

**Testimony before the
House Committee on Energy on Commerce, Subcommittee on Oversight and Investigations
United States House of Representatives**

April 13, 2011

**Allan Coukell
Director, Medical Safety Portfolio, Pew Health Group
The Pew Charitable Trusts**

Chairman Stearns, Ranking Member DeGette, and members of the Oversight and Investigations Subcommittee, thank you for the opportunity to submit testimony about the essential steps Congress must take to protect Americans and ensure the integrity of our drug supply.

A major focus of the Pew Health Group is identifying ways to address risks to the U.S. pharmaceutical supply chain. Last month, we hosted a two-day conference that included representatives of brand and generic pharmaceutical manufacturers, active ingredient makers, federal and state regulators, major and secondary pharmaceutical wholesalers, chain and independent pharmacies, consumer and health professional organizations and independent supply chain experts. The convening was structured around a discussion draft of a white paper entitled “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” which was shared with conference participants in advance.

The presenters at our meeting explained that pharmaceutical manufacturing has changed dramatically over the past decade. While the vast majority of drugs in our pharmacies and medicine cabinets are not counterfeit or adulterated, increasing globalization and reliance on outsourced manufacturing create new risks.

Heparin

The contamination of the blood thinner heparin dramatically illustrates the risks we face. In 2007, Baxter International, the major U.S. supplier of heparin, began to receive reports of unusual adverse reactions to the drug. The company informed the U.S. Food and Drug Administration (FDA) and the problem was traced to a contaminant that had been introduced during manufacture of the raw drug. The active ingredient had been sourced from a Chinese factory, which in turn relied upon a network of small suppliers. The evidence suggests that the toxic ingredient was introduced deliberately, for economic gain.¹ It was not a chemical that occurs naturally. Whoever made it likely knew that the substance would be undetected by standard tests then in use.² The toxic material eventually reached at least 11 countries. Based on an estimated three tons of product, this substitution has been estimated to have yielded \$1 million to \$3 million in gains for the individual or company that sold it.³ The FDA received reports of deaths and serious injuries associated with use of heparin.⁴

While failure to detect the contaminant during manufacture was a key factor, the case also illustrated other systemic problems, including:^{5,6,7,8}

- An absence of timely supplier audits and FDA inspections,
- Limits and errors in the FDA database of manufacturing facilities,
- The discovery of manufacturing quality issues, including poor control of incoming raw materials, and
- The fact that – even in the period after the deaths – neither the manufacturer nor the FDA was able to gain complete access to the upstream supply chain.

This incident represents a clear breach of the security of the U.S. pharmaceutical supply. To this day, no one in any country has yet been held accountable. Nor has Congress acted to update the statutes that govern drug manufacturing. Numerous experts have asserted that, absent changes to the system, another such event is inevitable.

Globalization/outsourcing

Heparin is far from the only pharmaceutical that is produced outside the U.S. for American consumers. The number of U.S. drugs and ingredients made at non-U.S. sites has doubled since 2001.⁹ An estimated 80% of the active ingredients and bulk chemicals in U.S. drugs is now sourced by industry from foreign countries,¹⁰ and up to half are purchased from plants in India and China.¹¹ The U.S. is the number one destination for Chinese pharmaceutical raw material exports.¹²

Despite globalization of manufacturing, FDA oversight is largely domestically focused. Current statute requires inspections of U.S. plants every two years, but specifies no inspection frequency for foreign plants.¹³ The FDA lacks the resources to inspect foreign sites with any meaningful regularity.¹⁴ The Government Accountability Office (GAO) has also found that FDA foreign inspections are shorter than inspections of U.S. plants and, unlike inspections at U.S. facilities, are pre-announced, because of cost and resource considerations.¹⁵

Quality/compliance

In the case of heparin, it appears that criminals deliberately sold unsafe product into the supply chain. At other times, consumers may be at risk because of failures by manufacturers to comply with quality standards. Poor adherence to quality standards has been observed both in the U.S. and abroad, but the shift of manufacturing to low-cost environments with reduced oversight creates an increased risk. According to one estimate, ignoring Good Manufacturing Practices (GMPs) can save up to 25% of a factory's operating costs.¹⁶ The expectation of inspections is an incentive for compliance with quality standards.

Compliance failures may be the result of poor performance, or they may be deliberate. One Chinese company was found to have exported heparin to the U.S. that they claimed to have made at their own factory, but was in fact made entirely at two external plants.¹⁷ The FDA has said that some of this heparin may have contained the same contaminant associated with the deaths in 2007 and 2008.¹⁸ Falsification of manufacturing location poses risks to patients, because regulators cannot ensure a product's quality without knowing the conditions of its manufacture.

In 2008, an Indian manufacturer was cited by the FDA for falsification of stability testing records¹⁹ and use of active ingredients made at unapproved sites.²⁰ In 2010, another Indian manufacturer was found to have falsified batch manufacturing records for an anti-platelet

medicine. The falsified records were discovered in the plant's waste yard by inspectors from the European Union.²¹

In Panama in 2006, dozens of people died after taking a cough medicine that had been made with diethylene glycol,^{22,23} a sweet-tasting, but poisonous solvent.²⁴ It had been wrongly labeled in China and passed through a series of Chinese and European brokers, who repeatedly re-labeled it without performing independent tests. The same problem has occurred with products in Africa, Haiti and India, and has been identified in consumer products in this country as recently as 2007.²⁵ Students of FDA history will know that diethylene glycol poisoning in the United States in 1937 was the disaster that led directly to the enactment of the Food Drug and Cosmetic Act (FDCA).²⁶ It is now time to update that statute for 21st century manufacturing.

Gaps and Solutions

The Pew convening in March was structured around a discussion draft of a white paper entitled “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” which was shared with conference participants in advance. At the meeting, we heard from a number of industry, government, professional groups and supply chain experts that real risks exist, and that the system can – and must – be improved. We heard that serious limitations to FDA's oversight of foreign plants making drugs and ingredients for the U.S. must be remedied. Representatives from several drug manufacturing groups agreed to back new industry fees to cover additional foreign inspections.

Experts also called for industry audits of every supplier and sub-supplier. Some companies already have best practices in place, but it is important that every company have systems in place to ensure the safety and quality of its upstream supply chain.

Some steps can be taken now. The FDA has opened offices in India, China, and other countries, and pursuing changes to standards to improve supply chain oversight. The agency is also implementing a new risk-based screening system for imports to speed the clearance of low-risk shipments and increase the predictive efficacy for identifying and targeting high-risk imports. In addition, FDA has entered into 22 confidentiality agreements with regulatory bodies in different countries and shares inspectional information with the European Union and Australia.²⁷ Many individual companies have also taken steps. Nevertheless, additional legislative changes are now

needed to give the FDA the tools it needs to ensure that every manufacturer is held to the highest standard. Pew prioritizes the following reforms:

1. Pharmaceutical companies must have comprehensive systems in place to assess risk and ensure the quality and safety of their manufacturing supply chains. Companies must audit suppliers on-site prior to engagement and institute supplier quality agreements.²⁸ Company management must be held accountable for implementing these systems.
2. Overseas inspections by FDA must be significantly increased. Inspections do not guarantee quality, but the reasonable expectation of inspections is an incentive for compliance with quality standards. We can and should ensure that inspection frequencies domestically and internationally are meaningful. The FDA has recently expressed its intention to increase its reliance on third-party sources of information, particularly inspections by other regulators, to supplement FDA's own ability to conduct inspections. This is a necessary step to preserve the integrity of the U.S. drug supply.
3. FDA authority and enforcement gaps must be addressed: FDA authorities and enforcement tools are often inadequate to properly regulate the pharmaceutical industry, particularly overseas. FDA does not currently have the authority to mandate a drug recall, nor may it halt product distribution (it can do both for medical devices) and must instead go through the courts to request a seizure.²⁹ In addition to mandatory recall authority for drugs, the FDA needs the authority to subpoena documents and witnesses, and an improved set of enforcement tools such as civil penalties for violations of the FDCA.
4. Improve the information flow to FDA: Drug companies are not currently required to inform FDA of many types of quality or safety issues that could present risks to U.S. patients, such as suspected counterfeiting or theft. Industry whistleblowers wishing to bring information to FDA are not currently covered by specific whistleblower protections. FDA is also limited in its ability to share information protected under the trade secrets provision of the Freedom of Information Act (FOIA) with other government agencies, which can hamper international investigations, and should be given clear authority to do so.

Protect American Consumers

The public expects that FDA will ensure that the drugs they take every day are safe from contamination and, at the same time, there is increasing concern about the safety of imported drugs. A poll commissioned by The Pew Charitable Trusts found that Americans are concerned about the safety of drugs from developing countries.³⁰ And Americans across the political spectrum overwhelmingly support giving FDA increased authority in order to protect the domestic drug supply. For example, 86% of respondents supported inspecting foreign facilities every two years; 94% supported mandatory recall authority for the FDA.

There is broad support among industry leaders, healthcare providers and the public for reforms to ensure the safety of the drug supply. We should not await another tragedy.

¹ Lutter, R., Deputy Commissioner for Policy, U.S. Food and Drug Administration. Addressing Challenges of Economically-Motivated Adulteration. May 1, 2009

² Testimony of Robert L. Parkinson, Chief Executive Officer, Baxter International Before Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives. April 29, 2008

³ Villax, Guy, Member of the Board and Head of Globalization Task-Force, European Fine Chemicals Group. "Business of Counterfeit Heparin and its Implications". Presentation at the 3rd EFCG Pharma Business Conference. 5/29/08. Lisbon, Portugal.

⁴http://www.fda.gov/Cder/drug/infopage/heparin/adverse_events.htm.

⁵ Testimony of Robert L. Parkinson, Chief Executive Officer, Baxter International Before Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives. April 29, 2008

⁶ The Heparin Disaster: Chinese Counterfeits and American Failures: Hearings before the Subcommittee on Oversight and Investigations, of the House Committee on Energy and Commerce, 110th Cong., 2d Sess. (2008) (Testimony of Robert L. Parkinson, Chief Executive Officer, Baxter International).

⁷ Warning Letter WL 320-08-01, April 21, 2008. To: Dr. Yan Wang, Ph.D., General Manager, Changzhou SPL Company, Ltd (a/k/a "Kaipu"). From: Food and Drug Administration, Division of Manufacturing and Product Quality Office of Compliance Center for Drug Evaluation and Research.

⁸ Bogdanich, Walt, 2008 "Heparin Find May Point to Chinese Counterfeiting" *The New York Times*, March 20, 2008. Accessed 03/20/2008. www.nytimes.com.

⁹ Woodcock, Janet. Director, Center for Drug Evaluation and Research, Food and Drug Administration. "The FDA's Response to Biogenerics, QA and Globalization." *Unbranding Medicines: The Politics, Promise, and Challenge of Generic Drugs*. Harvard Interfaculty Initiative on Medications and Society. December 12, 2008

¹⁰ U.S. Government Accountability Office. (2007, November). *Drug Safety: Preliminary Findings Suggest Weakness in FDA's Program for Inspecting Foreign Drug Manufacturers*. (Publication No. GAO-08-224T)

¹¹ *Potential Health & Safety Impacts from Pharmaceuticals and Supplements Containing Chinese-Sourced Raw Ingredients*. Prepared for the United States China Economic and Security Review Commission by NSD Bio Group. April 2010.

¹² *Potential Health & Safety Impacts from Pharmaceuticals and Supplements Containing Chinese-Sourced Raw Ingredients*. Prepared for the United States China Economic and Security Review Commission by NSD Bio Group. April 2010. http://www.uscc.gov/researchpapers/2010/NSD_BIO_Pharma_Report--Revised_FINAL_for_PDF--14_%20April_2010.pdf accessed 4/14/2010.

¹³ 21 USC §360 subsection (h)

¹⁴ U.S. Government Accountability Office. (2007, November). *Drug Safety: Preliminary Findings Suggest Weakness in FDA's Program for Inspecting Foreign Drug Manufacturers*. (Publication No. GAO-08-224T)

¹⁵ U.S. Government Accountability Office. (2007, November). *Drug Safety: Preliminary Findings Suggest Weakness in FDA's Program for Inspecting Foreign Drug Manufacturers*. (Publication No. GAO-08-224T)

¹⁶ Bruttin, Francies, and Dean, Doug. "Managing the Cost of Compliance in Pharmaceutical Operations" IBM Business Consulting Services, April 2004.

¹⁷ Warning Letter WL 320-09-01, April 14, 2009,. To: Dr. Mao Jian Yi, General Manager, Shanghai No. 1 Biochemical & Pharmaceutical Co. Ltd. From: Inspections, Compliance, Enforcement, and Criminal Investigations, Food and Drug Administration, Division of Manufacturing and Product Quality, International Compliance Team

¹⁸ Warning Letter WL 320-09-01, April 14, 2009,. To: Dr. Mao Jian Yi, General Manager, Shanghai No. 1 Biochemical & Pharmaceutical Co. Ltd. From: Inspections, Compliance, Enforcement, and Criminal Investigations, Food and Drug Administration, Division of Manufacturing and Product Quality, International Compliance Team

-
- ¹⁹ Memorandum to Mr. Malvinder Mohan Singh, CEO & Managing Director, Ranbaxy Laboratories Limited. Food and Drug Administration, Department of Health and Human Services. February 25, 2009.
- ²⁰ Motion to Enforce Subpoenas and Points and Authorities. United States of America, petitioner, v. Ranbaxy, INC., and Parexel Consulting, respondents. United States District Court for the District of Maryland (Southern Division). 7/3/2008
- ²¹ European Commission. Annex I: Scientific Conclusions And Ground For Amendments Of The Marketing Authorisation And Recall Of Batches Presented By The European Medicines Agency. Annex to multiple Commission Decisions of 29.3.2010: suspending the marketing and withdrawing, under Article 20 of Regulation (EC) No 726/2004 of the European Parliament and of the Council, certain batches of [multiple Clopidogrel products], a medicinal product for human use. http://ec.europa.eu/health/documents/community-register/2010/2010032978389/annx_78389_en.pdf. Accessed August 25, 2010
- ²² Rentz ED, Lewis L, Mujica OJ, *et al.* Outbreak of acute renal failure in Panama in 2006: a case-control study. *Bull World Health Organ* 2008; 86:749–756.
- ²³ U.S. Food and Drug Administration News Release. “FDA Advises Manufacturers to Test Glycerin for Possible Contamination: Glycerin Contaminated with Diethylene Glycol (DEG) Remains a Potential Health Hazard to Consumers.” May 4, 2007. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108909.htm>. Accessed September 27, 2010
- ²⁴ MEGlobal. Diethylene Glycol Product Guide. 2005
- ²⁵ U.S. Food and Drug Administration . Toothpaste imported from China may contain diethylene glycol. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153155.htm>, Accessed Sept 1, 2010
- ²⁶ U.S. Food and Drug Administration. Sulfanilamide Disaster. <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/ucm2007257.htm>, Accessed Aug 24, 2010
- ²⁷ Autor, Deb. Director, Office of Compliance, Food and Drug Administration. Closing remarks, 2010 PDA/FDA Pharmaceutical Supply Chain Workshop. Bethesda, MD. April 26-28, 2010.
- ²⁸ Rothman, Barry. Division of Manufacturing & Product Quality, Office of Compliance, Center for Drug Evaluation & Research, Food and Drug Administration “Pharmaceutical Ingredient Supply Chains”. Presentation at FDA News Supplier Management Congress. Arlington, VA. August 19-21, 2009
- ²⁹ 21 C.F.R. 7.40 (c)
- ³⁰ Hart Research Associates and Public Opinion Strategies. 802 likely voters. March 29- Apr 1, 2010. http://www.prescriptionproject.org/tools/initiatives_resources/files/Drug-Safety-Poll-Findings-2.pdf