Protecting Consumers from Adulterated Drugs

Comments of Allan Coukell
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Thank you for the opportunity to present comments and to participate today in this important discussion. My name is Allan Coukell. I am a pharmacist and director of the Pew Prescription Project – an initiative established by The Pew Charitable Trusts to represent consumer interests on a range of drug safety issues, including the risk of adulterated medicines.

Protecting consumers against the risk of adulterated products is, of course, the original mission of the FDA.[1] Today, the vast majority of pharmaceutical products sold in the United States today are not adulterated, but an increasingly complex supply chain creates new challenges and new risks – as recent events demonstrate.

Economically motivated adulteration includes the potential for contaminated, sub-potent or counterfeit medication to enter the supply chain at several levels, from the production of raw ingredients through to the point of retail sale.

The true prevalence of such adulteration is unknown. The severity of reactions associated with heparin in 2007 and 2008 made it likely that the contamination would be detected, albeit too late. However, a less toxic contaminant or an inert or sub-potent formulation would be more likely to escape notice.

In recent years, the pharmaceutical supply chain has become increasingly complex, extending beyond our shores in unprecedented ways. By one widely-cited 1998 estimate, nearly 80% of all active pharmaceutical ingredients now originate outside the United States, a trend that can only have increased in the past decade.[2] Americans now consume pharmaceuticals that originate in thousands of manufacturing facilities in developing nations outside the formal jurisdiction of FDA.

Even an adulteration rate of less than 1 percent, could equate to millions of American consumers exposed each year.[3]

To protect the supply chain, regulatory activity occurs at multiple levels:

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[1] Created through the Food and Drugs Act of 1906.

[2] 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)

[3] An estimate by FDA officials of the prevalence of counterfeit drugs in the US – one specific kind of economically motivated adulteration. Rudolph, PM and Bernstein, IBG. "Counterfeit Drugs" *N Engl J Med.* April 1, 2004. Vol. 350: 1384-1386

- Promulgation of good manufacturing practices and related standards
- Compliance reviews, including inspections of manufacturing facilities
- Review of pharmaceutical imports at the point of entry to the United States
- Oversight of pharmaceutical distribution within the United States

Heparin

As already mentioned today, contaminated heparin from China was associated with a surge of deaths in 2007 and 2008. We don't know how many, but probably many dozens. FDA reports 149 deaths with allergic or hypersensitivity symptoms during that period.[4] Although causality in all of those cases is uncertain, hypersensitivity reactions are consistent with an animal model of toxicity for the identified contaminant, over-sulfated chondroitin sulfate (OSCS).

In the US, the contaminated heparin was marketed by Baxter International Inc., but the same contaminant was detected in other companies' products elsewhere, and at least 10 Chinese companies were involved in the upstream supply chain.[5]

Baxter purchased its active pharmaceutical ingredient (API) from a factory in Changzhou, China – Scientific Protein Laboratories (SPL-CZ). In turn, this factory purchased the crude material to make heparin from Chinese workshops. The toxic contaminant was chemically similar to heparin and mimicked it on the standard assays performed by Baxter on the Changzhou API.

Subsequent investigations have shown that FDA did not inspect the Changzhou factory in 2004, when it gave approval for Baxter to list the plant as an alternate supplier of the API. Indeed, the plant had been producing heparin destined for US consumers since at least the year 2002, but had never been inspected by FDA.[6] (Baxter and another company, Wyeth, conducted their own inspections of SPL-CZ in 2007 and 2002, respectively.)

Crude heparin is made from pig intestines that are cooked and dried to yield the material that is processed into finished heparin API. This unprocessed material is harvested by numerous workshops, often run by small farmers, and subject to limited regulatory scrutiny. SPL-CZ did not deal directly with these raw material workshops, but purchased its material from two consolidators. There was no FDA oversight of these upstream suppliers. When inspectors were sent by Baxter in 2008 to retroactively

[4] The figure is from http://www.fda.gov/Cder/drug/infopage/heparin/adverse_events.htm. It is important to state that the exact number of deaths secondary to contamination is unknown. Adverse event reporting would likely have increased because of public attention. However, it seems clear that there were excess fatalities.

[5] http://www.fda.gov/bbs/transcripts/2008/heparin_transcript_042108.pdf

[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).

assess the heparin supply chain they were denied access to these workshops and to the consolidators.[7] Both FDA and Baxter are still reportedly unable to pinpoint the source of the contamination.

Circumstantial evidence strongly suggests that the contaminant was deliberately introduced into the supply chain. Firstly, OSCS is not a naturally occurring product. Secondly, it is made from a bulk commodity – chondroitin sulfate – which is much less expensive than heparin. It may not be coincidence that this material entered the supply chain during a period when Chinese pig herds were greatly diminished due to a widespread outbreak of swine virus.[8]

Other incidents

Other recent incidents of adulteration provide more reason for concern. In Panama in 2006, 115 individuals died, and many more were disabled,[9] after receiving cough syrup prepared with inexpensive diethylene glycol masquerading as the proper and more costly excipient, glycerin.[10] The contaminated excipient originated in China and passed through European brokers before its incorporation into cough medicine. DEG-contaminated medications were discovered in other countries in 1990, 1996 and 1998. These incidents occurred outside our borders, but illustrate the potential risk for US-based manufacturers and consumers.

Economically motivated adulteration also manifests as deliberate counterfeiting of finished products (as distinct from compromised manufacture). The UK and EU have recently reported a surge in counterfeit medication.[11] And the US experience includes instances of counterfeit Lipitor, Epogen and other products, illustrating the potential for counterfeits to enter our system in the current regulatory environment.[12] [13] [14]

Specific Concerns and Recommendations

The deaths caused by contaminated heparin vividly illustrate the shortcomings highlighted in a series of reports by GAO and other observers, focusing on the challenges of an increasingly complex supply chain

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

[8] Ibid.

[9] Autor, Deborah M. Director, CDER Office of Compliance. 2009, "Globalization: Challenges and Recent Case Studies" DCAT Week, New York.

[10] Bogdanich, Walt "FDA Tracked Poisoned Drugs, but Trail Went Cold in China" New York Times, June 17, 2008. Accessed 12/16/2008, www.nytimes.com.

[11] Organization for Economic Co-operation and Development (OECD) (2008) The Economic Impact of Counterfeiting and Piracy. www.oecd.org/dataoecd/13/12/38707619.pdf

[12] Neal, Rome "Lipitor Counterfeits Abound" CBS News. Accessed 04/27/09, http://www.cbsnews.com/stories/2003/06/04/earlyshow/health/main557016.shtml

[13] "19 Indicted in Florida In Case of Phony Drugs" New York Times. July 22, 2003. Accessed on 04/27/09, http://www.nytimes.com/2003/07/22/us/19-indicted-in-florida-in-case-of-phony-drugs.html

[14] Eban, Catherine. 2005. Dangerous Doses. Harcourt, INC.

and a manufacturing base that is rapidly expanding into the low-cost environment of developing economies, particularly India and China.

FDA's challenges include a lack of resources, outdated regulatory systems, inadequate information technology and legal and logistical challenges associated with oversight of foreign facilities.

It is essential that FDA receive increased resources and authorities in order to carry out its mission of ensuring the safety of pharmaceuticals – imported and otherwise.

What follows are a number of key priorities:

IT Systems

GAO's 2007 and 2008 reports highlight limitations in the FDA's current tracking systems for US product manufacturing overseas. Indeed, the exact number of such facilities is unknown.[15] The systems do not allow for sufficient risk-based targeting both at import and for site inspections, [16] nor do they allow border control officers to clearly see where product has previously been refused entry, thus limiting their ability to prevent "port shopping."

FDA must improve its tracking systems to facilitate information sharing and risk-based decision making. Without better IT infrastructure, increased regulation of overseas sites and imports will lack effective direction.

CDER is planning implementation of electronic drug regulation and listing submission (e-DRLS) to better capture manufacturing site information. The Drug and Device Accountability Act of 2009, introduced in the current Congress, would also establish an enhanced electronic regulation that would show connections between supply-chain affiliates and inspection histories.

Inspections

As the GAO has documented, foreign facilities are inspected at a far lower rate than domestic facilities – just 7% per year, compared with around 37% for domestic facilities.[17] Indeed, the exact number of foreign facilities is unknown.[18] Foreign facilities are outside the normal jurisdiction of US regulators and

[15] The parallel systems used by FDA to track manufacturing sites and imported products that are, by their own assessment, electronically irreconcilable. Two major systems, DRLS and OASIS, respectively estimate 3,000 and 6,700 foreign establishments subject to FDA inspection. 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] 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)

[17] US Government Accountability Office. (2008, September). Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program. (Publication No. GAO-08-970)

[18] Ibid. Two major systems, DRLS and OASIS, respectively estimate 3,000 and 6,700 foreign establishments subject to FDA inspection.

entail linguistic and other logistical challenges. But there is no rational basis on which to argue that non-US facilities deserve less scrutiny.

FDA must inspect more foreign manufacturing facilities more frequently. Given finite resources, it is essential that inspections be targeted using risk-based assessment methods. More sophisticated IT and informatics approaches will assist this targeting.

Currently, most FDA inspections of foreign sites are associated with new drug applications. Once approved, foreign facilities are unlikely to be re-inspected for good manufacturing practices (GMP). In contrast, over 75% of domestic facility inspections in 2007 were post-approval GMP inspections.[19] The GAO has documented that even foreign facilities in which violations have been identified are unlikely to be re-inspected.[20] And, as the heparin example illustrates, some facilities may never see an FDA inspection.

FDA must reliably conduct universal pre-approval inspections of all manufacturing facilities. It is also clear that increased GMP inspections of foreign facilities are necessary, but equally or more important is improved targeting of such activities. Although FDA currently uses risk-analysis to target its limited resources for inspections, the information it uses to assess risk at foreign sites comes from tracking systems that have acknowledged weakness and further, that were not designed for this purpose.[21]

Better information systems can likewise improve the efficiency of field exams (at the port or overseas), but the goal of a risk-based system must be improved efficacy (that is, the 'hit rate' for identifying problems) and not merely efficiency (clearance rate). FDA must assess the staff required to provide optimal safety and not the optimal level of safety that can be achieved with a given staff.

FDA has taken steps in this direction, with a notable effort being the PREDICT pilot, which was initially undertaken for seafood imports in a small number of ports (and is now being implemented more widely).[22] PREDICT was implemented at five Los Angeles ports, and saw the 'hit rate' – the proportion of field exams that found violations – increase from 3.7% to 7.0%. A similar approach could be implemented for pharmaceutical imports, and should draw on a broad range of data sources to target exams.

Done correctly, such an approach should not only improve the agency's ability to identify potentially adulterated medicines, it will also increase the speed at which compliant shipments are cleared.

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[19] Ibid.

[20] US Government Accountability Office. (2008, September). Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program. (Publication No. GAO-08-970)

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

[22] http://www.fda.gov/oc/initiatives/advance/imports/activities.html

In addition, certain industry initiatives, such as the Rx-360 consortium, also hold promise. While not a replacement for an effective regulatory system (and not intended to be), this new industry association has the potential to allow manufacturers to share best-practices, as well as supplier and audit information to improve safety.[23]

Other Authorities & Regulations

Congress must act to give FDA additional authority and capacity, including mandatory recall authority for pharmaceuticals, subpoena power, and the ability to hold or destroy adulterated products at the border to ensure that dangerous products are not able to enter the US through 'port shopping'.

In addition, FDA must require companies to know more about their upstream sites, including suppliers, and to better assess and document supplier compliance with GMP. Baxter and the FDA were unable to verify the origins of contaminated heparin largely because suppliers of the crude were not obligated to share this information.[24] As the Panama cough syrup example illustrates, GMP compliance requirements must extend to excipient suppliers.

The Drug and Device Accountability Act of 2009 would require companies to submit detailed documentation at registration of any and every site involved in drug or drug component preparation, including excipients and raw materials.[25]

In addition, FDA must have the capacity – including resources, technical expertise and accurate registration information from companies – to inspect upstream supplier sites and manufacturer contracts with suppliers, when necessary. Supplier contracts must include accurate contact information for suppliers including addresses, provide for periodic audits, establish protocol for supply chain changes, and ensure FDA access is a clear condition of the contract.

Pedigree

Counterfeit drugs can enter the chain of custody at numerous points both abroad and at home. FDA can facilitate industry protection of the distribution chain by establishing robust electronic pedigree and traceability standards. California has passed a comprehensive serialization and pedigree standard, which will become effective in 2015 if the federal government fails to adopt a national standard. It is time to adopt a national standard.

Harmonisation and Cooperation

While the aforementioned reforms will increase FDA's capacity to protect the US drug supply, the growing globalized manufacturing system cannot be regulated by FDA alone. A long-term goal for FDA must be to seek harmonized standards with other governments and to share registration and inspection

[23] www.Rx-360.org

[24] Testimony of Baxter International before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, April 29, 2008

[25] S.882 "Drug and Device Accountability Act of 2009" Senator Edward M. Kennedy and Senator Charles Grassley.

information gathered by countries with strong regulatory authorities. FDA must also work with countries with weaker regulatory systems to improve oversight capacity and standards, including surveillance of drugs and drug ingredients – many of which may be exported to the U.S.

Penalties

A component of a successful regulatory system is meaningful sanctions for failure to comply. Congress should increase criminal penalties for knowing production of, or trafficking in, counterfeit medications. Falsification of a pedigree record should be similarly sanctioned.

We do not equate compromised manufacturing with deliberate counterfeiting. Nevertheless, companies have elected to operate in, or source materials from, low-cost environments. That, too, is an economic motivation. Manufacturers that fail to meet specified standards of due diligence for ensuring the safety of their products should also face civil and criminal penalties.

Funding

To accomplish these reforms, FDA will need increased funding. Registration fees, as proposed in pending legislation, are likely the best way to fund needed improvements; however, it is essential that such fees not be associated with any quid pro quo that could put pressure on the agency to prioritize speed or other factors over safety. It is also important that fees not take the place of public appropriations to the FDA. Fees must also be applied fairly to companies across a diverse sector.

Fees must clearly fund the IT and regulatory reforms necessary for FDA to protect the safety of the US drug supply. Fee amounts must take into account additional staff, staff training, system development and infrastructure, as well as the cost of conducting sufficient site inspections overseas. Fees must also account for potential re-inspections in the case of discovered violations.

Pending Legislation

In the current Congress, legislative proposals in both houses offer the potential of increased resources (through new registration fees paid by industry), new authorities and also new requirements for FDA oversight. The Pew Prescription Project hopes to be a partner in shaping these bills and working for their success.

Bills regulating overseas drug manufacturing introduced in this session include:

- The FDA Globalization Act of 2009, Representatives Dingell, Pallone and Stupak
- The Drug and Device Accountability Act of 2009, Senators Kennedy and Grassley

Key elements of the bills include increased FDA authorities, increased inspections, industry user fees and provisions to improve documentation of upstream suppliers (see Appendix for further detail).

In addition, The Pharmaceutical Market Access and Drug Safety Act of 2009, introduced by Senators Dorgan and Snowe and in the House by Representatives Berry and Emerson includes additional provisions related to the safety of imported pharmaceuticals.

FDA should, as quickly as possible, analyze the impact of such legislation in terms of the need for increased staffing each would entail and the funds that will be needed. This analysis is essential to establishing whether the new mandate in the legislative proposals can truly be fulfilled.

Conclusion

The deaths caused by contaminated heparin have been called a "wake-up call" by FDA and by manufacturers. They are for consumers, too. Yet in some ways, the risks of a complex and increasingly globalized supply chain have been apparent for some time. Systemic improvement won't be easy, but is possible. With legislation pending and an increased focus on these issues inside and outside the agency, we believe now is the time to make the changes that will protect consumers now and in the future.

The Pew Prescription Project hopes to be a constructive partner in these efforts. Thank you for the opportunity to present comments today.

Appendix 1: Bills addressing regulation of overseas drug manufacturing and importation.* All modify FDCA.

	Provision	H.R. 759: FDA Globalization Act of 2009. Mr. Dingell, Mr. Pallone & Mr. Stupak	S.882: Drug and Device Accountability Act of 2009. Mr. Kennedy & Mr. Grassley
FDA Regulatory Capacity and Authorities	**New information systems for risk-based targeting**	Secretary shall establish IT capacity for risk-based surveillance of GMP compliance.	Not explicit
	Electronic registration and drug listing	—	Electronic registration and drug listing information. Database will link entities within a supply chain; will integrate with inspection histories and other FDA databases.
	Unique identifier / site tracking	Registration numbers	Registration numbers: D-U-N-S (will also be ID for importers)
	Inspections	All sites every 2 years, but Secretary may impose risk-based schedule. Risk based inspections not less than every 4 years. Mandatory inspection before a new or significantly altered drug enters into interstate commerce. Risk assessments may reference type of drug or device, inspection history, shipping and volume history.	All sites every 2 years, but Secretary may impose risk-based schedule. Risk based inspections may be as frequent as needed, not less than every 5 years. May include excipient sites. Risk assessments may reference type of drug or device, country of manufacture, record of inspections by FDA and other governments, inspections by 3rd parties for excipients. Annual reports on inspections must be publicly posted.
	Dedicated inspectorate	Secretary shall establish a dedicated foreign inspectorate	Secretary shall establish a dedicated foreign inspectorate
	Testing	—	Secretary shall identify assays that are no longer sound, prioritize assays for revision based on health risk, assess whether assays can distinguish between drug and possible contaminants.
	International information-sharing	—	Secretary may share confidential information with foreign government officials when safe and necessary, and may receive confidential information from said governments
	Recall	Secretary may order cessation of distribution or recall when necessary, if manufacturer does not take recommended action. Hearings on orders will be granted.	Secretary may order cessation of distribution or recall when necessary. Informal hearings on orders will be granted.
	Subpoena Power	Subpoena power for witnesses and documents	Subpoena power for witnesses and documents
	Hold / destroy products at border	Secretary may hold or destroy at the border products that pose a health risk. For articles valued greater than $2,000, Secretary shall provide the opportunity for an informal hearing.	Secretary may hold or destroy at the border products that pose a health risk.

	Whistleblower protections	Included	Included
Manufacturing Sites	**Registration**	Any product not required to be registered under any other section must be registered with FDA prior to import.	Registration to include all "precursor ingredient" sites. Both domestic and foreign sites must include payments of inspection fees at registration, and D-U-N-S number for all manufacturing sites.
	Legal responsibility	Submission of false and misleading data under the Act is prohibited for drugs and medical devices.	Manufacturers must certify under penalty of perjury that they have knowledge of this Act's requirements, knowledge of their submission (new product application, product report), knowledge that their submission complies with the Act and is not false or misleading, that all required clinical trial information has been submitted to FDA. If secretary determines violations, subsequent inspection costs will be assessed of submission sponsor.
	Fee structure	Required for registration, set by Secretary. Will increase each year at minimum of inflation. Other appropriations must increase by same amount.	Required for registration, set by Secretary. Cannot be greater than other appropriations or difference between other appropriations and needed funding. Fees for foreign sites will cover travel, lodging and translation in addition to the standard fee. Fees will be proportionally greater/less for sites that under a risk-based schedule are inspected more/ less than every two years.
	Fee coverage	Inspections & compliance: Personnel, IT, facilities & maintenance, accounting	Registration and Inspection activities
	Upstream supply chain / ingredients tracking	All manufacturing establishments must be able to provide electronic documentation of entire supply chain including suppliers and raw material manufacturers.	Manufacturers shall lists for all finished dose drugs containing identity of all establishments involved in their preparation including active, inactive, and precursor ingredient preparation. Drugs without correct purity and source information will be adulterated.
	Quality assurance	All manufacturing establishments must have Quality Risk Management Plans which shall provide for assessments of suppliers (raw material on), explain the quality control process and monitor and review supplier compliance, provide for effective testing specifications.	—
	Excipient mfrs	Not subject to fee. Secretary may create risk-based inspection schedule separate from other sites.	Secretary may eliminate exemption of excipient manufacturers from registration after review.
	Generic mfrs	Separate fee assessed at submission of an Abbreviated New drug application (ANDA) to cover generic drug pre-approval inspection costs.	—

	Small businesses	Fees may be waived if they would impose financial hardship	Fees may be waived or reduced for small drug companies and may be reduced to 1/4th of the normal fee for small device companies
	Repackagers	Only required to document establishment immediately preceding them in the supply chain	Drug is adulterated if not conveyed under good distribution and import practices
	Country of origin labeling	Manufacturers must list country of origin of their products and product APIs on their website	Drug is misbranded unless country of origin of drugs and APIs are listed on manufacturer website
Importers	**Registration / certification**	Importers must register if they are not already registered with FDA as a manufacturer.	Required importer registration and licensing. Registration includes name, places of business, D-U-N-S number.
	Fees	$10,000 importer registration fee	Importers must post a bond (amount to be set by Secretary) subject to forfeiture upon violation of the Act.
	Documentation	Importers must provide documentation of product identity, quality, safety, approval and registration.	Importers must provide D-U-N-S number, new drug application number, and other tracking numbers, records of inspections, for all drugs, APIs, API precursors. Excipients must provide the same as well as a 3rd party quality certification when secretary deems acceptable. Not required for imports subject to further manufacturing for export.
Penalties	**General Violations**	Max: $100,000 initial, $200,000 subsequent violation of same requirement.	Max: $100,000 per violation, assessed each day violation continues
	False Data at Import	Max: $200,000	Max: $150,000
	Failure to comply with orders (recall)	Max: $250,000/day	Under general violations
	False certifications of compliance	Not applicable	<u>False certifications of compliance</u>: Submission sponsors: max: $1 million. Responsible person (director of submission sponsor): max: $1 million, 10 years imprisonment. <u>Willful false certification of compliance</u>: Submission sponsors: max: $5 million. Responsible person: max: $5 million, 20 yeas imprisonment.

	Counterfeit	Max: fines in accordance with title 18, US Code, 20 years imprisonment. Max life imprisonment if counterfeit results in death.	Special penalties for counterfeit not discussed

*A related bill, S.525 & H.R.1289, the Pharmaceutical Market Access and Drug Safety Act of 2009 would create a pathway for drug reimportation into the U.S., including standards intended to ensure safety of such drugs.