1950s, which had been infrequently updated,⁶⁵ although it was in the process of being revised at the time of the incident. It seems likely that those who substituted OSCS for heparin crude used OSCS specifically because it would fool USP tests⁶⁶ by mimicking properties of heparin.⁶⁷ The responsible parties may have learned of OSCS's properties from published scientific papers that considered the material's use as an anticoagulant.⁶⁸ It is impossible to know whether they were aware that their actions would have adverse health outcomes. USP leadership believes that European requirements for additional heparin tests likely helped limit the distribution of material in the European Union, but this was a complex situation that is still not entirely understood.⁶⁹ Other U.S.-based companies working with heparin also assert that their screening techniques would have detected the adulterant.⁷⁰ Baxter reports that it performed tests in addition to those set out by USP, but that these, too, failed to detect OSCS.⁷¹ To avoid another tragedy, USP has updated its heparin monograph,⁷² and USP reports that it is working with European and Japanese pharmacopeias to harmonize standards.⁷³

Apart from the assay failure, the heparin incident exposed a number of significant supply chain management problems on the part of the manufacturer and the FDA. Baxter began receiving heparin made at SPL-CZ in 2004, but did not conduct its own audit of that plant until 2007, relying instead on an earlier assessment by a different company.⁷⁴ The FDA approved SPL-CZ as a supplier for Baxter without conducting a pre-approval inspection,⁷⁵ in part because the agency confused SPL-CZ with another site in its database. When the FDA finally inspected SPL-CZ after the adverse events occurred, its inspectors found a number of manufacturing quality issues,⁷⁶ including poor control of incoming raw materials.⁷⁷ When, in 2008, Baxter sent inspectors to retroactively evaluate its supply chain, they were denied access to upstream workshops and consolidators.⁷⁸ The FDA was also denied access to two upstream consolidators of heparin.⁷⁹ In these cases, the agency did not take further action or issue import alerts (to prevent product from these sites from entering the United States) for these firms.⁸⁰ However, the agency did place seven factories that produced heparin and were associated with OSCS contamination on import alert without physical examination of their facilities.⁸¹ SPL-CZ was classified within China as a chemical plant and therefore was not registered with the Chinese State Food and Drug Administration (SFDA).⁸² The FDA has been unsuccessful in getting cooperation from Chinese authorities to investigate beyond the API maker.⁸³ Ongoing investigations have revealed additional potential failures. In October 2010, an FDA inspection report of SPL's Wisconsin facility alleges that the company learned of the possible presence of OSCS in two lots of heparin API in 2008, but did not investigate the issue for nearly a year.⁸⁴ Both lots were distributed, although it is not known if those products ever reached patients.⁸⁵

The heparin tragedy may have been preceded by warning signs that could have suggested a heightened risk of economically motivated adulteration. The OSCS entered the supply chain at a time when a widespread swine virus outbreak had greatly diminished Chinese pig herds.⁸⁶ The price of pigs increased in 2007,⁸⁷ and the cost of pure heparin as well as heparin crude increased more than 100 percent between May and November 2007 (see figure 4). According to an expert in the pharmaceutical chemical industry, an alert purchasing department might have identified the price increase as a signal of potential risk to the product.⁸⁸ A shortage of raw ingredient provides a motivation for deliberate substitutions of cheaper materials.

Figure 4

Monthly Chinese export prices for crude and refined heparin, 2006 and 2007



Source: Beijing Orientbit Technology Co., Ltd.⁸⁹

Baxter reports that it has instituted a number of initiatives to secure its supply chain against future adulteration. It is examining its global supply chain practices to identify vulnerabilities, reviewing relationships with high-risk suppliers, reducing the number of suppliers, doing more concentrated audits and reviewing test methods.⁹⁰ Baxter does not sell heparin vial products today, although it continues to sell other heparin products, none of which is produced using the supplier implicated in the recalls.⁹¹

As FDA Commissioner Margaret Hamburg has noted, “In this day and age, companies must be able to effectively demonstrate that safety, quality and compliance with international and U.S. standards are built into every component of every product and every step of the production process.”⁹² Heparin’s complex supply chain was vulnerable to abuse by perpetrators that have not been identified and therefore never penalized, and Baxter failed to prevent a serious adulteration of its product. Chapter 1 reviews issues of outsourcing, globalization and supplier management.

1.1 Overview

The geography and complexity of drug manufacturing have changed dramatically during recent decades, presenting serious new challenges to oversight and increasing the risk that substandard drugs will reach patients. As drug manufacturing moves to foreign countries, and pharmaceutical ingredients are increasingly purchased from overseas suppliers, ensuring manufacturing quality has become much more challenging for industry and regulators alike.

The FDA’s regulatory presence in foreign countries is lower than in the United States, and FDA inspectors infrequently travel to developing countries such as India and China, where much of U.S. manufacturing has moved (see section 2.2.1).^{93–95} With less oversight, manufacturers may not rigorously observe quality measures, and in some cases individuals manage to deliberately substitute cheaper materials for high-quality ingredients (see section 1.3.2). While the vast majority of drugs in the United States is safe, these changes create significant risks of rare but potentially serious events by which U.S. patients are harmed by substandard or adulterated drugs. This chapter explores the trend toward globalized manufacturing and sourcing of ingredients, and the resulting challenges in industry supply chain quality control.

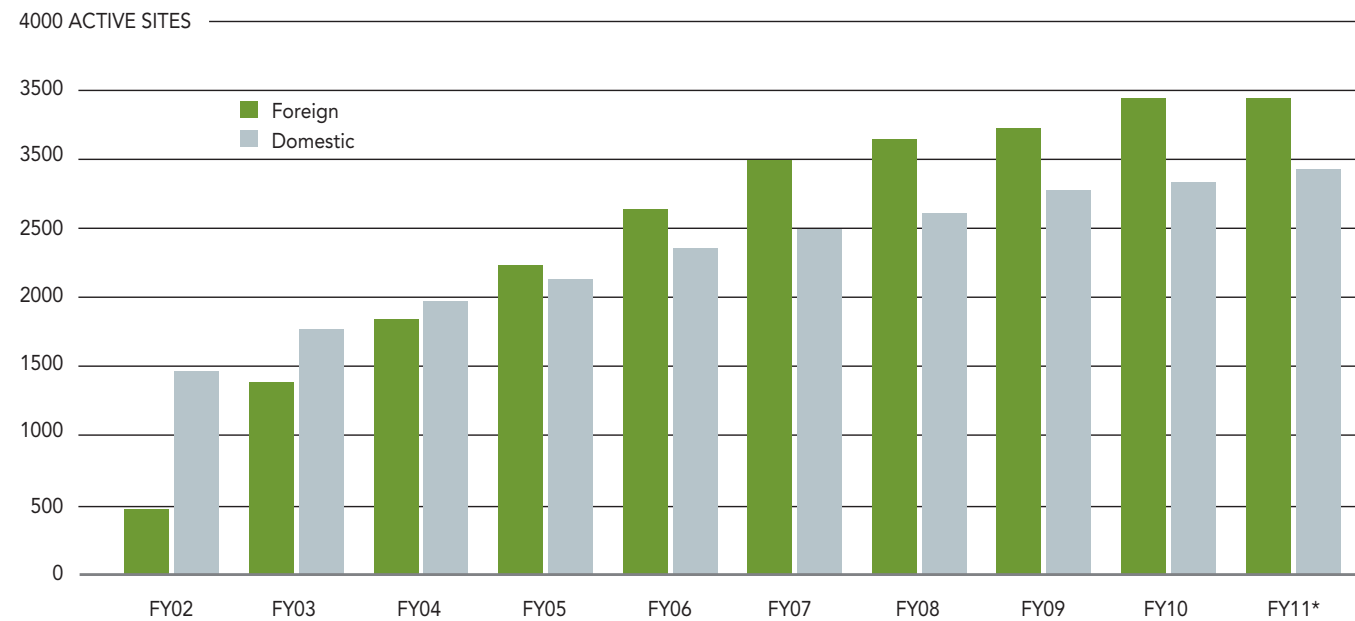
1.2 Globalization of manufacturing

1.2.1 Movement of U.S. drug manufacturing overseas

The number of drug products made at non-U.S. sites doubled between 2001 and 2008, according to FDA estimates.⁹⁶ An estimated 40 percent of finished drugs used in the United States are made abroad.⁹⁷ Non-U.S. manufacturing site registration with the FDA is growing rapidly, while domestic site registration has leveled off and begun to decline (see figure 5). Site registration in 2005 reached a milestone, according to the FDA’s estimates: for the first time, foreign sites registered with the FDA and subject to GMP inspections outnumbered those in the United States.

Figure 5

FDA-registered domestic and foreign establishments subject to GMP inspections, 2002-2011



* FY 2011 incomplete

Source: FDA estimates based on data from the Field Accomplishments and Compliance Tracking System.⁹⁸ Does not include medical gas establishments.

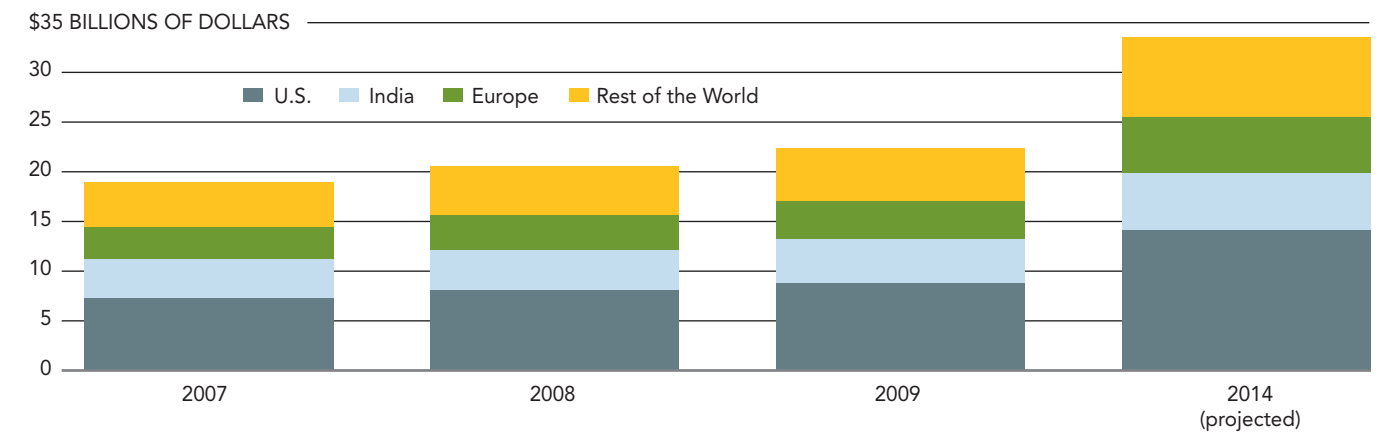
In 2007, India and China together housed nearly 70 percent of the world's active-drug-ingredient manufacturing sites, up from 49 percent in 2004.⁹⁹ Seventy percent of pharmaceutical executives surveyed in 2010 by the consulting firm Axendia reported having key suppliers in China, and 57 percent reported key suppliers in India, the top two countries so reported.¹⁰⁰

Global revenues for pharmaceutical contract manufacturing are on the rise, estimated at \$22.4 billion in 2009, with a projected value of \$33.5 billion in 2014 for active ingredients, and for finished drugs \$21.5 billion in 2009, projected to increase to \$39.6 billion in 2014 (see figures 6 and 7).^{101,*} While the United States and the E.U. still represent large revenue shares for contract manufacturing, they increasingly face competition from low-cost manufacturers in India and China.¹⁰² Large U.S. companies have reported intent to outsource more manufacturing. At a 2007 meeting in Hong Kong, the head of global research and development for Pfizer said that the company was considering doubling outsourced manufacturing from 15 to 30 percent, with most of the work going to companies in Asia.¹⁰³ That same year, the CEO of GlaxoSmithKline underscored the trend when he stated, "If we can buy it cheaper than we can make it, then of course that's what we're going to do."¹⁰⁴ In 2008, AstraZeneca's CEO related a plan to potentially outsource all active-ingredient manufacturing within the decade.¹⁰⁵

* Includes solid, semisolid, and both sterile and nonsterile liquid dosage forms.

Figure 6

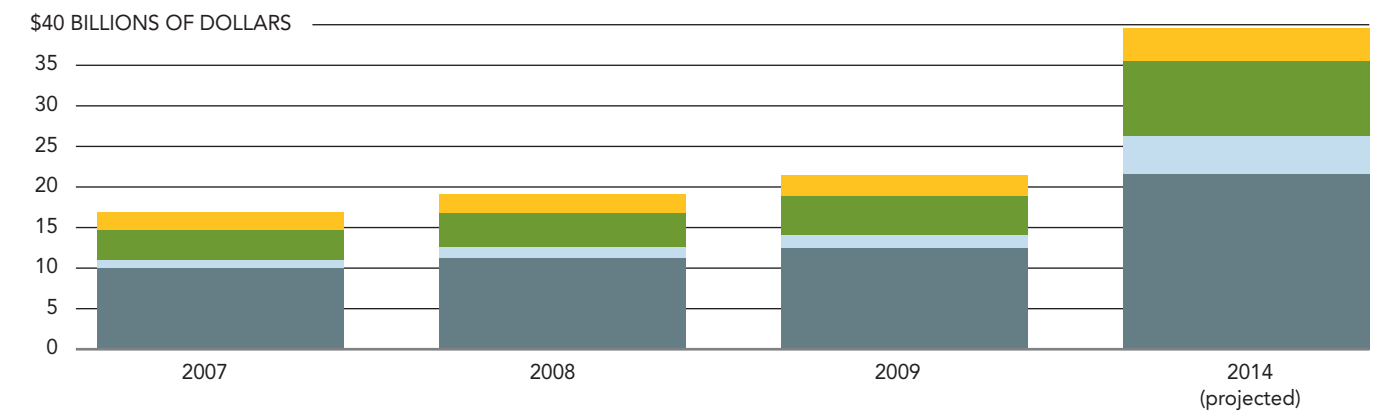
Outsourced active-ingredient manufacturing revenue: growth by region



Source of original data: BCC Research.¹⁰⁶

Figure 7

Outsourced finished drug manufacturing revenue: growth by region



Source of original data: BCC Research.¹⁰⁷

Emerging economies play increasingly larger roles in the U.S. drug supply. According to an analysis of import data from the U.S. Census Bureau's Foreign Trade Division, of the top 12 source countries for imported pharmaceuticals and medicines* by weight in 2009, four were emerging or developing economies: China, India, Brazil and Mexico.¹⁰⁸ The United States imported more than 80 million kilograms of pharmaceuticals and medicines from China in 2009 (see figure 8), by far the largest amount from any country that year and representing more than 20 percent of all imported pharmaceuticals and medicines into the United States by weight.¹⁰⁹ Pharmaceuticals and medicines from India were the third most imported by weight in 2009, after Canada, and showed tremendous growth in this period—approximately 30 million kilograms in 2009, compared with less than 5 million kilograms a decade earlier. Imports

* The category of pharmaceuticals and medicines is so defined by the North American Industry Classification System (NAICS). NAICS 3254: Pharmaceuticals and medicines may include substances for both human and veterinary use.

from Brazil grew in a similar fashion, mainly because of increased importation of lysine, a dietary supplement. While pharmaceutical and medical imports from the eight developed nations* decreased as a proportion of total imports over this period (dropping from 57 to 43 percent), imports from China and India combined significantly increased their share (up from 11 to 29 percent).¹¹⁰

Focus: China

The United States is the number one destination for Chinese pharmaceutical raw material exports—a \$2.2 billion business each year.¹¹¹ In particular, China is a major source for older and off-patent pharmaceutical ingredients in medicines sold in the United States.^{112,113,†} U.S. Census Bureau data from 2009 indicate that the United States imported large quantities of three major OTC pain relievers: ibuprofen, acetaminophen and aspirin (3 million, 3.5 million and 4 million kilograms, respectively).¹¹⁴ For all three products, the largest portion of imports came from China (see figure 9). China is also a major source of a number of older antibiotics. Ninety-four percent of imported tetracycline salts, an important class of antibiotics, originated in China from 2006 to 2008, as did three-quarters of imported streptomycin derivatives and salts used in injectable antibiotics and eye drops.¹¹⁵

The Chinese bulk pharmaceutical market grows by about 20 percent in production value each year,¹¹⁶ and China is home to thousands of domestic manufacturing facilities.¹¹⁷ The FDA has estimated that as many as 920 manufacturing plants in China may manufacture U.S. drugs and the ingredients used in them, and therefore may be subject to inspection by the FDA,¹¹⁸ an increase from 714 such sites in 2007.¹¹⁹

Focus: India

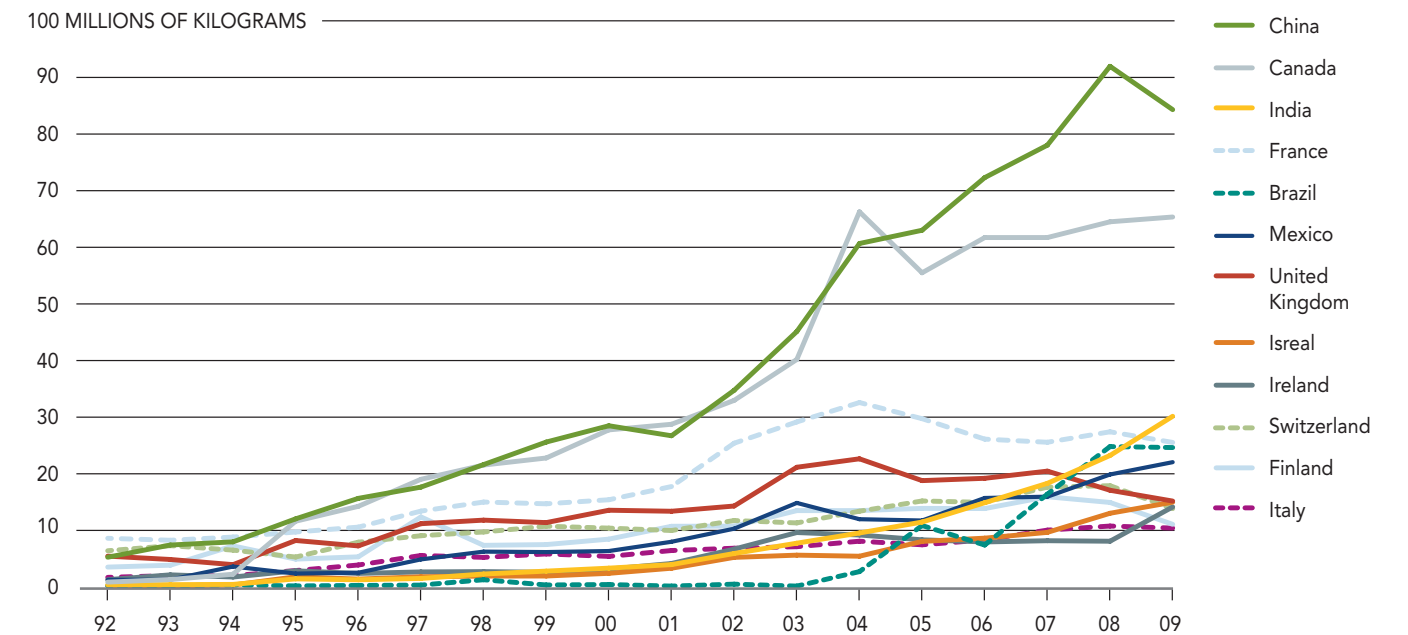
Indian pharmaceutical companies are actively pursuing U.S. market share.^{120,121} India was the third-largest source of U.S.-imported pharmaceuticals and medicines by weight in 2009,¹²² and as of 2007, India produced about 20 percent of the world's generic medicines.^{123,124} Indian plants are increasingly named in abbreviated new drug applications (ANDA), which companies file for approval to market generic pharmaceutical products. FDA estimates indicate that 40 percent of the active pharmaceutical ingredient factories listed in U.S. generic drug applications in FY 2009 were based in India, while 10 percent were sites in the United States. This is a change from FY 1997, when Indian API plants represented just 6 percent of those named in ANDAs.¹²⁵ As of June 11, 2010, Indian companies had filed 2,234 drug master files (DMFs) with the FDA, more than 30 percent of all active drug product DMFs and the most filed by companies in any country, including the United States, according to an analysis by India's Pharmaceutical Export Promotion Council.¹²⁶ DMFs document the facilities, processes or articles used during drug manufacture and are normally a part of drug marketing applications.

* Canada, France, the United Kingdom, Israel, Ireland, Switzerland, Finland and Italy

† Many newer drug products aren't individually identified in the specific data retrieved from the United States International Trade Commission, which lists commodities by 10-digit HTS code, and are therefore more difficult to track.

Figure 8

Top 12 source countries for U.S. imports of pharmaceuticals and medicines by weight (kg) from 1992 to 2009

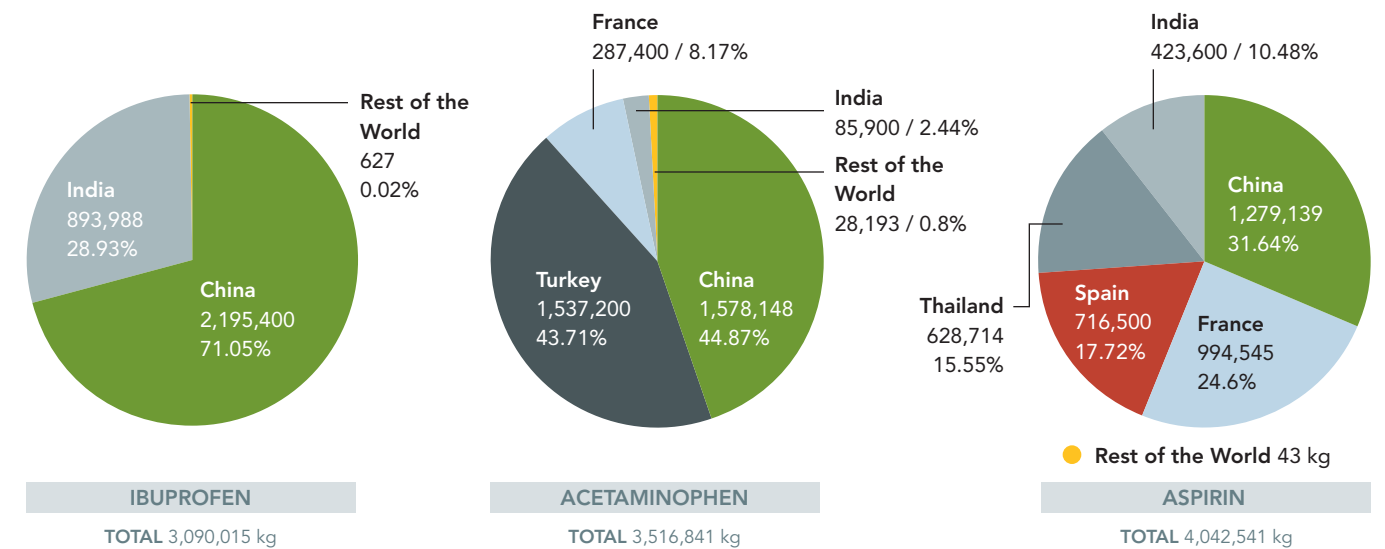


(Ranking based on 2009 data.)

Source: U.S. Census Bureau, Foreign Trade Division.¹²⁷

Figure 9

Top source countries for U.S. imports of ibuprofen, acetaminophen and aspirin by weight (kg) in 2009



Source: U.S. Census Bureau, Foreign Trade Division.¹²⁸

1.2.2 Globalization of medical device manufacturing

This report focuses on pharmaceuticals; however, medical devices and device components have related issues. Close to 5,000 non-U.S. manufacturing establishments for high- and medium-risk devices* were registered with the FDA as of 2007.¹²⁹ Chinese plants were the majority, with 675 sites.¹³⁰ A 2005 report by Millennium Research Group predicted that the global medical device outsourcing market would grow to \$8 billion by 2009, largely because of outsourced component manufacturing.¹³¹

Device recalls increased from 589 in 2005 to 616 in 2006, in part because of inadequate supplier controls, according to the former director of the Office of Compliance within the FDA's Center for Devices and Radiological Health.¹³² Forty-five FDA medical device warning letters went out in 2008 because of insufficient or nonexistent supplier evaluations.¹³³ As with pharmaceutical manufacturing, overseas device manufacturers are infrequently inspected. High-risk overseas device facilities are inspected every six years, and medium-risk facilities every 27 years, according to FDA estimates from 2008.¹³⁴ Although China is home to the largest number of FDA-registered device facilities outside the United States, the FDA inspects on average 10 Chinese device sites per year.¹³⁵ To help increase the number of inspections, the Medical Device User Fee Modernization Act of 2002 required the FDA to institute third-party inspection programs conducted by trained and authorized entities. Two such programs were launched in 2004 and 2006, respectively, but as of June 2009, only 21 third-party inspections had been conducted.¹³⁶

1.3 Gaps in ensuring quality and safety overseas

1.3.1 Manufacturing quality and regulation in India and China

Countries such as India and China, today's major players in drug manufacturing, have different regulatory and industry landscapes than the United States. Both countries have taken steps to strengthen oversight of pharmaceutical manufacturing and modernize GMP regimes. However, adherence to manufacturing quality standards—a critical means of safeguarding product quality and safety (see sidebar 2)—has been difficult and costly for many plants in both India and China. Also, measurements of drug quality have indicated that substandard and counterfeit products have been an issue in the domestic market in these countries. An expert committee organized by the government of India reported that the prevalence of substandard drugs in various Indian states ranged from 8.19 to 10.64 percent (based on data from 1995 to 2003),¹³⁷ and a survey of medicine quality by China's State Food and Drug Administration in the final quarter of 1998 found 13.1 percent of 20,000 batches tested to be substandard or counterfeit.¹³⁸

* Devices are generally divided into three classes: I, II and III. The classification is risk based: Class I includes devices bearing the lowest risk to patients, and Class III includes devices bearing the greatest risk; see www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm.

There are wide variations in production and quality capability among plants producing pharmaceutical products in both India and China.^{139–141} When GMP standards in China were made mandatory in 2004, up to one-third of Chinese factories were unable to meet the regulations, according to one estimate.¹⁴² In February 2011, China announced updated GMP requirements that incorporate concepts such as quality risk management and supplier audits.¹⁴³ Industry analysts predict that implementation of these new standards over the next five years will result in the closure of small firms that lack the resources to comply.¹⁴⁴ Plants that do not meet regulations are not lawfully allowed to sell their products for pharmaceutical use; however, experts with direct knowledge of the Chinese industry indicate that some of these companies' materials may still be purchased by pharmaceutical producers.^{145,146}

India announced a modernization of its GMPs in 2001.¹⁴⁷ As in China, implementation of the revised GMPs posed a challenge, because many smaller pharmaceutical companies did not have the resources to meet the new standards.¹⁴⁸ In 2008, India's National Productivity Council found that 40 percent of small pharmaceutical industries had closed down because of their inability to comply with revised GMPs.¹⁴⁹

In 2008 and 2010, respectively, two large Indian manufacturers, Ranbaxy Laboratories Limited and Claris Lifesciences Limited, were placed on import alert by the FDA,^{150,151} meaning they were prevented from exporting certain products to the U.S. market. In both cases, GMP failures observed by the FDA prompted this regulatory action.^{152,153}

Despite improved GMP standards in both China and India, enforcement concerns remain. At present, the FDA cannot conduct sufficiently frequent oversight visits to foreign sites that make drugs and ingredients for use in U.S. drugs (see section 2.1). But oversight regimes in India and China may not be sufficient to remedy this gap. An expert council convened by the Indian government in 2003 reported that there were serious inadequacies in India's regulatory system, including unsatisfactory levels of enforcement at the state level, shortages of trained personnel and inadequate testing facilities.¹⁵⁴ Pharmaceuticals exported from China receive lower scrutiny as a category.¹⁵⁵ Although China requires that exported medical products meet the regulatory standards of the destination country, it places full responsibility with the receiving party for ensuring that products meet those quality standards. China and the United States are working towards a system to ensure that certain products designated for export receive additional scrutiny from the Chinese authorities.¹⁵⁶

Adherence to GMPs is critical, yet also costly. Compliance with internal quality systems and regulations can represent up to 25 percent of a finished drug manufacturer's operating costs.¹⁵⁷ To offer more competitive pricing and gain market share, some plants may be tempted to forgo expensive quality standards. Regulatory oversight provides an incentive to ensure rigorous adherence to standards. Plants making generic and OTC medicines and ingredients may be particularly sensitive to the costs of compliance. In the United States, prices for generic drugs drop as more players enter the market.¹⁵⁸ Growing numbers of Indian and Chinese manufacturers making off-patent products and ingredients have made this sector increasingly competitive.^{159–161} As prices fall, companies may seek new efficiencies. India's emergence as a major exporter of generics was due in part to its ability to produce drug products much more cheaply than its competitors.¹⁶²

CASE STUDY 2

WHISTLE-BLOWER ALERT: RANBAXY LABORATORIES LIMITED

In 2008, the FDA suspended importation of more than 30 products from Indian generics company Ranbaxy Laboratories Limited after discovering manufacturing quality and safety violations.¹⁶³

Ranbaxy is one of the largest worldwide producers of finished-product generic medicines, as well as of generic active ingredients. Its products filled 52 million U.S. prescriptions in 2007.¹⁶⁴ The FDA conducted an in-depth inspection of two Ranbaxy plants in 2008 that revealed numerous alleged safety and quality issues affecting drugs destined for U.S. patients as well as drugs made for U.S.-sponsored aid programs.¹⁶⁵ Ranbaxy allegedly submitted false testing data to the FDA,¹⁶⁶ improperly conducted stability studies¹⁶⁷ and submitted records to the FDA signed by employees who were not present at the facility at the dates or times of their purported signature.¹⁶⁸ In addition to testing and documentation violations, the FDA warning letters also claim Ranbaxy exposed products to potential cross-contamination with penicillin,¹⁶⁹ had inadequate sterility procedures and failed to adequately investigate sterility failures.¹⁷⁰ According to a Department of Justice subpoena motion, Ranbaxy also used active ingredients made at sites not approved by the FDA, sometimes blending this material with active ingredient from approved plants, and delayed notifying the agency about drugs that did not meet established specifications.¹⁷¹

After notification of potential problems in 2005, the FDA began an investigation, inspecting two Ranbaxy plants in 2006.¹⁷² The FDA found significant GMP violations during these inspections and issued a warning letter to Ranbaxy regarding its Paonta Sahib facility in June 2006.¹⁷³ The FDA then met with Ranbaxy several times but did not take further disciplinary action.¹⁷⁴ In 2008, the agency returned to inspect the Ranbaxy plants and again found significant GMP violations in both locations.¹⁷⁵ The FDA subsequently blocked importation of more than 30 pharmaceuticals from the Ranbaxy plants located in Paonta Sahib and Dewas,¹⁷⁶ including drugs for epilepsy, diabetes and allergies.¹⁷⁷ Drugs from other Ranbaxy plants were not blocked. In 2009, citing ongoing violations, the FDA invoked its application integrity policy and halted reviews of all generic drug applications listing the Paonta Sahib plant as a manufacturing site.¹⁷⁸ In late 2009, the FDA issued another warning letter citing GMP violations, this time to a Ranbaxy facility called Ohm Laboratories in New York State.¹⁷⁹

While Ranbaxy violations were ultimately met with a strong regulatory response, this case calls attention to several weaknesses in existing regulations. The investigations were precipitated by information given to the FDA by a whistle-blower working at Ranbaxy rather than by a routine FDA inspection.^{180,181} Clearly, individuals within industry who wish to bring information to the attention of the FDA and other regulatory bodies need to be protected. Moreover, the agency currently lacks the general authority to subpoena witnesses and documents for violations of the Federal Food, Drug, and Cosmetic Act, and may not be able to thoroughly investigate safety issues without outside help such as from the U.S. Department of Justice, which subpoenaed internal company documents in the Ranbaxy case (see section 2.4.1). Increasing the FDA's on-the-ground presence in countries such as India could strengthen its oversight of imported drug products and help it identify issues more readily, according to U.S. Pharmacopeia experts and FDA staff.^{182,183}

Ranbaxy is not the only large Indian company to be placed on import alert by the FDA. In June 2010, an intravenous antibiotic product manufactured by Claris Lifesciences Limited, in India, was discovered to be nonsterile (which can cause infections) and to contain floating white particles, identified in at least one case as mold.¹⁸⁴ Three intravenous antibiotic products were then recalled by Claris and by three companies that sold the drugs in the United States under their labels through licensing agreements: Pfizer Inc., Sagent Pharmaceuticals and West-Ward Pharmaceuticals.^{185,186} In November 2010, the FDA placed Claris Lifesciences under import alert, preventing its products from entering the United States.¹⁸⁷

1.3.2 Drug ingredient quality issues resulting from deceptive practices

In emerging economies, highly competitive markets and lower regulatory enforcement may combine to encourage deliberate circumvention of costly quality regulations and certifications. Such deceptions have affected the U.S. drug supply (see case studies 1, 3, 4). The FDA has uncovered falsification of data several times in recent years. In a January 2010 warning letter, the FDA claimed that employees at XiAn Libang Pharmaceutical Co., Ltd., in Shaanxi Province, China, were manipulating testing data.¹⁸⁸ The agency informed the API manufacturing plant that it would not consider new marketing applications until the observed violations were sufficiently addressed.¹⁸⁹ In February 2010, Indian manufacturer Glochem was found to have falsified batch-manufacturing records for clopidogrel, an antiplatelet medicine. E.U. inspectors discovered at least 70 batch-manufacturing records in the plant's waste yard. All of the records had been re-written, and in some cases original entries had been changed.¹⁹⁰ And as discussed, in 2008, the FDA cited Indian manufacturer Ranbaxy Laboratories Limited for a number of U.S. GMP violations, including alleged falsification of stability testing records.¹⁹¹

Noncompliant drug-ingredient manufacturers may hide uncertified materials or production sites by physically concealing these factory rooms or warehouses (see figure 10) or through misrepresentations in documentation and packaging. One auditor in China suggested that some manufacturers claim regulatory certifications they do not possess.¹⁹² Such deceptions may permit unqualified manufacturers to gain business inappropriately, and may mislead regulators and industry efforts to assess quality and safety standards.

Another documented misrepresentation is the relabeling of materials produced at unknown or unapproved sites (see case studies 3 and 4). Such falsification poses risks to patients because neither the purchaser nor regulators can ensure a product's quality without knowing the conditions of its manufacture (which is why the FDA requires manufacturing sites to be listed in a drug's marketing application). While testing may ultimately show some improperly sourced materials to be safe, their untracked and unvalidated origins could conceal substandard material or poor production.

Economic motivation often drives these behaviors. Drug-ingredient suppliers may bring in additional material from unreported sources to meet growing product demand, as was the case for Biochimica

Opos, a company making antibiotics for the U.S. market (see case study 4). Pharmaceutical ingredients made at uncertified plants may be offered at attractively low prices if the factory is not committing operating expenses to complying with costly quality standards. Economic incentives may also encourage the introduction of substitute materials specifically designed to thwart standard tests. The adulterant found in heparin (see case study 1) was almost certainly chosen because it was a cheap substitute for the genuine product that mimicked the real drug in U.S. Pharmacopeia (USP) assays.^{193,194}

In some cases, companies may remain unaware for years of supplier deception. One Chinese supplier to U.S. manufacturer International Medication Systems, Limited (IMS) claimed to be a manufacturer of heparin but in reality was not. This “show” factory, Shanghai No. 1, was registered with the FDA as an exporter of heparin active ingredient to the United States and had an authorized U.S. agent, Amphastar Pharmaceuticals Inc., which in 2004 declared to the FDA that heparin was produced at Shanghai No. 1 under GMP conditions.¹⁹⁵ The FDA claims that Shanghai No. 1 had in fact been shipping heparin made at two external plants to the United States since 2001.¹⁹⁶ IMS had been importing this falsely labeled heparin as early as 2001 according to the FDA, but the fraudulent activity was only discovered seven years later. Further, the FDA alleges that some heparin shipped to the United States by Shanghai No. 1 in 2008 (but made elsewhere) may have contained the same heparin adulterant associated with U.S. patient adverse events.^{197,198,*}

APIs are at particular risk of falsification. One pharmaceutical auditor working in China observed during inspections and audits that for 39 percent of exported APIs, the final European or American customer was misinformed about the identity of the manufacturing site where all or part of the manufacturing took place.¹⁹⁹ He occasionally sees uncertified API concealed in hidden factory rooms or warehouses (see figure 10).²⁰⁰ Pharmaceutical brokers and traders have also been responsible for concealing the source of drug products, and failing to adequately verify the products they buy and sell. For instance, diethylene glycol (an industrial solvent) has been labeled as glycerin (a common inactive ingredient for cold and cough syrups) and sold into distribution numerous times, causing hundreds of deaths (see case study 5).

Figure 10



European inspectors in Zhejiang, China, found empty drums blocking access to part of a certified API plant exporting to Europe and the United States. Further investigation revealed a vast warehouse of substandard or falsely certified APIs.

Image courtesy of Philippe André, Associate Professor at the School of Pharmaceutical Science and Technology at Tianjin University, China (2008).²⁰¹

* Shanghai No. 1 was not part of Baxter Inc.'s heparin supply chain.

CASE STUDY 3

GENTAMICIN AND FLAVINE INTERNATIONAL: FALSE LABELING CONCEALS UNAPPROVED MANUFACTURING PLANTS

In the late 1980s and early 1990s, Flavine International Inc., a broker selling API to U.S. manufacturers, bought low-cost materials from plants in China that were not approved by the FDA and relabeled them as if they were active ingredients from the Long March Pharmaceutical Plant, an FDA-approved facility.²⁰² Flavine sold the falsely labeled APIs, which included bulk shipments of the antibiotic gentamicin to U.S. manufacturers.²⁰³ A few years later, these manufacturers recalled gentamicin products from the market.²⁰⁴

Flavine's labeling deception came to light because the broker was importing more product than Long March's facilities were physically able to produce, leading the FDA to suspect that some of the API came from other unspecified sources.²⁰⁵ In 1994, Long March officials confirmed that materials sold by Flavine had not been made at Long March, even though they were labeled as such.²⁰⁶ In 1997, Flavine International, Inc., was fined, and its owner sentenced to two years in prison.²⁰⁷ A Congressional review of the FDA's Flavine investigation showed that, although the FDA received reports of 1,974 adverse reactions (including 49 deaths) in patients taking gentamicin between 1989 and 1994, the agency's final report did not document any steps taken to alert the two companies that purchased the falsified product from Flavine or to track down suspect material that might remain on the market.²⁰⁸

In 1998, a year after Flavine was fined, the CDC identified 20 adverse patient reactions in California related to gentamicin made by Fujisawa USA (one of the manufacturers purchasing gentamicin from Flavine), including chills, shaking and drops in blood pressure. Thirty-seven similar events were identified in seven other states.²⁰⁹ The CDC report stated that the reactions were probably due to the method of administration, combined with high levels of endotoxin (a toxin produced by bacteria) in Fujisawa's product.²¹⁰

Although the FDA had suspicions about gentamicin packaged under the Long March Pharmaceutical label since the early 1990s, the agency did not recommend detaining gentamicin shipments from the plant until 1999, after an inspection found good manufacturing practice violations at the site.²¹¹

This case and more recent investigations^{212,*} underscore the importance of purchasing companies scrutinizing their suppliers to verify that all production is actually occurring at the declared sites, and that sufficient quality systems are in place.

* A recent examination of the impurity profiles of 39 samples of bulk gentamicin from the German and U.S. markets found drug substances listed from individual producers with different impurity profiles, suggesting that these producers may have brought in material from other undisclosed sources.

CASE STUDY 4

BIOCHIMICA OPOS: ANTIBIOTIC INGREDIENTS SOURCED FROM UNDISCLOSED SUPPLIERS

In the mid- to late 1990s, an Italian pharmaceutical manufacturer making bulk antibiotics for the U.S. market deliberately falsified records to conceal from the FDA its use of undisclosed manufacturing sites.^{213,214} The manufacturer, Biochimica Opos (Opos), was at the time a wholly owned subsidiary of French drug company Roussel-Uclaf.²¹⁵

The FDA visited Opos' factory in Agrate Brianza, Italy, in May 1996 for a post-approval inspection and became concerned by apparent inconsistencies in information given to them by employees at the plant, including records documenting where the materials used to make one antibiotic—cefactor—had been manufactured.²¹⁶ In October 1996, Roussel-Uclaf admitted it had not produced cefactor in accordance with its approved marketing application, and also admitted to similar infractions for antibiotics clindamycin and minocycline for the U.S. market. The company recalled the three products and withdrew its approved marketing applications.²¹⁷

The case was referred to the FDA's Office of Criminal Investigations in 1997²¹⁸ and culminated in multiple felony charges, including conspiracy and distribution of adulterated drugs in interstate commerce with intent to defraud or mislead.²¹⁹ On October 19, 2001, five years after the FDA's initial inspection, Roussel-Uclaf's successor, Aventis Pharma A.G., pleaded guilty to these charges and was ordered to pay a \$23,193,600 criminal fine and forfeit \$10 million in proceeds to the U.S. government.²²⁰

Roussel-Uclaf had falsified batch production records, raw material logs and work orders to create the appearance that all of its manufacturing occurred at sites designated in its approved U.S. marketing application.²²¹ In reality, the company was outsourcing the manufacture of materials used to make cefactor to facilities in Italy, France and Romania that were not listed in its application or inspected by the FDA.²²² This put Opos in knowing breach of its approved manufacturing pathway. Further, Opos was found to have used a different, unapproved chemical in place of a required chemical for cefactor processing.²²³

The Opos case represented the first time a foreign corporation making a drug product entirely outside of the United States received a criminal punishment for defrauding the FDA.²²⁴ One FDA agent reported that the investigation was made difficult by its foreign nature; in particular, some potential witnesses were not subject to U.S. subpoena.²²⁵ However, U.S. investigators did receive assistance from foreign authorities in accessing important documents and witnesses.²²⁶ To support this type of cooperation, the FDA should be allowed to share all information, including trade secret information, in a protected manner with foreign agencies—a general authority that it does not currently have (see section 2.4.3).²²⁷ As drug manufacturing becomes increasingly globalized, international collaboration is essential for improving oversight and identifying wrongdoing.

CASE STUDY 5

LETHAL COUGH SYRUP IN PANAMA

In Panama in 2006, cough medicine that had been manufactured using a toxic syrup originating in China was unknowingly distributed by the government.²²⁸ The official number of deaths was 78,²²⁹ but unofficial reports suggest the possibility of a much larger toll.²³⁰

The Taixing Glycerin Factory in Hengxiang, China labeled barrels of diethylene glycol (DEG), an industrial solvent often used in antifreeze formulations, as glycerin, a common excipient (inactive ingredient) used to make medicines into syrups.^{231,232} DEG is chemically similar to glycerin, but it is less expensive to make.²³³ The material passed through brokers in China and Spain, being relabeled at each step, before finally reaching Panama.^{234,235} In 2006, the Panamanian government purchased the material and used it to manufacture an estimated 60,000 units of medicines, which were distributed to patients.²³⁶

When patients began to suffer paralysis and die, medical personnel could not determine the cause until more than a month after the adulterated medicine was distributed. Even when the substitution of DEG for glycerin was discovered, relabeling by brokers prevented officials from quickly identifying the source. Each time the fake glycerin changed hands, an international broker created new certificates of analysis indicating identity and purity, presumably without independently testing the product. Obfuscation of records impairs investigations of this sort of deception and shields bad actors from identification and prosecution. As of early 2011, no one in China has been held accountable for the deaths in Panama.

This was not the first DEG poisoning. Indeed, the use of DEG to manufacture Elixir Sulfanilamide (a liquid antibiotic) in the United States in 1937 caused more than 100 deaths and led directly to the enactment of the Federal Food, Drug, and Cosmetic Act.²³⁷ Between 1937 and 2008, there were more than 750 documented deaths in 10 countries associated with exposure to drugs contaminated with DEG.²³⁸ The largest loss involved the deaths of 236 children in Bangladesh between 1990 and 1992.²³⁹ According to an investigation by the *New York Times*, 50 tons of fake glycerin shipped to the United States in 1995 were fortunately identified.²⁴⁰ But in 1997, at least 88 children in Haiti were reportedly killed by this adulterant,²⁴¹ which was also traced back to a Chinese manufacturer and involved one or more brokers.²⁴² In 1998, DEG poisoning was implicated in the deaths of 33 children in Guragon, India.²⁴³ After the disaster in Panama, the U.S. Food and Drug Administration issued guidance that all glycerin used in drug manufacturing, including glycerin imported into the United States, be tested for DEG.²⁴⁴ The U.S. Pharmacopeia released a more stringent monograph for glycerin with revised testing methods in 2009.²⁴⁵

1.4 Problems with domestic controls on supply chain and quality

1.4.1 Insufficiencies in supplier management

Outsourcing allows pharmaceutical companies to cut costs and reduce manufacturing time,²⁴⁶ but can also result in diminished control and transparency, particularly when contractors and suppliers are in distant geographic locations. According to a 2010 survey by the Axendia consulting firm, 94 percent of pharmaceutical executives think that raw material sourcing from foreign suppliers is a serious or moderate risk.^{247,*}

Members of industry and FDA experts recognize the need for strong contractor and supplier management.^{248–250} Ensuring that suppliers adhere to current good manufacturing practice (cGMP) standards[†] is a critical means of safeguarding product quality and safety (see sidebar 2). FDA guidance recommends that companies verify that a potential contractor is qualified before engagement and audit their suppliers in addition to testing incoming components.²⁵¹ However, these recommendations are not requirements, and FDA officials have expressed concerns about industry supply chain vulnerabilities, including insufficient knowledge of contract manufacturing sites, too little on-site auditing of suppliers and overreliance on supplier-provided documentation of testing.^{252–254} In a 2009 presentation, an FDA Office of Compliance official noted that industry supplier qualification programs, quality agreements and life cycle monitoring were often deficient.²⁵⁵ A surge in FDA warning letters to both foreign and domestic contract manufacturers illustrates the agency's concerns: the FDA sent 15 warning letters to contractors in the first half of 2010, up from just two for all of 2007.²⁵⁶ An FDA official noted that these increases specific to contractor problems probably were not attributable to changes in FDA activity, as the agency had not stepped up oversight of contract manufacturers as a category.²⁵⁷

While FDA guidance addresses supplier qualification and auditing, the FDA regulations do not. Current GMPs require manufacturers to control the quality of incoming drug components through testing. However, they do not explicitly require manufacturers to evaluate component suppliers prior to contracting with them, nor to engage in quality agreements with those suppliers, nor to conduct on-site audits of suppliers' plants (see sidebar 2). As long as manufacturers verify ingredient batches with an identity test (and conduct additional testing periodically to validate a supplier's results), U.S. cGMP allows them to rely on supplier-provided certificates of analysis (COA), which assert that the ingredient meets purity, strength and quality specifications.²⁵⁸ COAs may be of limited utility in assessing the actual quality standards and practices in place at a supplier's plant. COAs may even come from a broker that sells a drug ingredient rather than from the original ingredient manufacturer. In 2007, as described in case study 5,

at least 78 people in Panama died²⁵⁹ after taking cough medicine manufactured using a toxic ingredient that carried a falsified COA.²⁶⁰ Each broker that handled the syrup replicated the previous COA, presumably without independently testing the material.²⁶¹

Two factors make thorough evaluation of suppliers prior to contracting important. (1) Once a supplier relationship is established, the costs and risk of interrupted supply make breaking or altering that relationship difficult, especially if few alternatives are available. (2) In many cases, companies must obtain prior approval from the FDA in order to change suppliers^{262,263}—a regulatory hurdle that may further disincentivize terminating relationships.

The purity of raw ingredients and the safety of production methods are critical to the quality of a drug. Nonetheless, suppliers and brokers do not always allow FDA officials, or even the manufacturer of the finished product, to access plants at which key processes are performed. After the heparin contamination, for example, Baxter International could not gain access to Chinese raw material processing sites²⁶⁴ (see case study 1). And in December 2010, the FDA was denied access to an active-ingredient manufacturing facility in India.²⁶⁵

To address concerns about supply chain quality control, a number of companies have taken a private-sector collaborative approach to information sharing and leveraging one another's supplier audit results. Rx-360, an industry consortium, has created such a shared audit program and also disseminates information on risk signals to its members.²⁶⁶ The Federal Trade Commission has indicated that these activities do not constitute anticompetitive activity.²⁶⁷

Unlike most products, labels on drugs may not offer consumers a clear picture of the countries from which these medicines have come. U.S. statute requires all imported products to display their country of origin to the ultimate purchaser,²⁶⁸ defined as the last person to receive the product in the form it was imported.²⁶⁹ Imported finished drugs, therefore, must list the country where manufacturing occurred. But if a company imports a pharmaceutical active ingredient and then formulates that substance into a pill or liquid medicine in the United States, the form of that product has changed, and country-of-origin labeling requirements thus cease to apply. Although separate drug packaging regulations require some identification of origin of the finished drug product, companies may choose whether to display the name and address of the manufacturer, the packer or the distributor.²⁷⁰ If the manufacturer is named, it is the manufacturer of the finished drug product, and not the manufacturer of the active ingredient.

* The online survey included 112 respondents from 75 companies; 49 percent of these companies had annual revenues of more than \$1 billion.

† United States statute and regulation refer to "current" good manufacturing practice (cGMP), rather than good manufacturing practice alone, to indicate that these standards permit recognition of current and evolving industry technologies.

SIDEBAR 2

ENSURING QUALITY: GOOD MANUFACTURING PRACTICES

The FDA and its counterpart agencies worldwide monitor the quality and safety of drug and device manufacturing by inspecting plants and validating compliance with cGMPs, which are regulations that describe the methods, equipment, facilities and controls required for producing safe products. Because it is impossible to test every single pharmaceutical item produced, adherence to manufacturing quality standards is the most effective way that the FDA and industry can ensure drug quality and safety. While noncompliance with manufacturing quality standards does not necessarily mean that a drug is unsafe, it increases that risk by weakening the safeguards.

Both finished drugs and their components (ingredients) must be made under cGMP: although cGMP standards themselves address finished drugs and not drug components, the Federal Food, Drug, and Cosmetic Act considers any drug, including its ingredients, not made under cGMPs to be adulterated.²⁷¹ Contract manufacturer plants are also subject to the FDA inspections,²⁷² although ultimate responsibility in the eyes of the FDA rests with the manufacturer marketing the product in the United States.²⁷³ The FDA announced in April 2010 that it intends to revise cGMPs related to incoming components.²⁷⁴

Manufacturing quality standards for drugs are set by the FDA,²⁷⁵ by other regulatory authorities and also cooperatively in guidance through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH brings together the regulatory authorities of Europe, Japan and the United States (and experts from the pharmaceutical industry in the three regions) to discuss scientific and technical aspects of product registration. The ICH quality guidelines (Q1–Q10) have been largely accepted by the FDA and published in the *Federal Register*. The World Health Organization has also developed a number of guidelines on quality assurance, including pharmaceutical GMP.²⁷⁶ The FDA guidance describes ways that industry can comply with cGMP requirements, but these recommendations are nonbinding. The FDA can only enforce actual regulatory requirements and not recommendations in guidance.

The FDA has found that since the last substantive update to its cGMP regulations in 1978, there have been many advances in manufacturing quality systems and science.²⁷⁷ The agency promulgated guidance for industry in 2006 on a quality systems approach to cGMP regulations, which includes risk assessment, management responsibility and greater assessment of component suppliers. The FDA is also looking to update its GMP regulations to require manufacturers to audit component suppliers, including providers of raw materials.^{278,279} A quality systems approach is already in place in the United States for medical devices, known as Quality Systems Regulation (QSR),²⁸⁰ and has been embraced in international guidance such as the ICH Q10 Pharmaceutical Quality System.²⁸¹ Provisions covering supplier evaluation are found in both device QSR (“purchasing controls”)²⁸² and ICH guidance (“materials management”).^{283,284}

Guidance is an important tool to encourage companies to advance quality systems voluntarily, but these systems are not currently required through regulation or in the statute. As discussed above, important elements such as robust supplier qualification may not be uniformly adopted by industry (see section 1.4.1).

1.4.2 Manufacturing quality issues in the United States

Drug-quality problems are not restricted to emerging economies or to areas where oversight is weak. The FDA has observed quality failures at domestic manufacturers in recent years, and the United States has also experienced an upward trend in drug product recalls. The number of product recalls has consistently risen since 2005, with a sharp increase in 2009 (see figure 11). Drug product recalls in 2009 represented a fourfold increase over recalls in 2008 (1,742 and 426, respectively).^{285,*} Of the 2009 recalls, 1,384 (nearly 80 percent) were for problems with manufacturing or testing methods.²⁸⁶ This increase in recalls may not reflect an increase in manufacturing quality problems, as multiple products may be impacted by GMP violations at one plant. However, manufacturing issues have become a much more prominent concern in the FDA’s warning letters to industry, with 34 cGMP warning letters sent to drug companies in 2009, approximately double the total in 2008 (see figure 12).²⁸⁷ The recent events described below have, in many cases, been discovered because of FDA plant inspections, which occur much more frequently in the United States than overseas (see section 2.1).

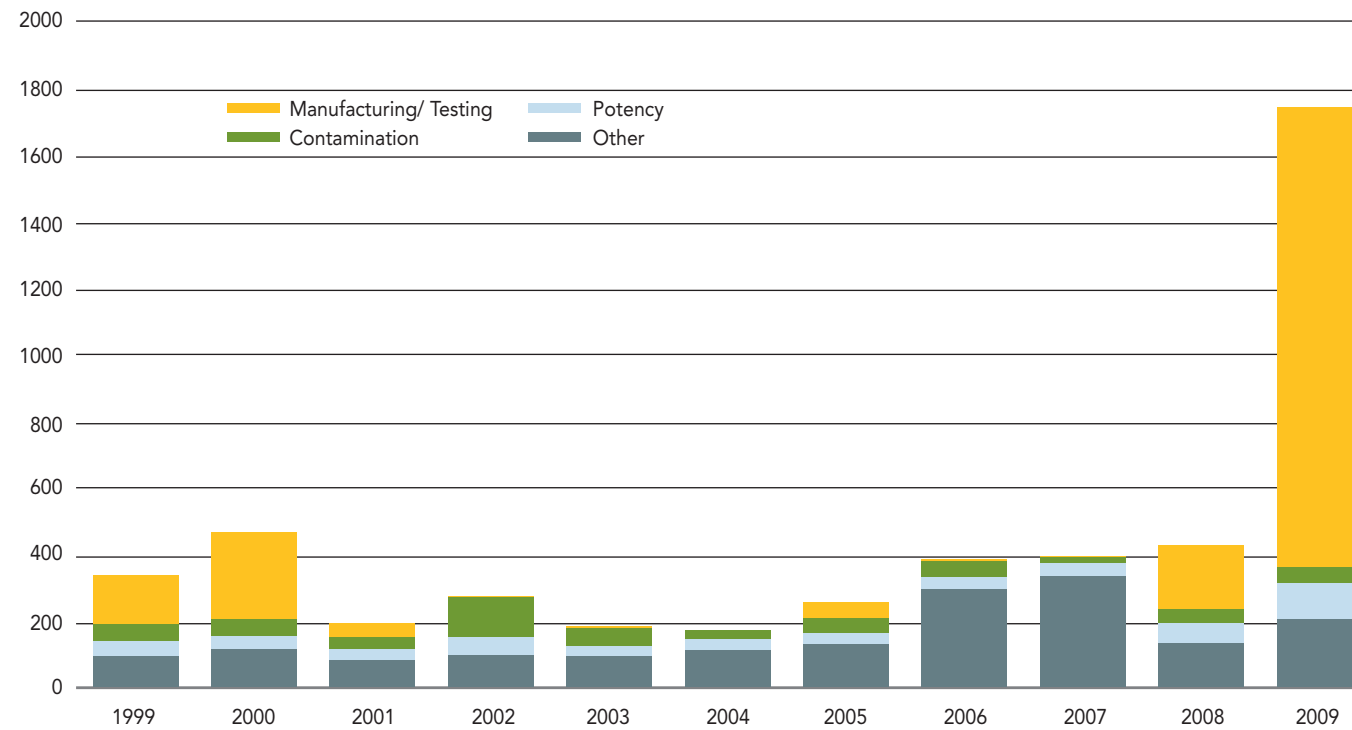
- In 2010, Johnson & Johnson recalled more than 130 million bottles of children’s cough and cold medicines²⁸⁸ after an FDA inspection revealed 20 alleged cGMP violations, including failure to conduct an adequate investigation of inactive ingredients that were contaminated with bacteria.²⁸⁹
- In April 2010, the FDA warned the Michigan-based L. Perrigo Co., which also manufactures OTC cough and cold medications, for multiple cGMP violations,²⁹⁰ including the discovery ibuprofen tablets contaminated with metal shavings.²⁹¹ The FDA has reported cGMP and compliance issues at Perrigo since 2005.²⁹² In 2006, that company recalled 384 lots of acetaminophen tablets after the discovery of metal particles in some of the drugs.²⁹³
- In October 2010, GlaxoSmithKline (GSK) agreed to pay \$750 million in a civil plea agreement for distributing adulterated drugs that did not meet necessary levels of strength, purity or quality. The United States contends that some of the drugs contained the wrong amount of active ingredient, and some were possibly exposed to contamination by microorganisms.^{294,†}
- In May 2010, Genzyme Corp. signed a consent decree with the FDA and agreed to pay \$175 million after the agency discovered serious manufacturing quality issues at the company’s Allston, Mass., plant. Alleged violations included drug contamination with metal, glass and rubber particles, and viral contamination in manufacturing equipment. The consent decree holds Genzyme to a strict schedule of improvements to bring its plant in line with FDA regulations.²⁹⁵

* Includes 50 recalls for dietary supplements found to contain pharmaceutical active ingredients.

† The charges against GSK were brought under the False Claims Act—a law providing remedy for false claims made against the government, including charges to Medicaid and Medicare for drugs. Most false claims cases in the pharmaceutical realm relate to the marketing of drugs for unapproved uses. This was the first settlement of a case brought under the False Claims Act regarding pharmaceutical manufacturing quality.

Figure 11

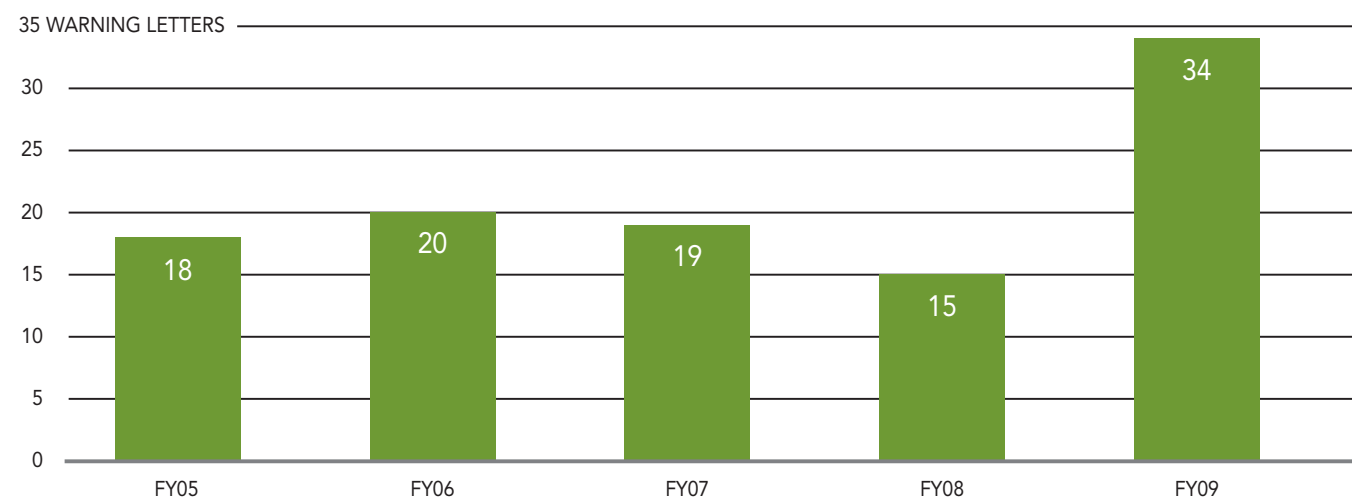
FDA drug product recalls from 1999 to 2009 by problem area showing recent increases in individual product recalls



Source: The Gold Sheet²⁹⁶

Figure 12

FDA warning letters from 2005 to 2009 concerning adherence to good manufacturing practice



Source: The Gold Sheet²⁹⁷

1.4.3 Challenges involved in testing

Pharmaceutical manufacturers must perform tests to ensure the identity, strength and purity of their drug products.²⁹⁸ Under cGMPs established by the FDA, testing must be performed on incoming drug components and in-process materials as well as finished drugs.²⁹⁹ Companies seeking to market a drug in the United States must specify the analytical methods necessary to ensure that drugs and their components meet established levels of quality in their applications to the FDA.³⁰⁰ Specifications may also be published publicly as a drug monograph in the U.S. Pharmacopeia and National Formulary (USP-NF).³⁰¹ The FDA can ensure that a drug meets established specifications by enforcing adherence to: applicable public monographs,³⁰² the terms of approved drug applications³⁰³ or GMP requirements.³⁰⁴ Failure to follow appropriate testing procedures has been implicated in a number of high-profile quality problems in 2009 and 2010.^{305–307}

An important function of testing is to screen for possibly harmful contaminants. But according to USP leadership, many existing tests are out of date,³⁰⁸ including, at the time of the adulteration, USP’s standard identity test for heparin (although revisions were in process).³⁰⁹ USP officials believe that an up-to-date heparin monograph might have prevented the adulterated product from reaching the U.S. market, and that Europe’s more robust test specifications for heparin may have helped limit distribution of the adulterated drug there.³¹⁰

USP estimates that as of June 2009, 44 percent of human drugs (both on- and off-patent) in the United States either had no public monograph, or a monograph that was out of date.³¹¹ Many on-patent products do not have public monographs because of industry trade secret concerns; however, USP reports that 16 percent of *off-patent* drugs also do not have USP-NF monographs.³¹²

Part of the challenge of updating testing specifications to anticipate intentional adulteration is predicting what the contaminants will be. Impurities measured by standard tests are normally process-related and thus simpler to anticipate. They can be by-products of chemical processes or residual materials such as metals or salts that may be introduced during manufacturing.³¹³ (The FDA recommends, in accordance with ICH guidelines, that companies identify and list impurities in their drug specifications.)³¹⁴

While designing a test to capture *any* unexpected substance in a drug is essentially impossible, better methodologies for predicting non-process-related adulterants are needed, according to academics regulators and members of industry.^{315–317} The FDA has emphasized the need to identify products at highest risk for economically motivated adulteration,³¹⁸ and has risk-ranked 1,000 APIs as of October 2010.³¹⁹ An expert at the National Institute for Pharmaceutical Technology and Education, an organization focused on increasing science-based understanding of pharmaceutical product development and manufacturing, further suggests that advances in manufacturing science are overdue in the pharmaceutical sector and are needed to ensure product quality.³²⁰ Leadership at the FDA’s Office of Pharmaceutical Science also assert that pharmaceutical science is not state of the art compared to other industries and is characterized by inefficiencies, inability to analyze failures and waste.³²¹

For drug specifications that are not publicly shared, the responsibility of developing robust testing systems lies with the manufacturer, and all companies must take steps to predict and respond to the risk of adulteration. For public standards, USP asserts that remedying its backlog of outdated drug monographs will require better participation from industry and the FDA.³²² The agency is working with USP to revise outdated USP-NF monographs.³²³ Because of their public nature, consideration should also be given to using multiple tests to make a standard harder to fool. The FDA and USP revised the monograph for heparin in 2008 to include new tests,³²⁴ and that monograph continues to be revised in collaboration with the international community.³²⁵

Testing alone is not sufficient to ensure product safety, but it is a critical element of an effective quality system.³²⁶

1.5 Pew conference and policy recommendations

Many of the active ingredients in the drugs that U.S. consumers take are made abroad, but there is insufficient oversight by the FDA and foreign authorities of materials made overseas for use in U.S. drugs. With extensive outsourcing and increased reliance on foreign suppliers, manufacturers may have less knowledge and control over production supply chains. These weaknesses are especially alarming in light of the risk of deliberate ingredient adulteration for profit.

To ensure the safety of the globalized pharmaceutical industry, companies must ensure greater control of manufacturing quality, both internally and with their suppliers. Companies sourcing pharmaceutical active ingredients and intermediates from emerging economies such as India and China have a responsibility to ensure that these drug components are safe and are made under appropriate conditions. These companies also must address proactively, to the greatest extent possible, the risk of economically motivated adulteration during stages of manufacturing.

Modern quality systems, including supplier management and risk assessment, must be required to ensure drug safety and address gaps in the FDA's cGMP requirements. Testing methods and standards must be continually reevaluated and updated to help protect against contamination and intentional adulteration.

On March 14 and 15, 2011, the Pew Health Group convened a roundtable meeting of key stakeholders to discuss concerns over safety of the U.S. drug supply and consider potential policy responses. Participants included representatives of the FDA, USP, state regulators, major pharmaceutical manufacturing and distribution trade associations, pharmacy organizations and medical professional groups, and academic and consumer organizations (see Appendix B for a complete list of participants).

Roundtable participants fully agreed that safety risks exist in our globalized pharmaceutical supply chain, and that the system can and must be improved. Participants called for improvements in quality systems, subcontractor agreements, supplier audits, supply chain documentation and transparency, as well as testing. Many present underscored the fact that you cannot inspect quality into a product; it must be built in to every process. One participant suggested the pharmaceutical industry still relies on “quality by inspection,” and made a comparison to other regulated industries that have embraced a “quality by design” concept. These industries have very rigid control over raw materials and low product defect rates.

Stakeholders supported strong supplier assessment and management. FDA representatives called for industry implementation of quality systems to identify and mitigate hazards, and ensure sufficient scrutiny of suppliers and contractors. There was strong agreement that manufacturers must be held accountable for their full supply chain and that they need to have concrete knowledge of suppliers when they are selected, rather than after they have become part of the supply chain. Before doing business with a supplier, drug license holders should be sure that a supplier has good quality systems in place. One industry representative recommended that every supplier and sub-supplier within a manufacturing supply chain should be audited by someone. Another important action for manufacturers to take, according to the FDA and other participants, is to insist that their pharmaceutical ingredient suppliers in China are licensed pharmaceutical manufacturers rather than chemical companies, which receive no Chinese government oversight.

Several commenters focused on the importance of information sharing between companies and through groups such as Rx-360, as well as clear communication between companies and suppliers. A representative of Rx-360 suggested that quality agreements should define GMP expectations, list approved raw materials and provide clarification on which companies are authorized subcontractors. A representative of European fine chemical manufacturers noted that companies should be on alert for clues that indicate increased risk of tampering (such as the doubling of the heparin price discussed above). Additional recommendations included expanding enforcement of cGMP regulations to include excipients.

Several participants called for greater transparency throughout the supply chain. Consumer representatives called for public engagement so that the public understands where medications come from, with the caveat that those messages be balanced so that consumers do not stop taking their medications. Active-ingredient manufacturers and others supported companies listing publicly the country of origin of their drugs and active ingredients. Regarding testing, USP leadership encouraged greater collaboration with the FDA to update USP public monographs to include the most relevant, up-to-date testing standards.

The policy recommendations that follow have been informed by the roundtable discussions and presentations, but are not intended to constitute a consensus position and may not reflect the views of every participating organization.

POLICY RECOMMENDATIONS

A. Require 21st-century quality systems to protect drug safety through statute and regulation.

1. **Companies selling drugs in the United States should have in place a quality system to ensure the safety and integrity of their products, including drug ingredients manufactured by a contractor or supplier.** A quality systems model is a holistic, preventive strategy to ensure that the drugs we take are safe. A quality systems provision in legislation would specify basic key components, but would not conflict with detailed technical requirements, such as those found in cGMPs (which are established through the FDA's regulation and permit recognition of evolving industry technologies). The FDA has shown clearly in guidance how a quality systems approach is harmonized with and can support adherence to cGMPs.
2. **Quality systems should have the following key components (see recommendations B and D for additional discussion):**
 - a. **Management responsibility:** Management should be responsible for establishing the quality systems and ensuring that they are adequately resourced and function appropriately.
 - b. **Supplier management:** Manufacturers should assess suppliers and contractors prior to engagement with them, and should perform periodic on-site audits to ensure adherence to quality and safety standards. Pre-assessment and periodic on-site audits are not currently required under U.S. cGMPs.
 - c. **Risk assessment:** Companies should establish procedures to identify, monitor and evaluate risk factors that could impact product quality, safety, strength, purity and identity.
 - d. **Assessment and revision of analytical methods:** Manufacturers should review and, where necessary, update tests to ensure that they are robust and are able to screen for substances that could affect product quality, safety, strength, purity and identity.

B. Industry should also independently improve its control of contract manufacturers and suppliers.

1. **Strengthen supplier contracts to facilitate and improve oversight.** Contracts should establish the authority of the purchaser to conduct on-site audits of suppliers. When necessary, contracts should specify that the drug company has the right to audit subcontractors involved in manufacturing the suppliers' products. Contracts should also specifically require drug company approval of any changes in ingredients sourcing or manufacturing processes.

2. **Require clear, strong, quality agreements for suppliers.** Quality expectations should be clearly established for, and contractually agreed to, by suppliers. Agreements should acknowledge U.S. quality requirements and establish that, if necessary, FDA officials will have access to a supplier's plant. Agreements should also require suppliers and contractors to report manufacturing changes to the purchasing company. If possible, quality agreements should be included as a part of main supplier contracts to clearly set expectations.
3. **Increase information sharing among industry to ensure supply chain safety.** Industry should share information on suppliers, risk signals, and other global market data that might help to ensure product quality and safety. Legal barriers to information sharing should be actively addressed through antitrust waivers, if necessary, or safe-harbor provisions in contracts.

C. Enhance documentation and transparency of the upstream manufacturing supply chain through legal requirements.

1. **Companies should know and be able to document the companies involved in their upstream manufacturing supply chain.** Drug companies must know the entities involved in the manufacture, processing, and transportation of their drugs and active ingredients. This documentation should be available to regulators on demand.
2. **Require all drug companies to state country of origin for their drugs and active pharmaceutical ingredients on their websites.** Pharmaceuticals should not be subject to less transparency than other consumer products. Country of origin should be listed for both the finished drug and the drug's active ingredients. While pharmacy dispensing may make country-of-origin labeling on drug bottles less useful for consumers, this information could be made available to the public through other means, such as package inserts or on a company's website.

D. Improve testing standards

1. **Industry and regulators must continually seek to develop better testing methods to ensure the identity, purity and safety of drugs.** Manufacturers must be responsible for ensuring the purity of their drugs and drug components through robust testing methods, and should review and update analytic methods in an ongoing manner. Regulators and industry stakeholders agree that better methods for detecting and measuring drug contamination are needed. In addition to improving their methods, drug companies could use multiple assays as a check against bad actors who might try to design fake ingredients that are able to fool specific tests.
2. **Require continual assessment and updating of public testing standards.** Compendial testing standards should be regularly reviewed to ensure adequacy. The FDA and USP should work together to ensure that public standards are robust and up to date, and identify and prioritize those assays that need to be updated and/or revised.

2.1 Overview

The FDA is responsible for protecting the public health by ensuring the safety and efficacy of human and veterinary drugs, vaccines and other biological products, medical devices, the U.S. food supply, cosmetics, dietary supplements and products that emit radiation.³²⁷

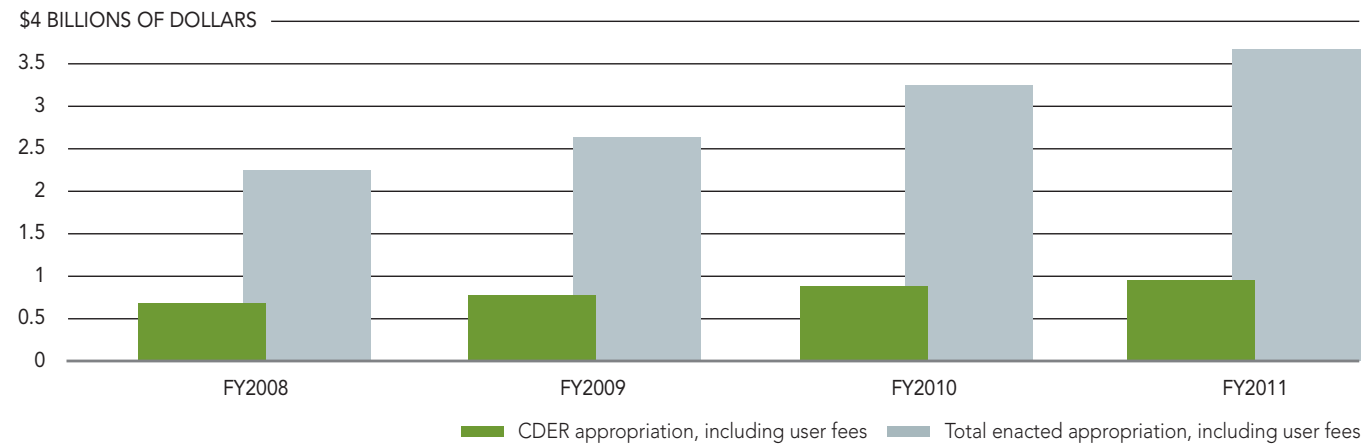
The precarious state of FDA resourcing and capacity is broadly recognized. The regulatory demands placed on the agency far exceed its ability to respond, according to a 2007 FDA advisory committee report that outlined serious scientific shortcomings within the agency.³²⁸ Between 1988 and 2007, Congress passed 123 new laws requiring FDA action, but according to the report, the agency was allocated only a 9 percent staffing increase through appropriations.³²⁹ The FDA's Principal Deputy Commissioner from 2009 to 2010, Dr. Joshua Sharfstein, testified at a Congressional hearing in March 2010 that the agency does not have the resources and authority it needs to ensure the safety of imported drugs and components, and is not currently able to prevent another tragedy like the heparin adulteration (see case study 1).³³⁰

The FDA has received some important augmentations to its budget in recent years. Total enacted appropriations, including user fees, were \$2.63 billion, \$3.25 billion and \$3.67 billion for fiscal years 2009, 2010 and 2011, respectively (see figure 13).^{331–334} The agency also received a supplemental appropriation of \$150 million in June 2008 to support regulatory activities in response to globalization, in particular food supply safety programs.^{335,336} Funding allocations for the FDA's Center for Drug Evaluation and Research (CDER) and related field activities in the Office of Regulatory Affairs (the office that conducts inspections, among other functions) have also increased, although at a slightly lower rate than overall appropriations. With these funds, FDA has begun to address issues such as understaffing and information technology (IT) capacity, but as outlined in this chapter, serious capacity and structural problems remain, and they weaken the agency's ability to regulate drug manufacturing and importation.

The FDA inspects foreign plants that make drugs and ingredients for the United States at much lower rates than it inspects domestic sites.³³⁷ IT systems for tracking drug manufacturing sites are archaic and contain data-entry errors.^{338,339} An estimated 20 million shipments of FDA-regulated goods entered the United States in 2010; however, border assessments are hampered by data systems that contain errors and do not permit effective risk-based targeting (see section 2.3.3). Oversight is also undermined by the FDA's lack of enforcement tools and needed authority, such as the power to mandate a recall or to subpoena documents for investigations.

Figure 13

FDA-enacted appropriations from fiscal years 2008 to 2011



Source: Appropriations acts for fiscal years 2008,³⁴⁰ 2009,³⁴¹ 2010³⁴² and 2011.³⁴³

2.2 Insufficient scrutiny of overseas manufacturing

2.2.1 Foreign and domestic inspection disparities

One of the FDA’s most important tools for ensuring the safety of drugs sold in the United States is the inspection of factories to verify compliance with GMP standards. The volume of drugs destined for the U.S. market makes it impossible to test samples of all products before they reach patients. Checking manufacturing quality, normally through inspections, is a critical preventive measure to protect the public from unsafe pharmaceuticals.

The FDCA, written when most drugs were manufactured domestically, requires regular, biennial inspections only for U.S.-based sites.³⁴⁴ Although FDA inspectors travel abroad, the FDA’s foreign inspection service lacks the resources to inspect manufacturing sites with any meaningful regularity (see section 2.3.1).³⁴⁵ The FDA reported that at least 242 foreign manufacturers of active pharmaceutical ingredients (API) had shipped product into the United States in 1999 without being inspected by the FDA.³⁴⁶ As many as 2,394 overseas plants on the FDA’s inspection planning list have never been inspected by the agency, according to FDA data analyzed by the U.S. Government Accountability Office (GAO).³⁴⁷ However, the FDA does not know with certainty how many of these sites are actively shipping product to the U.S. market.

Most inspections of foreign sites are pre-approval inspections (PAI), which are a component of a marketing application approval and are supported by special funding through the Prescription Drug User Fee

Act (PDUFA) of 1992.^{348,349} PDUFA funds do not cover PAIs for generic drug products. Foreign GMP inspections, when done, are most often completed at the same time as the PAI.³⁵⁰ By contrast, many more ongoing GMP inspections, separate from PAIs, are conducted for U.S. sites.³⁵¹ The FDA uses a risk-based assessment model to decide which plants to inspect for GMP, but the agency keeps separate risk-based lists for domestic and foreign plants.³⁵²

Sometimes, even PAIs are not performed. In September 2003, the FDA eliminated mandatory PAIs in certain categories and instead implemented a risk-assessment scheme to determine when a PAI should be performed.^{353,354} In addition, foreign companies making drugs that are not subject to FDA approvals, such as many over-the-counter medicines for the U.S. market (see section 2.2.2), may never receive PAIs—in practice, leaving them very unlikely to ever receive an inspection by the FDA.

When FDA inspections do occur, the GAO reports that non-U.S. plants face different scrutiny than U.S. sites: for logistical reasons, inspections of foreign facilities are shorter than those for domestic sites, and while many domestic inspections are surprise visits, foreign inspections are preannounced to ensure that necessary personnel are present.³⁵⁵ According to one industry expert, foreign firms typically have more than a year to prepare for FDA inspections because the agency is that far behind on its inspection queue. In addition, when the FDA discovers deficiencies at foreign sites, resource constraints may mean the agency does not return for more than two years, if at all. The GAO found that the FDA reinspected only four out of 15 noncompliant foreign plants. In those follow-up inspections, which occurred two to five years after the original inspections, three of the four were found to have additional deficiencies.³⁵⁶

With recent increases in budget appropriations (foreign inspection resources rose from \$12 million to \$41 million in fiscal year 2009), the FDA has begun to build its foreign inspections program.³⁵⁷ However, the agency is still unable to inspect non-U.S. plants with sufficient frequency.³⁵⁸

In fiscal year 2009, the FDA inspected 1,015 domestic sites³⁵⁹ and 424 foreign pharmaceutical manufacturing sites in the European Union (E.U.) and other parts of the world.³⁶⁰ In the United States, the FDA is close to meeting its statutory requirement to inspect factories once every two years. In contrast, overseas plants are inspected every nine years on average.³⁶¹ The frequency of foreign inspections is difficult to determine because the FDA’s current database systems do not provide an accurate count of the number of overseas sites producing drugs and drug components for the U.S. market.^{362,363} The FDA estimates that 3,765 foreign pharmaceutical facilities were subject to potential FDA inspection in fiscal year 2009 (identified through registration and U.S. Customs databases), but this could include companies that are registered with the FDA but may never have shipped product to the United States.³⁶⁴ The FDA registration is not equivalent to permission to market a drug, although it is a prerequisite.³⁶⁵ Registering with the FDA is a simple process that is free to the registrant, and some sites may register to obtain a competitive or marketing advantage associated with being “FDA registered.”

China is home to the highest number of sites subject to FDA inspection outside of the United States (920 in fiscal year 2009), but receives the lowest levels of oversight compared with other countries. The

FDA inspected only 5.6 percent of Chinese sites in fiscal year 2009 (with 52 inspections that year, up from 19 in 2007).³⁶⁶ Over an eight-year period (2002–2009), the FDA conducted 182 inspections in China (out of 920 total facilities), compared to nearly a combined 900 inspections in Ireland, Switzerland, Italy, France, the United Kingdom and Germany (out of 938 total facilities; see figure 14).^{367,368} The emphasis on European inspections is surprising considering that regulatory oversight and standards for E.U. manufacturers are generally on par with those in the United States (see section 2.4.4), and thus E.U. sites are arguably at lower risk for quality and safety issues. FDA inspections of Indian sites were more frequent than in China, but still less frequent than in Europe. The FDA conducted 322 inspections of Indian sites between fiscal years 2002 and 2009.^{369,370} The European Federation of Pharmaceutical Industries and Associations (EFPIA), which regularly surveys its member pharmaceutical companies on the number of regulatory inspections that occur at their sites, has also pointed out inspectional overlap between the E.U. and the United States. In 2009, members reported 47 inspections of U.S. plants by E.U. regulators, and 102 inspections of E.U. plants by the FDA.³⁷¹

2.2.2 Over-the-counter products receive less scrutiny

Plants making OTC medications or active ingredients receive less FDA scrutiny than those making prescription drugs, particularly when those plants are overseas. There are at least two reasons: first, the vast majority of the FDA's foreign inspections are pre-approval inspections,³⁷⁴ which do not apply for most OTC products.* Ibuprofen, acetaminophen and acetylsalicylic acid (aspirin)—three active ingredients for which the majority of U.S. imports originated in China in 2009—are among the OTC products in this category (see figure 9). Secondly, the FDA considers OTC products to be lower risk than prescription products within the agency's risk-ranking model for plant oversight.³⁷⁵ Despite this oversight disparity, numerous experts interviewed for this paper assert that the risks of GMP failures for OTC products are not intrinsically lower than for prescription products.^{376–379} Indeed, an auditor of Chinese manufacturing facilities considers the lack of oversight of the OTC sector to be a major problem, because large product volumes make it easy for suppliers to covertly introduce cheaper materials not certified for pharmaceutical use.³⁸⁰ While the United States rarely inspects overseas OTC plants, the E.U. authorities conduct more frequent OTC inspections. This oversight has sometimes identified quality issues that resulted in a suspension or withdrawal of approval to produce for E.U. markets.

2.3 FDA capacity and information systems

2.3.1 FDA's inspection staff

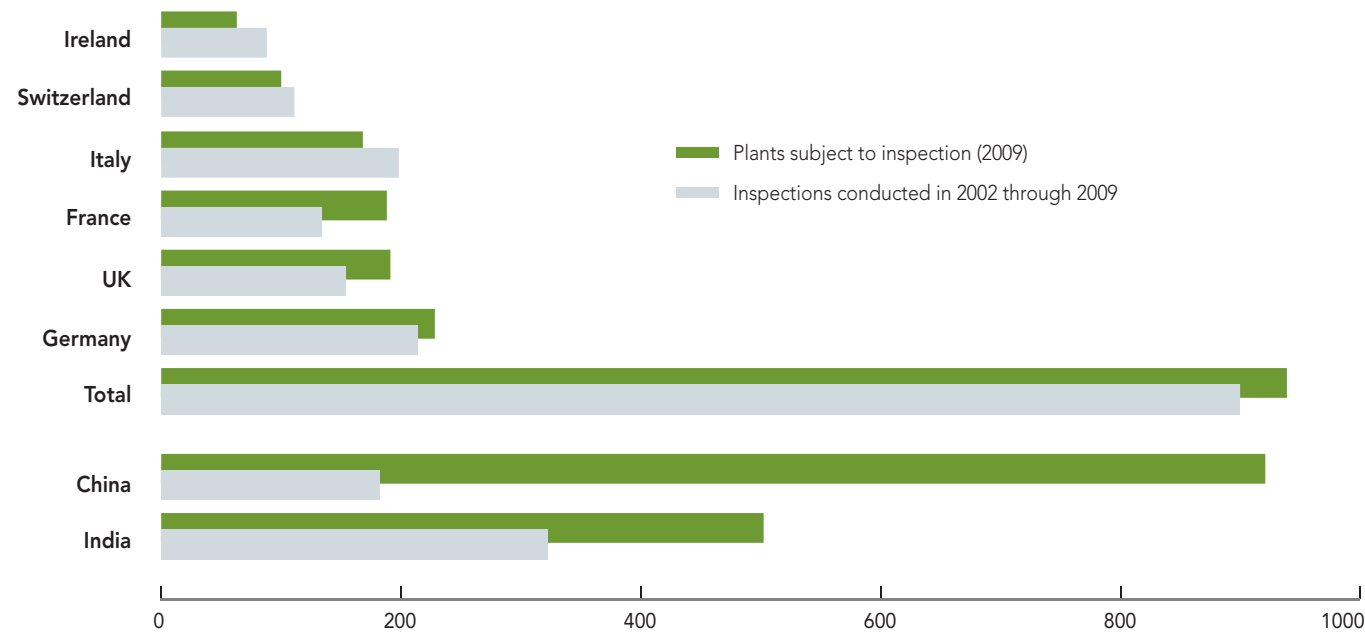
The FDA Office of Regulatory Affairs (ORA) is responsible for all agency regulatory activities, including oversight of drug and device manufacturing through physical inspection of plants and products in the United States, outside of the United States and at import. Despite industry globalization trends, ORA personnel and financial resources remain largely focused on domestic oversight. Until fiscal year 2009, the FDA did not have dedicated staff for foreign inspections; qualified employees would volunteer to travel abroad. The FDA estimated in 2007 that approximately 335 ORA employees were qualified to conduct foreign inspections, although only 102 did so in the year prior.³⁸¹ In fiscal year 2009, the FDA created a “cadre” of 15 inspectors dedicated to inspecting foreign manufacturing sites. These inspectors were based in the United States and performed about a third of all the FDA's foreign inspections in that year.³⁸² However, the GAO notes that these staffing increases have not yet resulted in sufficient levels of foreign oversight.³⁸³ The FDA committed a major part of its increased 2009 appropriations to hiring new staff, with a primary goal of bolstering ORA's inspectorate. However, hiring and retaining employees has been historically difficult, in part because of competition from the higher-paying private sector.³⁸⁴

To improve its overseas presence, the FDA has opened offices in key geographic regions: three in China, two in India and three in Latin America, with planned offices in the Middle East and Europe.³⁸⁵ These

* OTC medications fall into two categories: (1) those approved under a drug marketing application, and (2) those that comply with an existing OTC monograph. Manufacturers of OTCs in this second category are not required to submit pre-market applications to the FDA that describe manufacturing processes and sites. These products may be marketed without specific FDA approval and are therefore not subject to pre-approval inspection.

Figure 14

Number of foreign pharmaceutical manufacturing sites subject to FDA inspection in 2009 (estimated) and actual inspections performed in fiscal years 2002 through 2009



Source: GAO data.^{372,373}

foreign offices have helped the agency develop relationships with foreign stakeholders as well as deepen their understanding of foreign regulatory systems, according to the GAO's September 2010 report.³⁸⁶ With the focus on relationship-building, however, the staff in these foreign offices has performed few inspections of manufacturing sites. For example, from June 2009 to June 2010, the FDA staff based in offices in India and China conducted 24 inspections in those countries, while the U.S.-based FDA staff conducted 120.³⁸⁷

2.3.2 Limitations of tracking systems and data management

Outdated IT systems used for tracking drug-manufacturing sites impede access to data and inhibit the effective use of the FDA's limited resources.³⁸⁸ The FDA cannot manage or effectively use the information it collects about drugs, manufacturing sites and imports because the underlying data are often unreliable and not in a format readily amenable to data comparison or analysis.³⁸⁹

The two main databases that the FDA uses to track manufacturing sites have problems that call into question the accuracy of their content.³⁹⁰ The Operational and Administrative System for Import Support (OASIS) database, which lists manufacturing sites of imported products as entered by Customs agents, contains multiple spelling errors, duplicate entries and redundant identification numbers. The Drug Registration and Listing System (DRLS) database tracks plant registration information, but includes many facilities that register with the FDA, even if they do not manufacture drugs for the United States. In addition, some facilities in this database do not update their information annually as required, and the FDA does not verify registration accuracy.³⁹¹ The data in these two main systems cannot be electronically integrated, according to the agency, nor can the systems interact with one another. FDA staff must compare these data manually.^{392,*}

As discussed, because of database inaccuracies, FDA officials are unable to know exactly how many foreign sites produce pharmaceuticals for the U.S. market.³⁹³ Such problems can contribute to errors, such as with Baxter's heparin product when the FDA confused the plant processing the active ingredient with another similarly named site (see case study 1). The FDA recognizes the need to reform its IT infrastructure and has begun to create new systems. However, harmonization of data still presents significant challenges, including lack of sufficient personnel to effect and sustain necessary data transitions.³⁹⁴

Limited reporting requirements for industry also impede data collection. The FDA does not clearly require industry to report entities involved in the manufacture of their products beyond the sites that process their finished active ingredients. Current statute requires industry to report the facilities used for the manufacture, processing and packing of a drug in drug marketing applications,³⁹⁵ but FDA guidance only suggests that this should include, as appropriate, manufacturing facilities for finished drugs as well as bulk drug substances.³⁹⁶ Although information about precursor ingredient manufacturing sites is not always relevant, it can be important when a drug has a complicated manufacturing supply chain, such as

heparin (see case study 1). OTC drug manufacturers, which most often do not submit marketing applications, are required under cGMP to maintain records of the suppliers of their incoming components.³⁹⁷ However, the FDA may not ever review these records unless visiting a plant for an inspection, which is rare for foreign OTC manufacturers (see section 2.2.2).

2.3.3 Border assessments and importer oversight

More than 300,000 shipments of pharmaceuticals entered the United States in 2007, double the number in 2002.³⁹⁸ Agents from Customs and Border Protection (CBP), a division of the U.S. Department of Homeland Security, have the main responsibility for reviewing incoming goods and notifying the FDA of imports that fall under FDA jurisdiction. The FDA works closely with CBP agents to review information for these imported goods and decide whether additional information or product sampling is needed.³⁹⁹

As the volume of imported drugs grows, so does the volume of work for FDA reviewers and CBP agents. Current data system limitations seriously impair the FDA's ability to prioritize review of imported products. Carl Nielsen, former director of the Division of Import Operations and Policy at the FDA, noted in 2007 testimony that the FDA reviewers check technical requirements such as appropriate product registration and listing information, rather than data on manufacturing quality or product safety.⁴⁰⁰ Accessing databases to determine other information, such as whether the drug or API has a current marketing approval, can be cumbersome and extremely time-consuming.⁴⁰¹ CBP is developing a new Automated Commercial Environment (ACE) system to integrate FDA data on manufacturing sites with Customs data on importers and exporters. However, after more than a decade of development and billions of dollars invested, this system was still not fully operational as of May 2010.^{402–405} In the system's absence, the FDA has begun to test a program called PREDICT (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting), which combines existing Customs data on pharmaceutical manufacturing sites with additional relevant information (e.g., results of facility inspections, previous product sampling and other risk rankings).⁴⁰⁶ PREDICT would replace the admissibility screening functions of the FDA's legacy OASIS system.⁴⁰⁷ The FDA has implemented PREDICT for imported food, and plans to use the system to monitor imported drugs and medical devices. As of March 2011, PREDICT was implemented for drug commodities in four FDA districts.⁴⁰⁸

One means of ensuring that border agents have better information to assess imported drugs is to require importers to supply the information. Greater oversight of importers could include registration with the FDA as well as a requirement to provide documents that attest to the quality and safety of the imported drug or drug product. The FDA has taken a step toward such oversight through its Secure Supply Chain Pilot Program, which would permit abbreviated border reviews in exchange for additional recordkeeping on product movement and adherence to certain distribution safety standards. However, this voluntary program does not require documentation of GMP compliance.⁴⁰⁹

Finally, the FDA's authority at the border has some notable limitations. If a foreign facility refuses to permit an FDA inspection, the agency cannot use this as a reason to refuse products made at those

* A third database, the Field Accomplishments and Compliance Tracking System (FACTS), houses information entered by FDA agents concerning inspection results.

plants. However, the FDA does have this power for imported food products.⁴¹⁰ Further, under current regulations, when the FDA and CBP identify and refuse a violative product, that product may still make its way to the U.S. market. The FDA is authorized to refuse products at the border that appear to be adulterated or misbranded,⁴¹¹ but statutory remedies include reexportation of the refused item.⁴¹² This may allow potentially harmful drugs to be reshipped into the United States.

2.4 FDA enforcement

2.4.1 Limitations of current enforcement tools and authorities

The FDA lacks several key authorities that would permit more effective oversight of overseas manufacturing. Though the FDA has complete legal discretion under the statutory approval standard regarding whether to allow a drug to be sold in the United States, the agency's control over that product after approval is more limited. The FDA does not have the authority to order a drug recall, nor may it halt product distribution on its own (it can do both for medical devices, the latter authority known in the device world as administrative detention). If the FDA finds it necessary to forcibly remove a pharmaceutical product from the market, it must go through the courts to request a seizure,^{413,*} and a separate seizure action is needed for each court district where the product may be found.⁴¹⁴ In 2010, the FDA seized 11 lots of heparin from Celsus Laboratories, Inc., in Chicago after it discovered oversulfated chondroitin sulfate contamination in the products (the same substance associated with U.S. adverse events in 2007 and 2008). The FDA stated that this action was necessary because the company's efforts to inform consumers about the possible contamination were not sufficient to ensure a recall of the product.⁴¹⁵

The FDA also lacks the general authority to subpoena documents or witnesses for violations of the FDCA, and may not be able to thoroughly investigate safety issues without outside help such as from the U.S. Department of Justice. This may be a limiting factor for investigations into serious safety violations.[†] (Granting subpoena powers to federal agencies is not uncommon—at least 355 such authorities have been granted to executive branch entities.⁴¹⁶) Further, the FDA's authority to access manufacturing sites and records overseas is insufficiently delineated in statute, and could allow for challenges to the agency's inspection activities for foreign sites.[‡] The FDA also reports that it cannot, in most cases, justify detaining an imported drug or drug substance based on the refusal of the manufacturer to submit to an FDA inspection.⁴¹⁷

* The FDA may also enjoin further manufacturing through the courts.

† The FDA can examine drug-manufacturing documents during its inspections of drug facilities under section 704 of the FDCA. But this general authority is limited to the inspection context and does not authorize the FDA to summon witnesses or require production of documents, which can be critical for investigations. In addition, issues can arise during inspections about the scope of authority for document examination, which can lead to company refusals to cooperate (FDA Investigations Operations Manual, Section 5.2.5.2: Refusal to Permit Access to or Copying of Records). In these situations, the FDA must seek an inspection warrant from a federal court (FDA Regulatory Procedures Manual, Section 6-3-Inspection Warrants). Subpoena power is a more comprehensive and direct mechanism for obtaining specific documents and witness testimony.

‡ The Supreme Court has upheld the legal principle that Congress must express clear legislative intent for a statute to apply to entities overseas. "It is a longstanding principle of American Law that legislation of Congress, unless a contrary intent appears, is meant to apply only within the territorial jurisdiction of the United States." *EEOC v. Arabian American Oil Co.*, 499 U.S. 244, 248 (1991) (quoting *Foley Bros., Inc. v. Filardo*, 336 U.S. 281, 285 (1949)).

In addition, penalties for drug counterfeiting and adulteration are too small to be adequate deterrents. With some exceptions, the FDCA sets criminal penalties for violation of the Act (including adulteration, misbranding and counterfeiting) at a maximum of \$10,000 or three years in prison, and then only when intent to defraud or mislead is established. Otherwise, penalties are capped at \$1,000 or one year in prison.⁴¹⁸ These penalties are far lower than, for example, penalties associated with narcotics trafficking.⁴¹⁹ Counterfeiting can be prosecuted under trademark law, with a maximum sentence of 10 years, but the FDCA route is the most common for counterfeit drug cases.⁴²⁰ The utility of criminal penalties becomes further limited as drug manufacturing moves outside of the United States because the FDA may not be able to prosecute pharmaceutical companies overseas if foreign governments are unwilling to cooperate. Additional penalty options such as asset forfeiture may be more easily assessed against foreign entities (for example, if the assets to be seized were within the United States). Civil penalty options would also provide greater enforcement flexibility, but barring limited exceptions, the FDA cannot assess civil penalties for violations of the FDCA in relation to drugs.

2.4.2 Legal accountability of responsible individuals at companies

Enforcement may also be hindered by the lack of clearly established individual responsibility for product quality and safety within each company. For example, while GMP requires the existence of a quality-control unit that is responsible for drug and component quality,⁴²¹ companies are not required to appoint and name a specific employee with individual responsibility for ensuring product quality and safety. In contrast, for devices sold in the United States, QSR requires a named management representative who is responsible for implementation and oversight of quality systems.⁴²² In the E.U., a directive for companies with pharmaceutical manufacturing authorizations stipulates that the safety and quality of all drugs and active ingredients must be certified by a "qualified person" through signature.⁴²³

The FDA has indicated its intent to hold executives within industry accountable for violations of the FDCA, and specifically has suggested it will make increased use of a 1975 legal precedent, the Park Doctrine, also called the "responsible corporate officer" doctrine.^{424–427} These individuals may be held accountable for misdemeanor violations of the FDCA—even violations that may be unknown to them—if due to their position of authority they should have known about and been able to correct or prevent the violations.⁴²⁸ In *Park*, the Supreme Court ruled that the FDCA imposes on responsible corporate officials the duty to seek out and remedy violations, "and primarily, a duty to implement measures that will insure that violations will not occur."⁴²⁹ This responsibility exists independent of knowledge of, or intent to commit, a violation. Although the precedent has rarely been used since a period of frequent use in the 1970s,⁴³⁰ in 2010 the FDA repeatedly signaled its intent to once again pursue prosecutions of executives under the Park Doctrine.^{431–433,*}

* While *Park* prosecutions have historically resulted in small fines, the range of potential penalties for misdemeanor violations now includes substantial fines, jail time and debarment or exclusion from working for companies doing business with, or under the jurisdiction of, HHS and the FDA.

Revived use of the Park Doctrine may incentivize responsible corporate officials to proactively evaluate the potential for upstream supply chain violations. However, updating existing statute to more explicitly state management responsibilities with regard to manufacturing quality and safety could further encourage compliance, and provide a more reliable tool for enforcement.

2.4.3 Increased information flow to FDA needed

The FDA faces many obstacles to the collection of needed data from drug manufacturers as well as other regulatory agencies. Drug companies are not required to inform the FDA of many types of quality or safety issues that could present risks to U.S. patients, such as suspected counterfeiting, serious supplier quality problems or drug theft, and do so only on a voluntary basis. Current reporting requirements exist (within the FDA's Field Alert Program),⁴³⁴ but have limitations. They do not apply to manufacturers of OTC products, and are also constrained to a few specific issues: distributed drugs that are mislabeled, contaminated or do not meet required specifications. In addition, industry whistle-blowers wishing to alert their supervisors or the FDA about potential violations of the FDCA are not clearly covered by specific whistle-blower protections. Existing whistle-blower provisions have limitations; for example, the employee protections within the False Claims Act are tied to company retaliations for the filing of a whistle-blower lawsuit, which some employees may not wish to do, and protections within the Sarbanes–Oxley Act do not cover reporting of violations to supervisors.* Compliance with the current Field Alert Program is also imperfect. In a recent case, the FDA chastised McNeil Consumer Healthcare, a division of Johnson & Johnson, for not reporting consumer complaints about what was eventually discovered to be a chemical contamination of OTC medicine.⁴³⁵ Companies may be particularly reticent to share information on counterfeits (not required under the Field Alert Program) because of fears that negative publicity will impact sales.⁴³⁶ The Pharmaceutical Security Institute, a not-for-profit organization formed by drug companies to collect information on counterfeits and develop systems to address the issue, does not provide health authorities with full access to its extensive databank.⁴³⁷

The FDA is limited in its ability to receive or share certain kinds of information with other regulatory agencies, both domestic and international. The FDCA prevents the FDA from sharing trade secret information, including with other regulators, even in the interest of enforcement or public health.⁴³⁸ The agency may share commercial, confidential information with foreign government officials, but must overcome significant regulatory hurdles to do so.^{439,†} In addition, foreign regulatory bodies may be

* Whistle-blower protections created by the False Claims Act (31 U.S.C. § 3729–3733) apply when the violation in question can be shown to have created a false claim against the government, such as billing of Medicare for drugs that a company has promoted for an unapproved indication. The law is not clear whether manufacturing quality failures would fit within this scope, and despite a November 2010 GlaxoSmithKline settlement under the False Claims Act for drug manufacturing defects, courts have not resolved the issue. In addition, whistle-blower protections under the False Claims Act provide remedies to be “made whole” when a company retaliates against an employee for bringing a false claims (*qui tam*) suit, but it does not offer such retaliation protections for the act of information reporting itself. Protections under the Sarbanes–Oxley Act of 2002 (Pub.L. 107-204) establish penalties for retaliation against any person alerting law enforcement officers to violations of federal law. However, this act does not extend such penalties to retaliations against persons reporting violations to their supervisors, and does not contain provisions allowing a whistle-blower to be “made whole” by the retaliating company.

† In order to share commercial, confidential information with foreign government officials, 21 CFR 20.89 requires the Secretary of HHS to receive from the foreign government a written commitment not to disclose shared data, and establishing its authority to protect the data. Even still, the Secretary must receive written authorization from the company who owns the data, unless the Secretary makes a determination that sharing the information without such authorization is in the interest of the public health.

luctant to share confidential information related to public health risks with the FDA because the agency cannot always guarantee that the information will not become public under U.S. law.* Although the FDA has entered into more than 30 agreements with regulatory bodies in different countries to share some inspectional and other non-public information,⁴⁴⁰ Congress has yet to clearly establish the FDA's ability to share information with other regulatory agencies and foreign governments in a protected manner. Such protections would likely increase the amount of information the agency receives. In the aftermath of the heparin adulteration, a member of Congress asked the FDA if it was willing or able to share information with the Chinese government in an effort to investigate that case, and the FDA replied that it was constrained in doing so by U.S. law.⁴⁴¹

2.4.4 Harmonization of international standards and inspections

As drug manufacturing becomes increasingly global, the FDA, the European Medicines Agency (EMA) and other regulatory bodies have begun efforts to harmonize standards, share information and leverage each other's regulatory activities. Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the FDA and its E.U. and Japanese counterparts, together with industry representatives, have established quality assurance guidelines (Q1–Q10) that are now almost universally adopted as guidance by the FDA through publication in the *Federal Register*.

The agency has engaged with the EMA and Australia's Therapeutic Goods Administration on a pilot program to share inspectional information and conduct some joint inspections of active-ingredient manufacturing sites.⁴⁴² The program has reportedly resulted in meaningful increases in information sharing,⁴⁴³ and in 2011 was made permanent.⁴⁴⁴ However, these joint inspections may not always represent a substantial relief of FDA resources because FDA inspectors are still performing their own assessment of the site. Wyeth Europa, whose facility received a joint inspection by the FDA and the Irish Medical Bureau in Europe in 2009, reported that the reviews were consistent with one another, but that the double inspection entailed a duplication of work for the company, which had to deliver a separate report for each agency.⁴⁴⁵ An official at the FDA's Office of Regional Operations reported in September 2010 that the agency's goal is to conduct joint inspections in which EMA and the FDA look at different parts of the same plant, and that the agency will be using information from other regulatory agencies within risk determinations.⁴⁴⁶ As of January 1, 2011, the FDA is also a member of the Pharmaceutical Inspection Co-operation Scheme, which is an agreement between health authorities fostering cooperation on pharmaceutical GMP inspections.⁴⁴⁷

* The Freedom of Information Act, 5 U.S.C. § 552

2.5 Pew conference and policy recommendations

At the Pew Health Group roundtable conference (March 14 and 15, 2011; see Appendices B and C for list of attendees and full agenda), participants agreed that it is important to improve the FDA's oversight of foreign manufacturing. There was clear agreement among generic and brand industry representatives, API producers and consumer groups that inspections of foreign facilities should occur at the same rate as U.S. facility inspections and should be prioritized based on risk, as recommended by the GAO. One industry participant argued strongly that regulatory inspections should be unannounced whenever possible.

Several participants argued that the FDA must leverage the capacity of third parties, particularly other regulatory agencies, to achieve needed increased oversight. Suggestions included conducting cooperative inspections, reciprocal recognition of inspections by other qualified regulatory agencies and use of independent accredited inspectors. An industry participant suggested that the FDA could immediately alleviate resources by reducing its inspectional activity in the E.U. by relying on the results of inspections carried out by European regulators. One specific suggestion to the FDA was that the agency should participate in EudraGMP, a database launched by the European Medicines Agency in 2007 that catalogs suppliers with E.U. GMP certificates. A GAO official similarly encouraged the agency to take advantage of as much third-party information as is available.

FDA Deputy Commissioner John Taylor indicated that the FDA intends to make better use of third-party sources of information, and sought improved collaboration with foreign regulatory counterparts. The GAO called the FDA's effort to set up foreign offices a good first step, but noted that the staff in those new, small offices needs better feedback from headquarters on what it should be doing and how to manage a workload that can become overwhelming.

Representatives of generic drug and active-ingredient manufacturers spoke in support of new industry fees to cover the costs of increased foreign inspections and create a level playing field for U.S.-based manufacturers. However, a representative of the Pharmaceutical Research and Manufacturers of America (PhRMA) suggested that, while user fees have worked well in other contexts, Congress should offer additional appropriations so that the FDA can better oversee globalized manufacturing. FDA officials suggested that a potential ancillary benefit of facility registration fees would be to disincentivize foreign plants that do not export to the United States from registering with the FDA purely to obtain a "seal of approval." When such fees were introduced for medical devices, the number of registered facilities dropped by one-third.⁴⁴⁸

Stakeholders also discussed measures to improve the FDA's knowledge of foreign manufacturers and imported products. The GAO speaker delineated challenges to the FDA's database systems for overseas plants and emphasized the need to improve information entry for imported products at the border. The

FDA and GAO representatives agreed that a unique facility identifier for plants would help improve tracking. An FDA participant said it would help to have the authority to require the provision of additional information with imported products, such as documentation of manufacturer compliance with regulations, and establishing that the drug meets identity, safety and purity standards. An FDA official noted that, unlike most other countries that require companies to show why their product should be allowed *into* the country, U.S. regulators must prove that there is something wrong with a product to keep it *out* of the country.

There was widespread agreement among participants that penalties for drug counterfeiters must be stronger. Several speakers made the point that it is currently more profitable and easier to counterfeit and adulterate medicines than to sell illicit drugs. A March 2011 interagency report to the Office of the Vice President also calls for increased penalties.⁴⁴⁹ Penalties provide a deterrent only when coupled with enforcement, a fact noted by a number of stakeholders concerned that criminals may increasingly target the pharmaceutical pipeline.

FDA representatives acknowledged that the agency needs adequate funding for inspections and updated IT systems, as well as novel enforcement tools and new authorities (for example, more comprehensive requirements for industry to report quality problems to the FDA; currently, such reporting is required only in relation to batches of finished products, not components or counterfeits). In addition, FDA personnel suggested that the agency needs mandatory recall authority, subpoena authority (to allow for effective investigations) and authority to keep a product out of the country if the foreign producer of that product delays, limits or refuses inspection. In addition, agency staff indicated that the FDA now lacks the authority to destroy adulterated products at the border.

Finally, three participants stressed the risks associated with OTC drugs, which are produced in large quantities with little regulatory oversight, often by smaller manufacturers with few quality controls.

POLICY RECOMMENDATIONS*

A. Increase FDA oversight of overseas manufacturing

1. **Significantly increase FDA foreign inspections.** The FDA must inspect overseas plants at a rate that is high enough to encourage consistent conformance with quality and safety standards. Identified cases of noncompliance must be followed by appropriate sanctions. Inspections should be prioritized based on assessments of risk, but no plant should go uninspected indefinitely. If possible, the inspections should be unannounced as they are for U.S. inspections. Cooperation and coordination with local regulators could help achieve this goal. The FDA should also ensure that it inspects foreign plants making finished drugs, finished APIs or bulk APIs at least once before these facilities may export any such products to the United States. Increasing the FDA inspection rates will require more resources.

* The recommendations in this report have been informed by the roundtable discussions and presentations, but are not intended to reflect a consensus position and may not reflect the views of every participating organization.

2. **Use comprehensive risk assessment to prioritize inspections.** Because the frequency of inspections will depend on the availability of resources, the task of prioritizing oversight should rely on an intelligent risk-based assessment system, incorporating factors such as inspection histories, counterfeit risk and environmental influences. The FDA has begun to assess the risk of economically motivated adulteration of various APIs; as of October 2010, the agency had risk-ranked more than 1,000 API products.⁴⁵⁰
3. **Create a meaningful, dedicated foreign inspectorate.** The FDA's foreign inspection "cadre" should be further grown and developed.
4. **Add mechanisms to augment FDA oversight through recognition of independent inspections or audits.** Ideally, the FDA would have sufficient funding and capacity to conduct all needed inspections of manufacturing plants that make drugs and drug products for the U.S. market. Because this is an ideal that might take years to realize, the FDA should also consider alternate mechanisms for achieving sufficient oversight. There are several possible models for independent inspections or audits:
 - a. The FDA recognizes inspections by selected foreign regulatory agencies. The FDA's current authority to do this may not be clearly delineated in statute.
 - b. The FDA accredits independent third-party inspectors whose fees are paid by the FDA and supported by industry user fees.
 - c. The FDA accredits third-party inspectors whose fees are paid directly by industry. Such a system was created for Medical Device plants under the Medical Device User Fee Act of 2002.

Recognizing foreign agency inspections that the FDA considers equivalent to its own could spare significant FDA resources. The FDA could also use available resources to develop guidelines, and train and certify third-party inspectors, whose costs could be supported either through pooled industry user fees or by direct payment by industry. Option (c) may create a potential conflict of interest, as manufacturers are requesting and paying directly for the inspections. Ultimately, the FDA and HHS should have the discretion to recognize third-party inspections if they determine them to be necessary to achieve a sufficient level of oversight. The Food Safety Modernization Act establishes a third-party accreditation program for oversight of food production facilities.⁴⁵¹

5. **Make explicit through statute the extraterritorial applicability of the FDCA.** The U.S. Supreme Court has upheld the legal principle that Congress must express clear legislative intent for statute to apply to entities overseas. The FDA's authority to oversee foreign plants making drugs and ingredients for the United States is insufficiently delineated in statute, and could allow for challenges to the agency's inspection activities for foreign sites.

B. Ensure adequate FDA resources

1. **Consider new industry fees to support increased foreign inspections.** Manufacturer registration fees would represent a significant income source that the FDA could use to increase the number of inspections it conducts overseas; to support ongoing improvements of systems the agency uses to target inspections; and to track foreign manufacturing sites.
2. **Consider an importer fee.** Assessing a fee on importers would provide further funding for border oversight operations. An importer fee should not be required of manufacturers that import products if they are already assessed a fee when they register with the FDA.
3. **Ensure that other appropriations also increase.** The FDA has estimated that in fiscal year 2009 the cost of a foreign inspection was between \$60,000 and \$62,500.⁴⁵² To avoid exclusive reliance on industry fees to support expansion of the FDA inspections, increased public appropriations will also be necessary.

C. Improve FDA infrastructure and tracking systems

1. **Fix tracking systems for manufacturing sites.** Current tracking systems for manufacturing sites contain duplicates and errors, and must be overhauled to ensure accuracy and interoperability. The FDA must more diligently verify manufacturer registrations to ensure that information is current and correct. Updated systems should also be able to easily interface with each other and with risk-assessment systems to guide oversight and inspections.
2. **Establish a unique facility identifier for manufacturers, importers and brokers.** Manufacturers, importers and brokers should be required to submit this unique number to the FDA at various points, such as site registration and importation. This will help with accurate facility identification and will help prevent mistakes due to data errors and duplicate entries. One option for a unique facility identifier is D-U-N-S (Data Universal Numbering System)—a widely used system for identifying business entities.

D. Strengthen oversight of drugs and bulk drug substances at import

1. **Ensure that robust risk-assessment systems are used to guide border screening.** The FDA is implementing a risk-assessment system called PREDICT to assess imported food, devices and drugs.
2. **Give the FDA authority to destroy products at the border.** The FDA is currently authorized to refuse drug products at the border that appear to be adulterated or misbranded, but statutory remedies include reexportation of these potentially violative products.⁴⁵³ This may allow harmful drugs to reenter the United States. The FDA should have the power to destroy drugs and drug products that it determines could pose a threat of injury or death.

3. **Allow the FDA to refuse entry of a product if the site at which it was manufactured has refused an FDA inspection.** This will help the agency ensure that potentially compromised products do not enter the United States and will incentivize foreign manufacturers to allow the FDA to access plants and facilities.
4. **Require importer registration.** Tracking importers through a registration system will be an important element of supply chain transparency and will offer a framework for importers to provide more comprehensive documentation.
5. **Permit the FDA to require more comprehensive documentation at import.** The FDA should have the authority to require parties importing drugs and ingredients into the United States to provide more substantive information during the importation process. Documentation could also demonstrate compliance with U.S. requirements on product identity, quality, safety, FDA approval and FDA registration, as well as other categories at the discretion of the FDA.

E. Ensure the FDA has the regulatory authorities it needs to fulfill its mission

1. **Provide the FDA with the authority to require drug recalls and order the cessation of distribution in situations where a drug product could cause illness or injury.** Mandatory recall authority will help the FDA ensure patients are not exposed to harmful products, and will also act as an important deterrent to refusing or delaying appropriate action. The FDA may order a recall of medical devices, but may not do so for drugs, a significant limitation to its authority.
2. **Provide the FDA with the power of subpoena.** The ability to subpoena witnesses and documents will help the FDA quickly investigate issues of medical product quality and safety that may harm the public.

F. Strengthen the FDA's enforcement ability through tougher penalties and clearer accountability for industry

1. **Strengthen both criminal and civil penalties for violations of the FDCA.** With some exceptions, current FDCA criminal penalties for knowing adulteration, misbranding and counterfeiting of drugs are a maximum of \$10,000 or three years in prison. Both financial penalties and allowable prison terms should be increased for criminal violations, including drug and ingredient adulteration caused knowingly or through negligence. Creating new administrative civil penalties for violations of the FDCA will also help deter noncompliance and will give the FDA a much more flexible enforcement arsenal. Currently for drugs, the FDA may assess civil penalties only for violations of certain application requirements in the FDCA.

2. **Establish individual accountability for product quality and safety.** To permit meaningful enforcement, responsible corporate officials should be clearly responsible for ensuring manufacturing sites, including those of suppliers, comply with quality standards. Within companies, specific responsible individuals should be personally accountable for the quality and safety of drugs and active ingredients that reach U.S. patients. As noted previously, similar controls already exist for medical devices,⁴⁵⁴ and comprehensive requirements exist for a “qualified person” to assume responsibility for the safety of drugs and active ingredients in the E.U.⁴⁵⁵

G. Improve FDA access to information from other regulatory bodies and industry

1. **Require manufacturers, including OTC manufacturers, to inform the FDA of instances where exposure to a drug product may result in illness or injury.** All manufacturers should report contamination or failure to meet specifications in distributed products (currently not required of OTC manufacturers that are not subject to marketing applications), and should also report suspected counterfeiting and theft. Access to this information by the FDA should be a legal requirement and is paramount when a potentially harmful product may reach the public. Improved reporting requirements will ensure that the FDA has the best knowledge about drugs that may be adulterated, counterfeit or otherwise harmful and can fulfill its public health mandate.
2. **Allow the FDA to confidentially exchange information on manufacturing safety with other countries and government entities.** Global expansion of manufacturing increases the importance of information-sharing between regulatory bodies. In some cases, entities are reluctant to provide the FDA with sensitive data because the FDA is subject to the Freedom of Information Act, which could make those data public. Congress must allow the FDA to accept information in a manner that protects that information from public disclosure, and also to share information currently protected under the trade secrets provision of the FDCA.
3. **Whistle-blower protections.** Industry employees who have information on events that may threaten the public health must be able to share that information with the government or their supervisors without risk. Protections should prohibit retaliation by the whistle-blower's employers, and should permit adequate remedies if retaliation does occur.

3.1 Overview

The risk of stolen or counterfeit products reaching patients through the drug distribution system is small, but real. Pharmaceuticals move from manufacturer to patient through a variety of pathways. Most commonly, the product moves from a manufacturer to a major wholesaler to a pharmacy or hospital, which dispenses the drug to a patient. Manufacturers, wholesalers and pharmacies have taken steps to reduce the opportunity for drug diversion in recent years, but risks persist. Federal and state regulations are inconsistent, and no national system for tracking or validating drugs exists.

Numerous entities are involved in drug distribution, and the routes to market can be circuitous. Drugs can be bought and sold by wholesalers and their subsidiaries that move whole or partial lots, repackage or relabel product and/or handle importation. Drugs may be traded between distributors, and may travel back from distributors and pharmacies in local markets to major wholesalers through sales or returns before ultimately reaching patients. Distributors may also provide logistics services to manufacturers without actually purchasing lots of a drug; that is, the physical movement of drugs does not always conform to transfers of ownership, further complicating legitimate drug tracking.

In the United States, most drugs sold by manufacturers move initially through the three large national wholesalers: McKesson Corp., Cardinal Health and AmerisourceBergen, which collectively generated 85 percent of revenues in the drug wholesale market in 2010.⁴⁵⁶ These major wholesalers, as well as large regional wholesalers, sell to national pharmacy chains, hospitals or smaller “secondary” wholesalers. Secondary wholesalers often supply small hospitals, clinics and pharmacies that are unable to purchase pharmaceuticals in the large quantities sold by national and regional wholesalers. Similarly, small wholesalers may purchase product from regional or national distributors because they are unable to meet minimum requirements for purchase directly from the manufacturer. There were an estimated 7,000 secondary wholesalers in the United States in 2003,⁴⁵⁷ down to fewer than 1,803 by 2007.^{458,*} Wholesale trade of pharmaceuticals is not always unidirectional. For example, wholesalers sell to other wholesalers discounted products that they acquire from manufacturer clearances or pharmacy or wholesaler overstocks.⁴⁵⁹ In some cases, products travel from small wholesalers back into the distribution chain through national or regional wholesalers. In 2001, the National Wholesale Druggists Association—the trade association for major distributors (now called the Healthcare Distribution Management Association, or

* The trend is principally attributable to a shift in the business model away from wholesaler arbitrage of rising drug prices, a practice that accounted for up to 40 percent of wholesaler margin. The 2007 U.S. Census reported 1,803 U.S. wholesalers of prescription drugs, which would also include national and regional wholesalers.

HDMA)—reported to the FDA that up to 4 percent of the products handled by its members came from sources other than manufacturers.⁴⁶⁰ While it is only a small proportion of total sales, this represents a substantial absolute volume. According to HDMA, to its knowledge, the practice of a large wholesaler purchasing from secondary wholesalers no longer occurs.⁴⁶¹

3.2 Drug diversion and counterfeit drugs in U.S. distribution

3.2.1 Diversion, counterfeiting and theft are ongoing problems in the United States

The complex distribution system outlined above creates opportunities for stolen or counterfeit drugs to enter legitimate channels of distribution. One frequently documented drug-diversion scheme is illicit procurement of government-subsidized medicine for resale into the market. In 2008, there were two federal convictions involving human growth hormone products that were purchased from Medicaid patients on the streets of New York and resold into distribution with false documentation.⁴⁶² In 2010, three men were indicted for allegedly illicitly purchasing prescription drugs—some directly from patients—and selling them to pharmacies through a licensed wholesaler in Texas (see case study 6).⁴⁶³ In order to conceal a medicine’s original provenance, drug diverters commonly remove existing labels with various organic solvents and replace them with counterfeit labels (see figure 15).

As distinct from diverted drugs, outright counterfeits—products that imitate the dosage or packaging of a licensed manufacturer—may also enter regular distribution channels. In 2001, counterfeit Serostim[®], a human growth hormone used to treat AIDS-related wasting, was found in at least seven states and passed through multiple wholesalers.^{464–466} (The manufacturer of Serostim[®] has since put in place a secured distribution program, with a unique serial number assigned to each vial that must be verified by the dispensing pharmacy.)⁴⁶⁷

CASE STUDY 6

MEDICAID DRUGS PURCHASED ON THE STREETS AND RESOLD INTO DISTRIBUTION

Two men were convicted in 2008 for selling diverted Medicaid drugs back into distribution, where the drugs ultimately reached pharmacies and unsuspecting patients.⁴⁶⁸ According to the U.S. Attorney’s Office in the Southern District of Florida, a man named Michael Manno purchased the drugs—including medicines for treating cancer and controlling cholesterol, as well as human growth hormone—from Medicaid patients in New York.⁴⁶⁹ Manno, based in New Jersey, sold the drugs to Patrick Bronder in Boca Raton, Florida.⁴⁷⁰

Manno and Bronder made more than \$6.8 million by selling the drugs to a Florida wholesaler, who eventually sold the diverted drugs to pharmacies that dispensed them to patients.⁴⁷¹ Patients receiving the drugs were unaware that these medicines already had been dispensed to someone else, held under potentially unsafe conditions, and then issued to them as if they were a safe and legitimate product.⁴⁷²

This example of diversion of prescription drugs from the street, which took place in 2001 and 2002,⁴⁷³ is not unique. In 2010, three men were indicted for distributing prescription drugs without a license.⁴⁷⁴ Between 2002 and 2005, the defendants allegedly purchased drugs from the street and from other unlicensed sources.⁴⁷⁵ The men allegedly used these drugs to fill orders they solicited from pharmacies. By shipping the diverted medicine through a licensed wholesaler in Texas, they grossed more than \$13 million.⁴⁷⁶

Figure 15



Lighter fluid and other solvents are used to remove pharmacy labels prior to reintroduction of diverted drugs into the wholesale distribution system. These were discovered during a warranted search of an unlicensed warehouse in Miami, Florida.

Source: Cesar Arias, RPh, Stone Cold Healthcare Consultants. Image used with permission.

Counterfeits may originate wholly outside the regulated system, or they may be illicitly procured medicines that have been diluted, falsely labeled or otherwise adulterated and sold by unauthorized entities. In 2002, counterfeit high-dose Epogen® (see case study 7) was actually low-dose Epogen® that had been relabeled to resemble a higher strength, and successfully sold to legitimate distributors and pharmacies.

Overt pharmaceutical theft, particularly cargo theft, is a substantial problem, with a number of reports of patient adverse events from stolen drugs—likely due to improper storage and handling.⁴⁷⁷ In 2009, thieves stole 129,000 vials of insulin and likely stored them under improper conditions, according to an FDA report.⁴⁷⁸ According to an FDA affidavit, the stolen drugs resurfaced at retail chain pharmacies in Texas, Georgia and Kentucky.⁴⁷⁹ The stolen goods were sold by at least three wholesalers before reaching pharmacies.⁴⁸⁰ One of the wholesalers was discovered to have additional stolen and diverted goods.⁴⁸¹ Two months after this crime was discovered, the FDA had recovered only 2 percent of the missing vials.⁴⁸² In March 2010, more than \$70 million worth of pharmaceuticals was stolen from an Eli Lilly & Co. warehouse in Connecticut⁴⁸³—the single-largest cargo theft on record.⁴⁸⁴ The fate of these stolen drugs has not been determined.

Although there were fewer pharmaceutical cargo thefts in the first six months of 2009 than in the same period in 2008, the average value of loss increased dramatically from \$704,685 to \$6.7 million.⁴⁸⁵ The average loss value in 2010 was \$3.78 million, which was the highest average loss value of all stolen commodities that year.⁴⁸⁶

A 2006 report by the FDA's Counterfeit Drug Task Force expresses concern that U.S. drug distribution may be increasingly vulnerable to the introduction of sophisticated counterfeits.⁴⁸⁷ During fiscal year 2010, the FDA's Office of Criminal Investigations opened 72 counterfeiting cases—more than in any prior year.⁴⁸⁸ Fiscal year 2009 had also been a record for counterfeit investigations with 65 cases (see figure 16).⁴⁸⁹ In 2006–2007, the first year after Florida enacted new legislation to improve the safety of distribution, Florida's Diversion Response Team opened 50 new cases on drug diversion.⁴⁹⁰

CASE STUDY 7

A COUNTERFEIT INJECTABLE DRUG ELUDES TRACKING

Epogen® is a high-cost injectable drug used to treat anemia. A counterfeit version was sold into legitimate distribution in 2002, resulting in subtherapeutic dosing and, reportedly, severe, painful side effects. Criminals in Florida relabeled up to 110,000 bottles of low-dose Epogen® (2,000 units/mL) to create a counterfeit high-dose (40,000 units/mL) Epogen® and a similar drug, Procrit®.⁴⁹² They acquired at least some of the low-dose Epogen® from a Florida pharmacy that falsified records to indicate that local patients had purchased the drugs.⁴⁹³ By one calculation, the relabeling of low-dose Epogen® to resemble a stronger product yielded the criminals a \$46 million profit.⁴⁹⁴

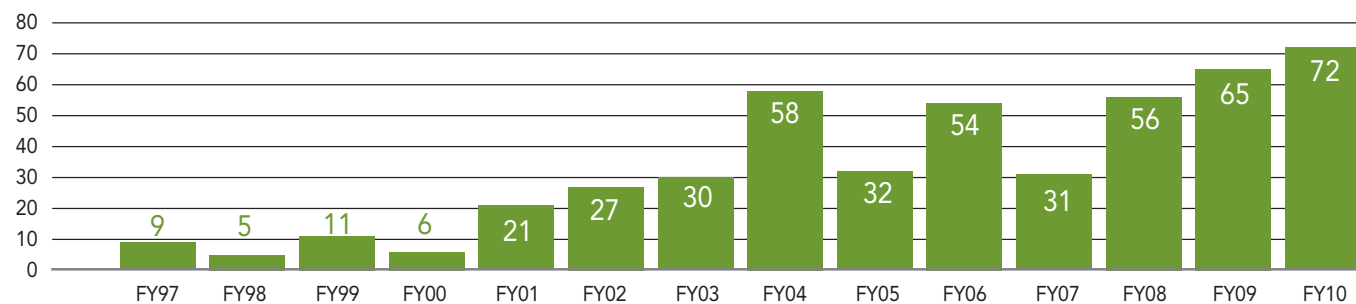
The counterfeit high-dose drugs passed through several registered and unregistered intermediaries⁴⁹⁵ before a portion was allegedly sold to a national wholesaler.⁴⁹⁶ Although federal statute requires smaller wholesalers to track the drugs they buy and sell, those listed as authorized distributors by manufacturers, most often the larger distributors, are exempt from the requirement (see section 3.3.2).⁴⁹⁷ Thus, the provenance of products entering an exempted wholesaler's warehouses would not be passed on to subsequent purchasers. The counterfeit drugs were eventually sold to patients by a major chain drugstore.⁴⁹⁸

Recovering from a liver transplant, 19-year old Tim Fagan of New York⁴⁹⁹ received counterfeit Epogen®, and cancer patient Maxine Blount⁵⁰⁰ received counterfeit Procrit®. These patients and others received lower levels of life-preserving therapy than they needed, and they suffered painful side effects. According to his father's testimony, Tim Fagan endured excruciating side effects every time he injected the counterfeit medication.⁵⁰¹

FDA investigators were able to recover less than 10 percent of the counterfeit medicine;⁵⁰² more than 90,000 vials may have reached patients.

Figure 16

Counterfeit cases opened by the FDA's Office of Criminal Investigations, 1997–2009



Source: FDA.⁴⁹¹

3.2.2 Risks originating outside the United States

The U.S. drug supply also is vulnerable to counterfeit drugs produced overseas, smuggled into the United States and sold into normal distribution. Estimates of counterfeit drugs in other parts of the world run as high as 30 percent.⁵⁰³ In 2003, counterfeit Lipitor® from Central America was illegally imported and sold into U.S. distribution.⁵⁰⁴ In 2009, a Chinese national was sentenced to prison for distributing counterfeit and misbranded pharmaceuticals in the United States. His counterfeits contained low levels of active ingredient, and many had impurities.⁵⁰⁵

As international pharmaceutical trade grows, traders may take advantage of free-trade zones where scrutiny of broker and trader behaviors is low, thereby enabling, for example, the repackaging or relabeling of products to conceal their origins, according to the World Health Organization.⁵⁰⁶ This practice may help hide the provenance of counterfeit drugs as well as drugs and drug ingredients that are not made at approved manufacturing sites, as discussed in section 1.3.2. Wholesalers and pharmacies that use or are willing to ignore these suspicious chains of custody risk passing on potentially unsafe products to consumers.

Online pharmacies are another way that problematic products can make their way into the United States. While not examined in depth in this paper, there is no doubt that by indiscriminately purchasing drugs from online sources, consumers expose themselves to a large safety risk. While many legitimate online pharmacies exist, there have also been documented sales of counterfeit, diverted, misbranded or adulterated medicine through online pharmacies. In the summer of 2010, the FDA alerted the public that counterfeit Tamiflu® was being sold online.⁵⁰⁷ When the FDA staff ordered samples of the advertised antiviral drugs, they received a shipment from India. The agency determined that the medicine contained the wrong active ingredient, and that this substituted material, similar to penicillin, could cause severe reactions in allergic patients.⁵⁰⁸ In March 2009, the FDA discovered that consumers received counterfeit Xenical®, an FDA-approved diet drug, from at least two different Web sites. The counterfeits did not contain any active drug.⁵⁰⁹ In the spring of 2009, a man in Dallas was convicted of buying and selling counterfeits online. The counterfeits were traced to China.⁵¹⁰ In November 2009, the FDA issued 22 warning letters to online pharmacies that appeared to be selling unapproved or misbranded drugs to U.S. consumers.⁵¹¹

The National Association of Boards of Pharmacy (NABP) has created the Verified Internet Pharmacy Practice Sites (VIPPS), an accreditation program for U.S.-based pharmacies to guide consumers to safe online options.⁵¹²

SIDEBAR 3

PARALLEL IMPORTATION, REIMPORTATION AND PERSONAL IMPORTATION

In many jurisdictions, individual consumers or commercial entities purchase prescription drugs across national borders to take advantage of cost differences created by local market conditions or price controls. Three terms commonly describe forms of importation:

Parallel importation: most often used to refer to the legal, commercial importation of drugs from a foreign country, as long as the drug is legally marketed in both the country of export and the country of import. Parallel importation is legal in the European Union but is not legal in the United States.

Reimportation: normally used in the U.S. context, refers to the importation of drugs from a foreign country that were made for that foreign country market. (The term reimportation is applied because in some cases the drugs have been manufactured in the United States and exported.)

Personal importation: Noncommercial reimportation by individuals. These purchases often occur online.

Neither parallel importation nor reimportation is legal in the United States. Although the FDA cannot verify the safety of any drug purchased outside of the U.S. market, written FDA procedures recommend against prosecution for personal importation in certain situations.⁵¹³ For an individual patient unable to afford drugs in the United States, the potential to obtain identical products at lower cost is understandably attractive. Congress has considered legislation to legalize large-scale, cross-border purchasing of drugs from select countries, subject to FDA oversight.⁵¹⁴ Were such a provision enacted, safety questions would arise from the risk that a large volume of cross-border demand could exceed local supply, providing motivation for unscrupulous sellers to source products from unapproved third-party countries. It would be essential that the FDA had the resources and capacity to fulfill its safety mandate.

3.3 Barriers to drug tracking and oversight of distribution

3.3.1 Limits of current drug tracking requirements

Drug distribution occurs nationally or regionally, but wholesalers are registered and regulated at the state level, usually through the state’s board of pharmacy. The FDA and the U.S. Drug Enforcement Administration investigate suspected illegal activity by wholesalers and pharmacies when it crosses state lines, but states are responsible for most compliance oversight. Both state and federal investigative resources are limited. Controlled drugs, it should be noted, are subject to separate requirements (see sidebar 4).

In the early 2000s, wholesaler licensure requirements in many states were minimal, presenting attractive opportunities to individuals willing to abuse the system for profit. In particular, Miami Dade County, Florida, was associated with a number of high-profile diversion cases in the early 2000s (see case study 7). To the dismay of law-abiding secondary wholesalers, insufficient regulation, combined with large financial incentives, encouraged the proliferation of bad actors, seriously eroding trust in the secondary market.

To address this criminal activity, many states have endeavored to tighten their wholesaler licensure requirements, in some cases based on best-practice standards established by the NABP.⁵¹⁵ As of February 2011, 29 states (as well as the federal government) have established pedigree requirements, according to HDMA.⁵¹⁶ To address shortfalls in drug tracking, the laws require entities involved in distribution to maintain “pedigrees,” or transaction histories, of the products they sell. (The intent of a pedigree requirement is to make the concealment of illicit activity more difficult by increasing transparency, and to support enforcement of responsible purchasing by wholesalers and pharmacies. Weak or nonexistent tracking systems make it difficult to find stolen merchandise and to implement recalls, when necessary. For example, the California Department of Public Health estimated that 7,832 patients in the state were exposed to adulterated heparin *after* the recalls were issued because of communication failures among wholesalers, hospitals, hospital pharmacies and the manufacturer.⁵¹⁷

Despite efforts at the state level, weaknesses in regulation remain. Varying state laws make compliance more complicated for companies operating in more than one state. Wholesalers licensed in states with weaker oversight may still sell nationally, often without having to meet additional, possibly more stringent, requirements of other states. Most state pedigree standards allow for paper-based documentation,*

which is easily falsifiable, and many standards exempt large wholesalers from tracking requirements, as does federal law (see section 3.3.2). In addition, industry concerns about commercial confidentiality have meant that some state laws, such as Florida’s, allow redaction of certain information from pedigrees. Within its model rules on the Licensure for Wholesale Distributors, NABP suggests that state boards of pharmacy eventually require all entities involved in distribution (manufacturers, wholesalers and pharmacies) to maintain and pass pedigrees for the medical products they distribute.⁵¹⁸

Furthermore, most state laws pertaining to tracking do not require companies to track bottles or packages of drugs (the drug “unit”), instead allowing tracking by the drug “lot,” a nonstandardized metric that provides low-resolution data and possibly represents thousands of product units. Often a full lot of drugs does not travel in one shipment, so if that one shipment is stolen, the entire lot is compromised: if any portion of a given lot of drugs is stolen, patients in possession of units from one lot cannot know if they have potentially substandard product. When stolen insulin was discovered in Texas in 2009, these units were readily identified because the stolen goods happened to comprise three complete lots.⁵¹⁹ Had the stolen material compromised only part of a lot, there would have been no way to distinguish legitimate products from stolen and potentially compromised drugs.

SIDEBAR 4

REGULATION OF CONTROLLED SUBSTANCES BY THE U.S. DRUG ENFORCEMENT ADMINISTRATION (DEA)

Although not a focus of this paper, the diversion of controlled substances for nonmedical use is an important issue with serious public health consequences. Many controlled substances are particular targets for theft and diversion because of black market demand. The DEA has established special distribution and tracking requirements to address systematic diversion of controlled substances into the black market or other illegal channels, as well as illicit procurement of controlled drugs by patients. All manufacturers, wholesalers and pharmacies that make or distribute controlled substances must register with the DEA,⁵²⁰ and may only trade a controlled substance with another registered entity. Each transaction is authorized by a special form issued by the DEA,⁵²¹ which names the parties to the transaction, their registration numbers, and a product description and amount.^{522–524} Manufacturers and distributors are also required to report transactions of controlled substances to the DEA through the Automation of Reports and Consolidated Orders System (ARCOS).⁵²⁵ The DEA uses this information to identify suspicious transactions and diversion.⁵²⁶

* Colorado, Oregon and California are the only states that require electronic pedigrees. Colorado’s requirement only applies to transactions outside of the “Normal Supply Chain”—a direct pathway from manufacturer to authorized distributor to pharmacy.

3.3.2 The Prescription Drug Marketing Act

In 1988, Congress passed the Prescription Drug Marketing Act (PDMA) to improve regulation of drug distribution and address drug diversion. Key PDMA provisions include:

- a prohibition of sale or trade of any drugs purchased by hospitals and clinics;⁵²⁷
- a requirement that HHS establish guidelines for states on minimum wholesaler licensure requirements,⁵²⁸ which have since been codified through regulations;⁵²⁹ and
- a requirement that entities involved in pharmaceutical distribution maintain pedigrees for the products they sell.⁵³⁰

A 1992 amendment to the PDMA further expanded the scope of information required in pedigrees.⁵³¹ These measures sought to increase transparency during distribution and to make concealment of illicit activity more difficult. However, the PDMA pedigree requirement is limited in scope, in that it applies almost exclusively to secondary wholesalers while exempting wholesalers that have ongoing purchasing agreements with pharmaceutical manufacturers.⁵³² These “authorized distributors of record” (ADRs) include the three major national wholesalers (McKesson Corp., Cardinal Health and AmerisourceBergen) and the approximately 30 regional wholesalers.* Requiring pedigrees only from secondary wholesalers assumes that diverted or counterfeit product never moves through the hands of major distributors. History has shown this not always to be the case (see case study 7). Moreover, when ADRs purchase product from entities other than manufacturers (although this is now rare), their exemption from tracking requirements effectively clears any existing pedigree from the record—a data gap that can conceal problematic distribution histories from subsequent purchasers.

In addition to these weaknesses, meaningful implementation of the pedigree provision has been indefinitely delayed by a court-ordered injunction—the result of a lawsuit filed by secondary wholesalers.⁵³³ The PDMA requires all entities engaged in distribution, except manufacturers and ADRs, to provide transaction histories along with the drugs they sell.⁵³⁴ Early implementation guidance from the FDA suggested that these pedigrees reflect transactions back to the manufacturer or the ADR.⁵³⁵ The FDA’s stated intention regarding this guidance was that distributors should report transactions back to the ADR that originally purchased the drugs from the manufacturer.⁵³⁶ In the years after PDMA passage, however, many smaller non-ADR wholesalers tracked back only to the most recent sale by any authorized distributor.⁵³⁷ The FDA attempted to remedy this gap in pedigree requirements in a final rule issued in 1999 that required transaction histories back to the manufacturer. However, this move met with opposition by smaller wholesalers who asserted that they would not be able to comply because the exemption of authorized distributors rendered it impossible for them to obtain reliable sales histories all the way back to the manufacturer.⁵³⁸ The effective date of the 1999 rule was delayed five times by the FDA, and when

the agency attempted to hold to a 2006 date, secondary wholesalers filed a lawsuit to stop the action. A U.S. district court granted a stay on grounds that the FDA’s rule was inconsistent with the authorized distributor exemption. The court also expressed concern that the FDA rule promotes anticompetitive behavior because of this apparent inequity toward smaller wholesalers.⁵³⁹ The rule is still not in effect.

3.3.3 Electronic tracking system proposals

Changes in wholesaler purchasing practice suggest that large ADRs generally no longer purchase medicines from other wholesalers. However, lack of a uniform and comprehensive federal pedigree standard (the PDMA) and the varying strength of pedigree requirements in states have driven regulators and members of industry to seek new federal standards to better ensure distribution safety and security as well as facilitate compliance. Some are looking to address pedigree limitations through new electronic “track-and-trace” systems. Under these systems, manufacturers would apply electronically readable tags at the product unit level (the smallest package or container sold to a pharmacy or hospital). By scanning the tags, wholesalers and pharmacies would be able to verify the legitimate origins of the drugs they purchase. Each time the tagged unit is transferred and scanned, new electronic data would be generated and stored (see sidebar 5). Electronic unit-level tracking by all entities involved in distribution could help create a more secure tracking system, and facilitate more targeted responses to theft, adulteration and counterfeiting. The FDA Amendments Act of 2007 (FDAAA) requires the FDA to develop standards for the tracking and tracing of drugs, although the FDAAA did not place a time line on this requirement.⁵⁴⁰ The FDA held a workshop for industry stakeholders on the parameters of a track-and-trace system in February 2011. Thus, while the development of standards specified in the FDAAA is under way, it is unclear whether the FDA can require compliance without additional statutory authority. Recently, both the U.S. Counterfeit Pharmaceutical Inter-agency Working Group and the office of the United States Intellectual Property Enforcement Coordinator have recommended implementation of a track-and-trace system to secure drug distribution against counterfeits.^{541,542}

Not every stakeholder embraces the idea of track-and-trace systems. According to a report commissioned by two pharmacy trade associations, implementation of track-and-trace at the retail level will entail an inordinately high cost for pharmacies that would not be warranted by the rare incidence of counterfeit drugs found in normal U.S. distribution channels.⁵⁴³ Critics of this report say it examines only the most onerous option of many track-and-trace system proposals—and that it also explicitly ignores efficiencies or cost savings that could result from such a system.⁵⁴⁴ Despite industry disagreement on track-and-trace, recent examples of stolen products appearing on the shelves of U.S. pharmacies, such as insulin in 2009 (see section 3.2.1), are evidence of an ongoing problem. Any solution will require the participation and cooperation of the pharmacy sector.

* Based on the number of regional or specialty wholesalers that are members of HDMA, excluding McKesson Corp., Cardinal Health and AmerisourceBergen. Being an ADR is a requirement for active HDMA membership. Some secondary wholesalers are also ADRs for certain products.

SIDEBAR 5

WHAT IS “TRACK-AND-TRACE”?

Any system to allow automated drug tracking requires two distinct, but related, technological components. First, each individual unit to be tracked must have a unique identification—or serialization—number. Second, the system requires an efficient means of embedding and reading these numbers as products move through the distribution supply chain.

Serializing drug products at the unit, or package, level would permit tracking of drugs at a much more granular level than the current lot level. In 2010, the FDA released a final guidance on a standard form for serial numbers, suggesting that the number be an alphanumeric code of up to 20 digits following the product’s national drug code.⁵⁴⁵ The FDA states in its guidance that this “serialized national drug code” is compatible with existing serialization systems such as the Global Trade Item Numbers system put forward by the GS1, a nonprofit standards-setting organization.⁵⁴⁶

For a functioning track-and-trace system, serial numbers would be embedded in an electronically readable tag, allowing wholesalers and pharmacies to scan serialized products as they move through their facilities. Most track-and-trace requirements, such as those included in California’s pedigree law, are technology-neutral, meaning they do not specify how the serial number will be applied or recorded. However, there are two principal technologies in use: 2-D bar codes and RFID.* The latter approach offers an advantage over bar codes in that the tags can be read through packaging. Drug units are often packaged together for bulk shipping, and entities authenticating units serialized by bar code must either rely solely on an overall shipment tag (and infer the validity of the product within, which is a lower measure of confidence), or must open the shipping case to scan individual units. One limitation to RFID is the potential for interference between frequencies to affect read rates, according to a 2006 pilot of the technology by Cardinal Health, a national drug distributor.⁵⁴⁷ RFID is also a costlier tagging system than 2-D bar codes, although its price continues to decrease.⁵⁴⁸

In addition to serialization and electronic tagging, a third critical parameter to track-and-trace is an effective data management system (or systems) that will house transaction information, and which wholesalers and pharmacies may query to check a product’s transaction history.

3.4 Pew conference and policy recommendations

Despite actions by industry and regulators, counterfeit and diverted products continue to enter the U.S. distribution market, a complex system involving many companies. To better secure distribution, as well as to greatly increase the effectiveness of drug recalls, drug tracking must be improved and regulation of distribution strengthened.

Participants at the Pew Health Group roundtable recognized that counterfeit and stolen drugs have been able to enter the legitimate U.S. distribution system, and that this ongoing risk must be addressed. A number of participants referred to the current benefits of a closed distribution system, from manufacturer to distributor to pharmacy. However, one state regulator gave a 2010 example of a counterfeit product discovered at a chain retail location that purchased its products from a national wholesaler, suggesting that even an apparently closed supply chain would benefit from measures to secure distribution.

There was broad agreement among participants that the United States needs uniform national standards for licensure of pharmaceutical wholesalers to overcome a patchwork of sometimes lax state requirements. One pharmacy representative said that additional certification or some additional accountability for distributors is necessary so that, if a pharmacy needs to turn to an alternate supplier for product, it will have some assurance that the distributor is legitimate.

In addition to wholesaler licensure improvements, many participants also supported a national drug traceability system. However, retail pharmacy representatives expressed concerns about implementation costs and had questions about how a track-and-trace system would be operationalized at the pharmacy level. If track-and-trace were to be required, however, most participants, including pharmacy trade association representatives, expressed a preference for uniform national standards rather than state-by-state regulations.

Regulators, manufacturer representatives, large and small distributors, and consumer groups supported nationally applied serialization and electronic tagging systems to track drugs. The FDA would like to see a system that includes tracking and traceability for all components throughout the supply chain. Just like other products contain a bar code that can be scanned for information, drugs should be able to carry the same type of identifier. Wholesalers agreed to a need for a tracking system, noting that small distributors are able to pass pedigree now, without a great cost burden. Participants noted that such a system has been under discussion for many years, but that agreement on uniform standards has not been reached. The majority of participants who voiced an opinion believe that implementing such a system will require a new federal statute.

* Radio Frequency Identification (RFID) Technology uses electronic tags and readers to pass data through radio waves.

One concern expressed by pharmacy groups in particular was data security within a track-and-trace system. The representative from the National Association of Chain Drug Stores also noted that pharmacy inventory information has a proprietary value, which retailers worry could be threatened under a national system that permits others to access such data. This representative suggested that pilot projects could provide an early sense of how data would move between groups, and said that if track-and-trace were put in place, peer-to-peer authentication may be most appropriate. In this scenario, participants would only check a product with their immediate trading partner rather than providing visibility all the way back to the manufacturer. One wholesaler representative preferred a de-identified system, in which users could query the system with a given serial number and receive a green or red light to signal acceptable or not acceptable without revealing company information.

Finally, several participants expressed concern about the costs of implementing a stronger, more uniform system, particularly representatives from small pharmacies, who cautioned that some don't even have Internet access, so technology would need to be made accessible and cost effective for these stakeholders.

POLICY RECOMMENDATIONS*

A. Improve drug distribution security through a federal serialization and verification system

1. **Require each drug package to bear a unique serial number.** Drugs should be serialized at the level of the smallest container from which a drug may be repackaged or dispensed (also called a “unit”). Repackagers should be required to re-serialize product and link new serial numbers to original serial numbers.
2. **Create a uniform federal system for verification of distribution transaction history.** Requiring verification of a drug's transaction history—as well as the systems necessary to support that verification—will enable responsible purchasing and provide an important tool to regulators investigating issues of counterfeiting, diversion and theft.
 - a. The system must apply to all entities involved in distribution. Requiring all manufacturers, wholesalers and pharmacies to participate in a federal pedigree system through a new federal law or revisions to existing law will ensure that bad actors have no clear regulatory exception to abuse.
 - b. Regulators must be able to access full transaction histories for any drug when needed.
 - c. Strong consideration should be given to implementation of an entirely electronic system, wherein serial numbers are embedded into electronic tags that may be scanned by each entity to authenticate the transaction history of a product.

- d. If the system requires the passage of a more traditional “pedigree” document, these documents should be electronic to better protect against falsification.

B. Strengthen wholesaler regulation and oversight

1. **Improve standards for wholesaler licensure and oversight.** Federal guidance on minimum standards for wholesaler licensure should be strengthened to include a requirement for pre-licensure warehouse inspections, whether by federal or state officials, and for periodic inspections thereafter. Standards should also include required background checks for individuals in charge of wholesale operations prior to licensure. These principles are also included in the robust requirements for wholesaler licensure set forth in the NABP model rules. In the absence of stronger federal requirements, states should independently strengthen wholesaler licensure requirements where necessary to conform to these principles.⁵⁴⁹
2. **Require distributors and pharmacies to alert the FDA of any suspected product adulteration, counterfeiting, diversion or theft.** Distributors and pharmacies should also report to the FDA any case in which they are unable to validate the transaction history of a drug. As with manufacturers, distributors are not required to report this information to the FDA; any sharing is done on a voluntary basis. FDA access to this information must be the priority when there is a public health risk of exposure to a potentially harmful product.

* The recommendations in this report have been informed by the roundtable discussions and presentations, but are not intended to constitute a consensus position and may not reflect the views of every participating organization.

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Expert Interviews

Bill Allmond, Vice President, Government Relations, Society of Chemical Manufacturers and Affiliates; **Philippe Andre, MScPharm, MA**, Director, Qualiau Pharmaceutical Auditing Co., Ltd., and Associate Professor at the School of Pharmaceutical Science and Technology, Tianjin University; **Deborah M. Autor, Esq**, Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration;* **James Bao, PhD**, Professor of Analytical Chemistry, Tianjin University; **Nick Basta**, Editor-in-Chief, Pharmaceutical Commerce; **Prabir Basu, PhD**, Executive Director, The National Institute for Pharmaceutical Technology and Education; **Roger Bate, PhD**, Legatum Fellow in Global Prosperity, American Enterprise Institute; **Peter Beckerman, JD**, Senior Policy Advisor, Office of Policy, U.S. Food and Drug Administration; **Ilisa B.G. Bernstein, PharmD, JD**, Director of Pharmacy Affairs, Office of Policy, Office of the Commissioner, U.S. Food and Drug Administration;* **Arline Bilbo**, Director, Member and Professional Relations, U.S. Pharmacopeial Convention; **Carmen Catizone, M.S., RPh, DPh.**, Executive Director, National Association of Boards of Pharmacy; **Robert Celeste**, Director, GS1 Healthcare United States; **James D. Coffey**, Director, Massachusetts Board of Pharmacy; **Marcia G. Crosse, Ph.D.**, Director, Health Care, U.S. Government Accountability Office; **Diane Darvey, PharmD, JD**, Director, Federal and State Public Policy, National Association of Chain Drug Stores; **Benjamin England, Esq**, Founder, Benjamin L. England & Associates, LLC, and FDAImports.com, LLC, former Regulatory Counsel to the Associate Commissioner for Regulatory Affairs, U.S. Food and Drug Administration; **Adam J. Fein, PhD**, Pembroke Consulting, Inc.; **Ben Firschein**, Director, Government Affairs, U.S. Pharmacopeial Convention; **Elizabeth A. Gallenagh, Esq**, Vice President, Government Affairs, Healthcare Distribution Management Association; **Erin M. Gardiner**, Director, Corporate Communications, Baxter International Inc.; **Daniel H. Gold, PhD**, President and CEO, D.H. Gold Associates, Inc.; **James C. Griffiths**, Vice President, Food, Dietary Supplement and Excipient Standards, U.S. Pharmacopeial Convention; **Virginia Herold, MS**, Executive Officer, California State Board of Pharmacy; **Matthew Heyman**, Vice President, External Affairs and Strategic Integration, U.S. Pharmacopeial Convention; **David J. Horowitz**, Assistant Commissioner for Policy, U.S. Food and Drug Administration; **Jeanne Ireland**, Assistant Commissioner for Legislation, Office of the Commissioner, U.S. Food and Drug Administration; **Brenda Kelly**, Vice President of Marketing, SupplyScape; **Robert Kennedy**, Manager of Industry Research, Healthcare & Science, Thomson Reuters; **David A. Kessler, MD**, Professor of Pediatrics and Epidemiology and Biostatistics at the School of Medicine, University of California, San Francisco, Former Commissioner,

* Title at time of interview

U.S. Food and Drug Administration; **William F. Koch, MS, PhD, FACB**, Chief Standards Acquisition and Metrology Officer, U.S. Pharmacopeial Convention; **Peter Maybarduk, JD**, Director, Access to Medicines Program, Public Citizen; **Scott M. Melville**, Senior Vice President of Government Affairs and General Counsel, Healthcare Distribution Management Association; **Kevin Nicholson, RPh, JD**, Vice President of Government Affairs and Pharmacy Advisor, National Association of Chain Drug Stores; **Steven Niedelman**, Senior Consultant, Crowell & Moring LLP, former Deputy Associate Commissioner for Regulatory Operations, U.S. Food and Drug Administration; **Carl R. Nielsen**, Founder and President of C. Nielsen Consulting, LLC, former Director, Division of Import Operations and Policy, Office of Regulatory Affairs, U.S. Food and Drug Administration; **Chris Oldenhof, PhD**, President, Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Manager, External Regulatory Affairs, DSM; **Steve Perlowski**, Vice President of Industry Affairs, National Association of Chain Drug Stores; **Dirk A. Rodgers**, Owner and Sole Contributor, www.RxTrace.com; **Marianne Rowden**, President and CEO, American Association of Exporters and Importers; **Paul Rudolf, MD, JD**, Partner, Arnold & Porter, LLP; former Senior Advisor, Office of the Commissioner, U.S. Food & Drug Administration; **Peter Scarafile, MS, RPh**, Director of Pharmacy Services, Cape Cod Hospital; **Stuart Schweitzer, PhD**, Vice-Chair and Professor of Health Services, School of Public Health, University of California Los Angeles; **Marvin D. Shepherd, PhD**, Director, Center for Pharmacoeconomic Studies, College of Pharmacy, University of Texas-Austin, President, Partnership for Safe Medicines; **Jeffrey Shuren, MD, JD**, Associate Commissioner for Policy and Planning, U.S. Food and Drug Administration; **Matt Simmons**, Executive Director, National Coalition of Pharmaceutical Distributors; **Peter D. Smith**, Vice President, Pharmaceutical Compliance, PAREXEL Consulting; **V. Srinivasan, PhD**, Head, International Sites and USP Verification Programs, United States Pharmacopeia; **Martin VanTrieste, RPh**, Chair, Rx-360, Senior Vice President, Quality, Amgen; **Guy Villax**, Board Member of the European Fine Chemicals Group and of Rx-360, CEO, Hovione; **Robert Weissman**, President, Public Citizen; **Roger L. Williams, MD**, CEO, United States Pharmacopoeial Convention; **Connie Woodburn**, Senior Vice President, Professional and Government Relations, Cardinal Health; **Alastair Wood, MD**, Partner, Symphony Capital, LLC; Professor of Medicine and Professor of Pharmacology at Weill Cornell Medical School; **Michael Woody**, former Director, Pharmaceutical Research and Manufacturers of America; **Brant Zell, MBA**, Past Chair, Bulk Pharmaceuticals Task Force, Society of Chemical Manufacturers and Affiliates, Vice President, Quality, Polypeptide Laboratories; and **Heather Zenk**, Director, Integrated Solutions, AmerisourceBergen.

Pew Stakeholder Conference Roundtable Participants

Philippe Andre, MScPharm, MA, Director, Qualia Pharmaceutical Auditing Co., Ltd., and Associate Professor at the School of Pharmaceutical Science and Technology at Tianjin University

Cesar Arias, RPh, PI, Partner, Stone Cold Healthcare Consultants, LLC; former drug inspector, Florida Bureau of Statewide Pharmaceutical Services

Deborah M. Autor, Esq, Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration

Prabir Basu, PhD, Executive Director, National Institute of Pharmaceutical Technology and Education

Roger Bate, PhD, Legatum Fellow in Global Prosperity, American Enterprise Institute

Ilisa B.G. Bernstein, PharmD, JD, Deputy Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration

Marcie Bough, PharmD, Senior Director, Government Affairs, American Pharmacists Association

Heather Bresch, MBA, President, Mylan Inc.

Carmen Catizone, MS, RPh, DPh, Executive Director, National Association of Boards of Pharmacy

Allan Coukell, BScPharm, Director of Medical Programs, Pew Health Group

Marcia G. Crosse, PhD, Director, Health Care, U.S. Government Accountability Office

Ryan Crowley, Senior Analyst, Health Policy, American College of Physicians

Diane Darvey, PharmD, JD, Director, Federal and State Public Policy, National Association of Chain Drug Stores

Richard L. Friedman, MS, Director, Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research, Food and Drug Administration

Elizabeth A. Gallenagh, Esq, Vice President, Government Affairs, Healthcare Distribution Management Association

Ahaviah Glaser, JD, Senior Legislative Representative, AARP

Marcia Hams, MA, Director, Prescription Access and Quality, Community Catalyst

Suzanne Henry, Policy Analyst, Consumers Union

Virginia Herold, MS, Executive Officer, California State Board of Pharmacy

Joseph Hill, MA, Director, Federal Legislative Affairs, American Society of Health-System Pharmacists

Gordon Johnston, MS, RPh, Vice President, Regulatory Sciences, Generic Pharmaceutical Association

Kendra A. Martello, JD, Assistant General Counsel, Pharmaceutical Research and Manufacturers of America

Karen Moody, President, National Coalition of Pharmaceutical Distributors

Susan Pilch, JD, Director, Policy and Regulatory Affairs, National Community Pharmacists Association

Leigh Purvis, Senior Strategic Policy Advisor, AARP

Cynthia Reilly, BS Pharm, Director, Practice Development Division, American Society of Health-System Pharmacists

Ann Van Meter, International Pharmaceutical Excipients Council of the Americas; Senior Quality System Specialist, The Dow Chemical Company

Martin VanTrieste, RPh, Chair, Rx-360; Senior Vice President, Quality, Amgen

Guy Villax, Board Member of the European Fine Chemicals Group and of Rx-360; CEO, Hovione

Roger L. Williams, MD, CEO, United States Pharmacopeial Convention

Brant Zell, MBA, Past Chair, Bulk Pharmaceuticals Task Force, Society of Chemical Manufacturers and Affiliates; Vice President, Quality, Polypeptide Laboratories

Pew Stakeholder Conference Agenda

MONDAY, MARCH 14

Day 1: Globalization of Pharmaceutical Manufacturing: Updating Quality Systems and Oversight

Moderator: William K. Hubbard, Advisor, Alliance for a Stronger FDA

9:00–9:20 a.m.	<p>Welcome Remarks</p> <p><i>Speaker:</i> Allan Coukell, BScPharm, Director of Medical Programs, Pew Health Group</p>
9:20–9:45 a.m.	<p>Opening Keynote</p> <p><i>Speaker:</i> John M. Taylor III, Esq, Acting Principal Deputy Commissioner, FDA</p>
9:45–10:30 a.m.	<p>Q&A</p>
10:45–11:45 a.m.	<p>Session 1: Ensuring quality and safety across manufacturing supply chains</p> <p><i>Panelists:</i> Martin VanTrieste, Chair, Rx-360, Senior Vice President, Quality, Amgen Roger L. Williams, MD, CEO, United States Pharmacopeia Philippe Andre, MScPharm, MA, Director, Qualiau Pharmaceutical Auditing Co., Ltd., Associate Professor at the School of Pharmaceutical Science and Technology at Tianjin University</p>
11:45–12:20 p.m.	<p>Roundtable Discussion</p> <p><i>Key Questions:</i></p> <ol style="list-style-type: none"> 1. What steps should manufacturers take to safeguard global supply chains? 2. How should companies assess suppliers? 3. Are there policy mechanisms that could improve compliance with quality standards? 4. How can analytical standards and tests be improved?
12:20–12:30 p.m.	<p>Q&A</p>

1:30–2:30 p.m.	<p>Session 2: Ensuring sufficient regulatory oversight of foreign manufacturers</p> <p><i>Panelists:</i> Marcia G. Crosse, PhD, Director, Health Care, U.S. Government Accountability Office</p> <p>Brant Zell, MBA, Past Chair, Bulk Pharmaceuticals Task Force of the Society of Chemical Manufacturers and Affiliates; Vice President, Quality, Polypeptide Laboratories</p> <p>Guy Villax, Board Member of the European Fine Chemicals Group and of Rx-360; CEO, Hovione</p>
2:30–3:05 p.m.	<p>Roundtable Discussion</p> <p><i>Key Questions:</i> 1. How frequently should the FDA inspect foreign plants? 2. Is there a role for third-party inspections? 3. What would constitute an effective system for tracking foreign manufacturing sites? How can tracking systems integrate with risk assessment and Customs activity?</p>
3:05–3:15 p.m.	Q&A
3:30–4:30 p.m.	<p>Session 3: Ensuring a robust regulatory system</p> <p><i>Panelists:</i> Heather Bresch, MBA, President, Mylan Inc.</p> <p>Prabir Basu, PhD, Executive Director, National Institute for Pharmaceutical Technology and Education</p> <p>Deborah M. Autor, Esq, Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration</p>
4:30–5:05 p.m.	<p>Roundtable Discussion</p> <p><i>Key Questions:</i> 1. How should the FDA oversight of foreign plants be funded? 2. Does the FDA need new tools to oversee global supply chains? 3. Are international harmonization and reciprocal recognition of inspections part of the solution?</p>
5:05–5:15 p.m.	Q&A
5:15–5:25 p.m.	Concluding Remarks Allan Coukell , Pew Health Group

TUESDAY, MARCH 15

Day 2: Pharmaceutical Distribution: Risks and Responses to Counterfeit and Diverted Drugs

Moderator: Allan Coukell, Pew Health Group

9:00–9:40 a.m.	<p>Opening Keynote</p> <p><i>Speaker:</i> U.S. Senator Michael Bennet (D-CO)</p>
9:40–10:00 a.m.	<p>Session 4: Protecting U.S. drug distribution</p> <p><i>Panelist:</i> Ilisa B.G. Bernstein, PharmD, JD, Deputy Director, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration</p>
10:15–11:00 a.m.	<p>Session 4 (Continued): Protecting U.S. drug distribution</p> <p><i>Panelists:</i> Cesar Arias, RPh, PI, Partner, Stone Cold Healthcare Consultants, LLC; former drug inspector, Florida Bureau of Statewide Pharmaceutical Services</p> <p>Roger Bate, PhD, Legatum Fellow in Global Prosperity, American Enterprise Institute</p>
11:00–11:30 a.m.	<p>Roundtable Discussion</p> <p><i>Key Questions:</i> 1. Where and how serious are the weaknesses in the distribution system? 2. What are the implications of international counterfeits for the U.S. market? 3. What improvements should be made to penalties for counterfeiting, adulteration and other violations of the FD&C Act?</p>
11:30–11:45 a.m.	Q&A
12:45–1:45 p.m.	<p>Session 5: Serialization, pedigree and tracking</p> <p><i>Panelists:</i> Virginia Herold, MS, Executive Officer, California State Board of Pharmacy</p> <p>Elizabeth A. Gallenagh, Esq, Vice President, Government Affairs, Healthcare Distribution Management Association</p> <p>Diane Darvey, PharmD, JD, Director, Federal and State Public Policy, National Association of Chain Drug Stores</p>
1:45–2:30 p.m.	<p>Roundtable Discussion</p> <p><i>Key Questions:</i> 1. Should there be a universal system for tracking drug distribution? 2. What would the elements of a successful system be? 3. What changes to regulation and oversight of distributors and pharmacies would help identify and deter bad actors?</p>
2:30–2:45 p.m.	Q&A
2:45–3:00 p.m.	Concluding Remarks Allan Coukell , Pew Health Group

List of Acronyms

ADR	Authorized Distributor of Record	HHS	United States Department of Health and Human Services
ANDA	Abbreviated New Drug Application	ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
API	Active Pharmaceutical Ingredient	NDA	New Drug Application
CBP	United States Customs and Border Protection	OCI	Office of Criminal Investigations (Food and Drug Administration)
CDC	United States Centers for Disease Control and Prevention	ORA	Office of Regulatory Affairs (Food and Drug Administration)
CDER	Center for Drug Evaluation and Research (Food and Drug Administration)	OSCS	Oversulfated Chondroitin Sulfate
COA	Certificate of Analysis	OTC	Over-the-Counter
DEA	United States Drug Enforcement Administration	PAI	Pre-Approval Inspection
DEG	Diethylene Glycol	PDMA	Prescription Drug Marketing Act
DMF	Drug Master File	PDUFA	Prescription Drug User Fee Act
EMA	European Medicines Agency	QSR	Quality Systems Regulation
EU	European Union	RFID	Radio Frequency Identification
FDA	United States Food and Drug Administration	SFDA	Chinese State Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act	TGA	Australian Therapeutic Goods Administration
FDCA	Federal Food, Drug, and Cosmetic Act	USP	United States Pharmacopeial Convention
GAO	United States Government Accountability Office		
GMP	Good Manufacturing Practice		

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EXTERNAL REVIEWERS

Philippe Andre, MScPharm, MA, Director, Qualiau Pharmaceutical Auditing Co., Ltd., and Associate Professor at the School of Pharmaceutical Science and Technology, Tianjin University

Prabir Basu, PhD, Executive Director, The National Institute for Pharmaceutical Technology and Education

Carmen Catizone, MS, RPh, DPh, Executive Director, National Association of Boards of Pharmacy

Adam J. Fein, PhD, Pembroke Consulting, Inc.

Steven Niedelman, Senior Consultant, Crowell & Moring LLC;* former Deputy Associate Commissioner for Regulatory Operations, U.S. Food and Drug Administration

Guy Villax, Member of the Board, European Fine Chemicals Group, Rx-360; CEO, Hovione

Roger L. Williams, MD, CEO, United States Pharmacopeial Convention

Alastair Wood, MD, Partner, Symphony Capital, LLC; Professor of Medicine and Professor of Pharmacology at Weill Cornell Medical School

Brant Zell, MBA, Past Chair, Bulk Pharmaceuticals Task Force, Society of Chemical Manufacturers and Affiliates, Vice President, Quality, Polypeptide Laboratories

* Title at time of review

PROJECT TEAM

Allan Coukell
Director of Medical Programs
Pew Health Group

Gabrielle Cosel
Manager, Pew Prescription Project

PEW HEALTH GROUP

Shelley A. Hearne
Managing Director

MEDIA CONTACT

Linda Paris
Communications Manager
202-540-6354
lparis@pewtrusts.org

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901 E Street NW,
Washington, DC 20004



2005 MARKET STREET, SUITE 1700 • PHILADELPHIA, PA 19103

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