Testimony before the

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Chairman Harkin, Ranking Member Enzi and members of the HELP Committee, thank you for the opportunity to testify about the essential steps Congress must take to protect Americans and ensure the integrity of our drug supply.

The Pew Charitable Trusts is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public and stimulate civic life. Based on research and critical analysis, the Pew Health Group seeks to improve the health and well-being of all Americans.

A major focus of the Pew Health Group is identifying ways to improve the safety of the U.S. pharmaceutical supply chain. In July of this year, we released a report entitled "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs."[1] The report, which underwent extensive external review, was based upon information from regulatory and public documents, peer-reviewed journal articles and interviews with dozens of supply chain experts from numerous perspectives. It was informed by a two-day conference we hosted earlier this year that included representatives of brand and generic pharmaceutical manufacturers, active drug ingredient makers, major and secondary pharmaceutical wholesalers, chain and independent pharmacies, consumer and health professional organizations, the U.S. Food and Drug Administration (FDA), state regulators and independent supply chain experts. I am including the report as part of my testimony.

The key message is that pharmaceutical manufacturing has changed dramatically over the past decade. While the vast majority of drugs in American pharmacies and medicine cabinets are not counterfeit or adulterated, increasing globalization and reliance on outsourced manufacturing creates new risks, including the risk of deliberate tampering or counterfeiting of ingredients as well as the risk of inadequate safety or quality controls in a manufacturing environment that is largely outside the scrutiny of the FDA. Along with

some serious recent safety problems, we have seen recently seen shortages of important medicines, in part due to manufacturing quality problems.

We are encouraged by ongoing Generic Drug User Fee discussions and press reports that generic drug companies and active ingredient makers have agreed to pay fees that will enable the FDA to conduct more inspections of overseas manufacturing facilities. Indeed, at our recent public meeting, these sectors emphasized the importance of stepping up to ensure stronger oversight of their products. There is no doubt that this step, if taken, would move us closer to a system that better protects the health of American patients.

However, the problem of pharmaceutical supply chain safety is not confined to generic drugs. As FDA officials and other experts have emphasized, this is an issue for all drugs, brand and generic alike. It is essential that Congress ensure that we have a system that enables FDA, in conjunction with other regulators and third parties, to inspect all high-risk overseas facilities. Further, increasing FDA's oversight capacity, while critical, is only one of several necessary steps that Congress must take to ensure safety. Our analysis of supply chain risks has identified the need to ensure stronger baseline quality management standards for industry, and the need to update FDA tools and authorities that will allow the Agency to operate effectively in the 21st Century environment.

Heparin

The contamination of the blood thinner heparin dramatically illustrates the risks we face. 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 in patients undergoing dialysis.[2] The events were subsequently linked to heparin, a widely used blood thinner.[3] Additional analysis led to the identification of an adulterant that standard tests were unable to detect.[4] Heparin was made by an American company, but the heparin active ingredient had been sourced from a Chinese factory, which in turn relied upon a network of small suppliers. The FDA and others believe that persons in China added the cheaper adulterant to crude heparin to cut costs.[5,6] 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.[7] The FDA received reports of deaths and serious injuries associated with use of heparin.[8]

While failure to detect the contaminant during manufacture was a key factor, the case also illustrated other systemic problems, including:[9,10,11]

- 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.

Indeed, as recently as last month, the FDA issued a warning letter to a Chinese manufacturer of heparin for failure to conduct adequate quality control, failure to evaluate raw ingredients test each batch of incoming material and failure to adequate assess suppliers. Although the firm in question was supplying the US market, it was not registered with the FDA, as required under law.[12]

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.[13] An estimated 40% of all finished pharmaceuticals,[14] and 80% of the active ingredients and bulk chemicals in U.S. drugs, are now sourced by industry from foreign countries,[15] and up to half are purchased from plants in India and China.[16] The U.S. is the number one destination for Chinese pharmaceutical raw material exports. [17]

A recent survey of pharmaceutical industry executives determined that 70 percent had key suppliers in China and close to 60 percent in India. About half of those surveyed were from companies with annual revenues of one billion dollars or more. 94% of those surveyed saw their greatest supply chain risk as raw materials sourced outside the United States.[18]

Despite globalization of manufacturing, FDA oversight is largely domestically focused. The Food, Drug and Cosmetic Act (FDCA) requires inspections of U.S. plants every two years, but specifies no inspection frequency for foreign plants.[19] The FDA lacks the resources to inspect foreign sites with any meaningful regularity.[20] 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.[21]

Quality/compliance

In the case of heparin, it appears that criminals deliberately introduced a substandard active ingredient 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.[22] 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.[23] The FDA has said that some of this heparin may have contained the same contaminant associated with the deaths in 2007 and 2008.[24] 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 alleged falsification of stability testing records and use of active ingredients made at unapproved sites, according to a Department of Justice subpoena motion. [25,26] In 2010, another Indian manufacturer was found to have falsified batch manufacturing records for an anti-platelet 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.[27]

In Panama in 2006, dozens of people died after taking a cough medicine that had been made with diethylene glycol,[28,29] a sweet-tasting, but poisonous solvent.[30] It had been wrongly labeled in China and passed through a series of Chinese and European brokers, who repeatedly re-labeled it, presumably 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.[31] Students of FDA history will know that diethylene glycol poisoning in the United States in 1937 was the disaster that lead directly to the enactment of the FDCA.[32] It is now time to update that statute for 21st century manufacturing.

Gaps and Solutions

At the Pew convening in March, we heard clearly 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 robust systems 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 is 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 more than 30 agreements with regulatory bodies in different countries to share some inspectional and other non-public information.[33] Finally, this June, the FDA released an important strategy paper outlining its intent to form a global consortium of regulators and to increase the agency's reliance on third-party sources of information.

Many individual companies have also taken steps, and as mentioned, the focus on increasing FDA oversight capacity in the current GDUFA negotiation process is an important move forward. Nevertheless, additional legislative changes are now needed to give the FDA the tools it needs and to ensure that every manufacturer, whether generic or brand, 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. Company management must be held accountable for implementing these systems.

While the FDA already has the authority to establish "current good manufacturing practices," or cGMPs, these regulations do not extend to the assurance of quality at ingredient suppliers. The FDA has issued guidance explaining how a quality systems approach complements GMPs. Legislation should require companies to develop such quality systems, but must allow for companies and FDA to update standards and practices in keeping with advances over time.

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 for both generic and brand companies. 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, but the agency also needs additional resources to conduct overseas inspections. As noted above, the proposed user fee agreement with the generic industry and active ingredient makers to help fund inspections will be extremely helpful. Congress should ensure that FDA is able to provide effective oversight on the basis of a risk-assessment, regardless of whether the facility is covered by a user fee agreement.

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.[34] 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. Granting subpoena power to federal agencies is not uncommon – at least 355 such authorities have been granted to other executive branch entitities.

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. This reform would also facilitate the sharing of inspectional information between FDA and its counterpart agencies.

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.[35] 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. We can avoid future tragedies by adopting policies that are supported by drug manufacturers, health professionals, and the vast number of Americans who take medicines such as prescription and over the counter drugs at their peril. Congress should act now.

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